PASS Information

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Research question and objectives	This study aims to evaluate the utilisation and long-term safety of galcanezumab in the United States, including serious cardiovascular events and malignancies, and serious hypersensitivity reactions in routine clinical practice. The safety profile will be characterised over a period of up to five years. The primary objectives of this study are: 1) To describe the utilisation of galcanezumab overall, in migraine patients and cluster headache patients as well as in special populations of interest including patients 65 years or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk. 2) To estimate incidence rates of serious hypersensitivity reactions, serious cardiovascular events and malignancies excluding non-melanoma skin cancers (NMSC) among patients exposed to galcanezumab overall, in migraine patients, and cluster headache patients, as well as in subgroups of patients aged 65 years or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk.

Approval Date: 19-Nov-2019 GMT

	The secondary objectives of this study are: 1) To provide context for incidence rates of serious hypersensitivity reactions, serious cardiovascular events and malignancies excluding NMSC among the galcanezumab-exposed migraine cohort by estimating the incidence among migraine patients receiving other migraine prophylactic medication(s). 2) If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort, to conduct comparative analyses for serious cardiovascular events and malignancies excluding NMSC using migraine patients treated with other prophylactic medication(s) as the control. No formal comparative analyses are planned for serious hypersensitivity reactions due to due uncertainty in the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group; however, incidence rates for hypersensitivity reactions in a comparator cohort will be provided for context. Given the low prevalence of cluster headache, comparative analyses within the cluster headache cohort are not expected to be feasible.
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2. List of Abbreviations

Abbreviation	Term
AAN	American Academy of Neurology
ADIN	Action, Decision, Issue, Notification
AE	Adverse event
AHA	American Heart Association
AR	Adverse reaction
ATC	Anatomical Therapeutic Chemical
CABG	Coronary artery bypass graft surgery
CGRP	Calcitonin Gene-Related Peptide
CPT	Current Procedural Terminology
CI	Confidence intervals
CV	Cardiovascular
DALY	Disability-adjusted life year
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethical review board
EU	European Union
FDA	Food and Drug Administration
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
HIRD	HealthCore Integrated Research Database
HIRE	HealthCore Integrated Research Environment
HRQoL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICSI	Institute for Clinical Systems Improvement
IHS	International Headache Society
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities

Mg	Milligram
MI	Myocardial infarction
NCHS	National Center for Health Statistics
NDC	National Drug Codes
NDI	National Death Index
NMSC	Non-melanoma skin cancers
No.	Number
NSAIDs	Non-steroidal anti-inflammatory drugs
PAS	Post-authorisation studies
PCI	Percutaneous coronary intervention
PSUR	Periodic safety update reports
QALY	Quality adjusted life years
QC	Quality control
RMP	Risk management plan
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TIA	Transient ischemic attack
US	United States
WHO	World Health Organization

3. Responsible Parties

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4. Abstract

- **Title**

A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients in the Course of Routine Clinical Care

Version 1.0

PPD

- **Rationale and background**

Galcanezumab was approved for the preventive treatment of migraine in adults by the United States (US) Food and Drug Administration (FDA) and for the prophylaxis of migraine in adults by the European Commission (EU). Certain aspects of the safety profile of continuous or intermittent long-term use of galcanezumab in routine clinical settings remain unclear. Patients 65 years of age or older, and patients with recent acute cardiovascular (CV) events and/or serious cardiovascular risk were not included in the clinical trials, yet the use of galcanezumab in these populations may occur in routine clinical practice. Additional data are desired to characterise the safety of galcanezumab among these special populations. Therefore, the long-term safety of galcanezumab in a larger real-world patient population requires further characterisation.

- **Research question and objectives**

This study aims to evaluate the utilisation and long-term safety of galcanezumab in terms of serious cardiovascular events and malignancies, and rates of serious hypersensitivity reactions in US routine clinical practice. The long-term safety profile will be characterised through assessment of pertinent data for a period up to 5 years.

The primary objectives of this study are:

- To describe the utilisation of galcanezumab overall, in patients with migraine or cluster headache , as well as in special populations of interest including patients over 65 years of age, and patients with recent acute cardiovascular events and/or serious cardiovascular risk.
- To estimate incidence rates of serious hypersensitivity reactions, serious cardiovascular events, and malignancies excluding non-melanoma skin cancers (NMSC) among patients exposed to galcanezumab overall, patients with migraine or cluster headache, and in the subgroups of patients aged 65 years or older, and patients with recent acute cardiovascular events and/or serious cardiovascular risk.

The secondary objectives of this study are:

- To provide context for incidence rates of serious hypersensitivity reactions, serious cardiovascular events, and malignancies excluding NMSC among the galcanezumab-exposed migraine cohort by estimating the incidence rates of these

outcomes among migraine patients receiving another migraine prophylactic medication.

- If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort, to conduct comparative analyses serious cardiovascular events, and malignancies excluding NMSC using migraine patients treated with other prophylactic medication(s) as the control. Formal comparative analyses for serious hypersensitivity reactions will not be conducted due uncertainty in the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group; however, incidence rates for hypersensitivity reactions in a comparator cohort will be provided for context. Also, given the low prevalence of cluster headache, comparative analyses within the cluster headache cohort are not expected to be feasible.

- **Study design**

This will be a secondary database cohort study using data from US administrative claims and will include the following two phases.

Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drugs

The number of patients exposed to galcanezumab overall and the duration of galcanezumab exposure will be monitored and described. Patients who are exposed to galcanezumab will be classified according to the indication for use into migraine, cluster headache, and neither migraine nor cluster headache diagnosis cohorts. The number of the safety outcomes from the galcanezumab cohorts and a comparator drug-exposed migraine cohort will also be monitored and described. Uptake monitoring will occur annually and is expected to last up to five years. This phase will facilitate sample size projections and the decision on when to initiate comparative analyses if feasible.

In each of the galcanezumab exposed cohorts, patients 65 years or older, and patients with serious cardiovascular risk defined by recent acute cardiovascular events, will be monitored and described. The incidence rates of the safety outcomes of interest in these cohorts and sub-cohorts will be estimated and stratified by duration of exposure.

Phase 2: Comparative Analyses

If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort (see Section 9.6), comparative analyses for serious cardiovascular events and malignancies excluding NMSC, comparing the galcanezumab-exposed migraine patients with propensity score matched migraine patients receiving other prophylactic migraine medication(s) will be conducted. A new user, active comparator design will be used for serious cardiovascular events and malignancies excluding NMSC. A prevalent new user, active comparator design will additionally be used for serious cardiovascular events as a complement for a greater number of galcanezumab exposures.

No formal comparative analyses are planned for serious hypersensitivity reactions due to due uncertainty in the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group; however, incidence rates for hypersensitivity reactions in a comparator cohort will be provided for context.

Given the low prevalence of cluster headache, comparative analyses within the cluster headache cohort are not expected to be feasible and will not be conducted.

- **Populations**

Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drugs

The galcanezumab exposed cohort will include all patients who have at least one pharmacy dispensing or injection procedure of galcanezumab, and continuous medical and pharmacy health plan coverage for at least 183 days on or before the first dispensing or injection date. This look-back period will allow for sufficient time to ascertain information on baseline covariates, prior to index treatments, and prevalent safety outcomes. This cohort will be divided into three cohorts according to the indications for galcanezumab treatment: migraine, cluster headache, and unknown indications (see Figure 1). Galcanezumab patients with migraine, will be defined by having a diagnosis of migraine or a dispensing/injection of triptans (i.e., a proxy of the presence of migraine when a diagnosis is missing) on or before the first galcanezumab dispensing or injection date. Galcanezumab patients with cluster headache, will be defined by having a diagnosis of cluster headache on or before the first galcanezumab dispensing or injection date. Galcanezumab-exposed cohorts are defined in detail in Section 9.2.1.1.

The comparator cohort will consist of patients who have at least one pharmacy dispensing of migraine prophylactic medications other than calcitonin gene-related peptide (CGRP) inhibitors including galcanezumab (see Section 9.2.1.2), have continuous medical and pharmacy health plan coverage for at least 183 days on or before the first dispensing date, and have a diagnosis of migraine or a dispensing/injection of triptans. Patients may have dispensings of more than one migraine prophylactic medication.

Within the galcanezumab-exposed cohorts and the base comparator cohort, we will identify two special populations of interest including (1) patients 65 years of age or older, and (2) patients with serious cardiovascular risk defined as recent acute cardiovascular events (See Section 9.2.1.3).

Incidence rates will be estimated within the cohorts/sub-cohorts identified above. The follow-up of the specific cohorts starts on the day after the index date and ends at the earliest date of the events defined in Section 9.3. The index date is defined as the date of the first dispensing of galcanezumab or the comparator drug.

Phase 2: Comparative Analyses

If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort (see Section 9.6), we will conduct comparative analyses among migraine patients

comparing new users of galcanezumab with propensity score-matched patients who are exposed to other prophylactic medication(s) for serious cardiovascular events and malignancies excluding NMSC. The comparator cohort will be sampled from the base Comparator Drug Migraine Cohort with additional inclusion/exclusion criteria specific to each safety outcome and study design (See Section 9.2.1.4). Each selected comparator patient will also be matched on treatment lines (i.e., observed treatment sequences in the claims) of patients in the Galcanezumab Migraine Cohort (See Section 9.2.1.1) to minimise lag-time bias. Specifically, for serious cardiovascular events, topiramate is chosen as the comparator drug. For malignancies excluding NMSC, new use of a list of eligible migraine prophylactic treatments is chosen as a composite comparator group (see Section 9.2.1.2). Formal comparative analyses for serious hypersensitivity reactions will not be conducted due uncertainty around the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group since non CGRP prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. However, incidence rates for hypersensitivity reactions in the galcanezumab-exposed migraine cohort will be determined and rates in a comparator cohort will be provided for context .

- **Variables**
    - Exposure: Galcanezumab will be ascertained from pharmacy claims for outpatient dispensings and medical claims for injections administered in a health care setting. Exposure to o eligible comparator migraine prophylactic medications will be ascertained from pharmacy claims (See Section 9.4.1).
    - Outcomes: Diagnosis and procedure codes in claims will be used to identify provisional cases of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC (See Section 9.4.2). Serious cardiovascular events will be defined as a composite and individual outcomes. Malignancies excluding NMSC will be analysed overall and by organ system. A random sample of medical records will be sought for adjudication of selected outcomes and the National Death Index (NDI) will be linked to identify deaths due to safety outcomes that occur outside of the health care system. The augmentation of claims data with review of medical records and NDI linkage will improve the validity of outcome classification.
    - Covariates: Demographic characteristics, comorbidities, medication use, and healthcare utilisation will be ascertained during the baseline period using administrative claims(See Section 9.4.3).
- **Data sources**

This study will be conducted in the HealthCore Integrated Research Database (HIRD). The HIRD is a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from approximately 48 million private commercially insured lives across the US. This study will seek medical records for safety outcome adjudication and NDI linkage to supplement to death ascertainment.

- **Study size**

The available number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in the US. The accrual for the composite serious cardiovascular events will determine the feasibility of comparative analysis. Approximately 71 serious cardiovascular events from 5,099 galcanezumab-exposed migraine patients are needed to achieve 80% power to detect a two-fold increased risk of serious cardiovascular events at a significance level of 0.05 in a two-sided log-rank test, assuming a background rate of approximately 7.00 per 1,000 person-years among migraine patients, a comparator-to-galcanezumab ratio of 4:1, and an average of approximately four months of continuous exposure.

- **Data analysis**

Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drugs

The number of patients exposed to galcanezumab overall and by indication of use, the duration of galcanezumab exposure, and the number of safety events will be periodically monitored and described.

In addition, the distributions of covariates including demographic characteristics, comorbidities, concomitant medications, and health care utilisation in the galcanezumab-exposed cohorts and the outcome-specific comparator drug-exposed migraine cohort will be determined and described. The distribution of covariates in the special populations of interest i.e., patients 65 years of age or older, and patients with serious cardiovascular risk within both the galcanezumab and comparator cohorts will also be determined and described, (See Section 9.2.1.3).

The crude incidence rates of the safety outcomes of interest will be determined in the galcanezumab-exposed cohorts (see Section 9.2.1.1), the base Comparator Drug Migraine Cohort, and the special populations of interest within both the galcanezumab and comparator cohorts (See Section 9.2.1.3). The crude incidence rates in all cohorts and in the special populations of interest will be stratified according to duration of galcanezumab use. The incidence of serious cardiovascular events will be presented as a composite outcome and individual outcomes (see Section 9.4.2 Outcomes). The incidence of malignancies excluding NMSC will be presented overall and by organ site. Incidence rates will be adjusted based on predictive positive values from outcome adjudication and additional safety outcomes via NDI linkage to account for potential misclassifications of the fatal outcomes.

Phase 2: Comparative Analysis

If a sufficient number of serious cardiovascular events accrue in the galcanezumab-exposed migraine cohort (see Section 9.6), we will estimate hazard ratios and 95% confidence intervals (CIs) for serious cardiovascular events and malignancies excluding NMSC comparing propensity score-matched new users of galcanezumab with new users or prevalent users of other prophylactic medication(s) among patients with migraine using Cox proportional hazards regression models. To control for confounding, we will construct propensity scores from baseline covariates. Distinct propensity scores will be estimated for analyses for each outcome. For composite serious cardiovascular events using a new user design, propensity score will be

generated for the first index treatment episode using patients initiating topiramate as the reference group in logistic regression models. For composite serious cardiovascular events using a prevalent new user design, time-conditional propensity scores will be generated using all the exposure sets in logistic regression models. For composite malignancies excluding NMSC, propensity score will be generated for each index treatment episode at treatment initiation or switch in logistic regression models. Standardised differences will be used to assess baseline comparability between exposure groups. Covariates with an absolute standardised difference greater than 0.10 will be included in the statistical model to control for remaining imbalances in baseline covariates.For serious hypersensitivity reactions, formal comparative analyses will not be conducted due uncertainty around the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group since non CGRP prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. However, incidence rates for hypersensitivity reactions in both the galcanezumab exposed and comparator exposed migraine cohorts will be provided for context.

- **Milestones**

The start of data collection is 2020. Annual product uptake monitoring in Phase 1 will monitor galcanezumab uptake and is expected to last until Q4 2023. An interim analysis will be performed in Q4 2024. Patient accrual in Phase 1 will be compared against the target size of serious cardiovascular events to determine the feasibility of comparative analyses in Phase 2. The study will last for a total of seven years with the first five years and a half for patient accrual against the target sample size of serious cardiovascular events and the last year and a half for final analyses and study report. In this case, the end of data collection is anticipated to be Q2 2025. The final study report will be submitted with the periodic safety update reports (PSUR)/Risk Management Plan (RMP) within 12 months of study completion. If a sufficient number of serious cardiovascular events do not accrue by June 2025, we will not conduct comparative analyses but will continue patient accrual until 2025 and submit the final report in 2026 according to regulated timelines, per commitments to European regulators.

5. Amendments and Updates

Amendment or update No.	Date	Section of study protocol	Amendment or update	Reason
None				

Abbreviation: No. = number.

6. Milestones

Milestone	Planned date
Start of data collection	31 December 2020[a]
End of data collection	30 June 2025
Study progress report 1	30 November 2019
Study progress report 2	30 November 2020
Study progress report 3	30 November 2021
Study progress report 4	30 November 2022
Study progress report 5	30 November 2023
Study progress report 6	30 November 2024
Interim report	31 December 2024
Registration in the EU PAS Register	17 January 2019
Final report of study results	31 December 2026[b]

[a] Reflects the date of first data extraction.

[b] The study will last for a total of seven years with the first five years for patient accrual against the target sample size for comparative analyses and the last two years for a final analyses and study report.

7. Rationale and Background

Migraine is the second leading cause of disability in the world with an estimated 1.04 billion individuals with the disease in 2016 (1). It is a recurrent headache disorder characterised by painful attacks lasting four to 72 hours often accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and changes in vision (2). The clinical symptoms vary along a continuum from episodic migraine to chronic migraine. Episodic migraine is characterised by no more than 14 headache days per month.Chronic migraine is characterised by 15 or more headache days per month for 3 or more months, of which 8 or more days meet criteria for migraine without aura and/or respond to migraine-specific treatment (2) and is much less common than episodic migraine (3, 4). Migraine is two to three times more prevalent in women than men (5) and its prevalence peaks in the middle of life in both sexes (1). Migraine has been consistently associated with increased risk of ischaemic stroke and myocardial infarction, with a significantly higher risk among patients who had migraine with aura versus without, and among women compared with men (6, 7). The majority of migraine patients use acute treatments such as triptans or nonsteroidal anti-inflammatory drugs for migraine attacks. However, preventive treatment is underused with approximately 3–12% of patients receiving such (8, 9). Low persistence and adherence rates have been reported for existing oral prophylactic medications (antidepressants, anticonvulsants, and beta-blockers) with approximately 25% still on the drug after six months and only 14% remaining on the initial drug at 12 months (10-12).

Cluster headache is one of the most severe primary headache disorders, and is characterised by recurrent attacks of intense headaches on one side of the head, frequently associated with pain behind or around one eye, restlessness, and agitation (13). A cluster period generally lasts from six to 12 weeks and a single attack typically lasts between 15 minutes and three hours. Cluster headache has been associated with seasonal changes with a higher incidence of attacks reported in the fall and spring. The International Headache Society (IHS) classified cluster headache into two major types: episodic (85–90%) and chronic (10–15%) (14). The lifetime prevalence of cluster headache overall is approximately 0.12% and it mostly affects men with overall male-to-female ratio of 4 to 3 (15). The mean age of onset is approximately 31 years old (16).

Galcanezumab is a humanised monoclonal antibody that selectively binds to the calcitonin gene-related peptide (CGRP), and inhibits its biological activity. Elevated blood concentrations of CGRP have been associated with migraine and cluster headache attacks (17). Three placebo-controlled phase-III clinical trials have demonstrated a reduction in the number of monthly migraine headache days for galcanezumab among patients with episodic migraine (EVOLVE-1 and EVOLVE-2) and patients with chronic migraine (REGAIN) (18). Another placebo-controlled phase-III study of patients with episodic cluster headache has also shown a significant reduction of weekly cluster headache attacks from baseline across weeks 1-3 comparing galcanezumab with placebo (19). Given the positive benefit-risk profile of galcanezumab, Emgality™ (galcanezumab) 120 milligram (mg) injection has received approval from the United States (US) Food and Drug Administration (FDA) for the preventive treatment of migraine in adults and a marketing authorisation from the European Commission for migraine prophylaxis in

adults who have at least four migraine days per month. Emgality is available as a once-monthly, subcutaneous injection and can be self-administered via a single-dose prefilled pen or syringe.

Although galcanezumab was generally well-tolerated in clinical trials, adverse effects that have a longer latency period such as malignancy, and/or are infrequent among migraine or cluster headache patients such as serious hypersensitivity reactions could occur with the use of galcanezumab for the preventive or prophylactic treatment of migraine or cluster headache in routine clinical settings. Additionally, patients older than 65 years of age, as well as patients with recent acute cardiovascular events and/or serious cardiovascular risk were not included in clinical trials. The use of galcanezumab in these populations may occur in real-world clinical practice. Given the short follow-up in the trials, the implications of long-term inhibition of CGRP remain unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in a larger patient population requires further characterisation.

Administrative claims data contain information on millions of patients, including patients with migraine or cluster headache, and reflect routine clinical practice with diagnoses and procedures, outpatient prescription drug use, outpatient laboratory test result data, as well as health care utilisation. These data include patients who may not be referred to or choose to participate in clinical trials and can be readily used to investigate potential safety signals. Limitations, particularly related to uncertain diagnostic validity for the outcomes and lack of detailed clinical information, can be addressed through linkage to medical records and/or the National Death Index (NDI). To fill the knowledge gap of the trials, this protocol outlines an observational study using claims data to evaluate the long-term safety of galcanezumab in routine practice in the US.

8. Research Question and Objectives

This study aims to evaluate the utilisation and long-term safety of galcanezumab in the US routine clinical practice. The long-term safety profile will be characterised over a period of up to five years. The safety outcomes of interest are serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding non-melanoma skin cancers (NMSC).

The primary objective of this study are:

1) To describe the utilisation of galcanezumab overall, in migraine and cluster headache patients, and in special populations of interest including patients 65 years of age or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk.
2) To estimate incidence rates of the safety outcomes of interest among galcanezumab-exposed patients overall, galcanezumab-exposed patients with migraine or cluster headache, and in special populations of galcanezumab exposed patients including patients 65 years of age or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events only).

The secondary objectives of this study are:

1) To provide context for incidence rates of the safety outcomes of interest among the galcanezumab-exposed patients with migraine by estimating the corresponding incidence rates among migraine patients exposed to other migraine prophylactic medications.
2) If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort, to conduct comparative analyses for serious cardiovascular events, and malignancies excluding non-melanoma skin cancers (NMSC) using migraine patients initiating another migraine prophylactic medication as the control. No formal comparative analyses are planned for serious hypersensitivity reactions due to uncertainty in ability to capture hypersensitivity outcomes in secondary data and lack of an appropriate comparator group. Incidence rates for serious hypersensitivity reactions in the galcanezumab-exposed migraine cohort will be determined and rates in the comparator drug exposed migraine cohort will be provided for context. Also, given the low prevalence of cluster headache, comparative analyses within the cluster headache cohort are not expected to be feasible.

9. Research Methods

9.1. Study Design

This secondary data based cohort study will use data from US commercial administrative claims (i.e., the HealthCore Integrated Research Database [HIRD]) and will include two phases:

Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drug

- Monitor the number of patients exposed to galcanezumab overall and in patients with migraine, cluster headache, or neither, as well as the duration of galcanezumab use and the number of safety outcomes of interest from these cohorts. Uptake monitoring will occur annually and is expected to last up to five years. This phase will facilitate sample size projections and the decision on when to initiate comparative analyses if feasible.
- In the interim report, describe patient characteristics including demographics, comorbidities, concomitant medication use, and health care utilisation among galcanezumab-exposed cohorts identified during uptake monitoring, and in comparator drug-exposed migraine patients. Among each of the cohorts, describe patient characteristics in special populations of interest including patients 65 years or older and patients with serious cardiovascular risk defined by recent acute cardiovascular events.
- In the interim report, estimate incidence rates for serious cardiovascular events, serious hypersensitivity reactions and malignancies (excluding NMSC) in these cohorts and sub-cohorts. Incidence rates will also be stratified by duration of the exposure. For serious cardiovascular events, the incidence rates will be presented for a composite outcome and individual outcomes and will be stratified by serious cardiovascular risk defined by recent acute cardiovascular events. The incidence of malignancies will be presented overall and by organ site.

Phase 2: Comparative Analyses

- If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort, we will conduct comparative analyses among migraine patients for safety outcomes, comparing new users of galcanezumab with propensity score-matched patients treated with other prophylactic migraine medications.
- For serious cardiovascular events, we will use both a new user design (20) and a prevalent new user design (21) with topiramate as the control.
- For serious hypersensitivity reactions, no formal comparative analyses are planned due uncertainty around the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group since non CGRP prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. Incidence rates for serious hypersensitivity reactions in the galcanezumab-exposed migraine cohort will be determined and corresponding rates in a comparator drug exposed migraine cohort will be provided for context.

- For malignancies excluding NMSC, we will use a new user design (20) with a composite comparator group of prophylactic migraine medications other than CGRPs including galcanezumab.

The study will seek to validate selected safety outcomes using a sample of medical records. Among patients who disenrol from the health plan during the study period, deaths from safety outcomes (e.g., ischaemic heart disease, ischaemic cerebrovascular disease, or serious hypersensitivity events) that do not result in health care utilisation will be ascertained and supplemented by NDI linkage.

9.2. Setting

The study will be conducted using the HIRD. The HIRD is a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from approximately 48 million private commercially insured lives across the US. The uptake monitoring and follow-up for safety outcomes will be restricted to the period after galcanezumab approval in the US, from September 2018 until the most recent available data. Claims data will be utilised as the main source for exposure status, safety outcomes and covariates. Medical records will be sought for outcome adjudication and NDI will be linked for deaths due to serious cardiovascular events or serious hypersensitivity reactions that occur outside of the health care system.

9.2.1. Study Population

We will form base cohorts of patients who receive galcanezumab or the comparator medications. Additional exclusions will be applied depending on safety outcomes and study designs for risk estimates and comparative analyses (if feasible).

9.2.1.1. Base Galcanezumab Cohorts

To form the **Galcanezumab Cohort**, we will identify new users of galcanezumab meeting all of the following inclusion criteria and none of the exclusion criteria (Figure 1):

Inclusion criteria:

- At least one pharmacy dispensing or a procedure of injection of galcanezumab on or after 28 September 2018, the day after galcanezumab was approved by FDA.
- Continuous medical and pharmacy health plan coverage (i.e., gaps no longer than 30 days) for at least 183 days on or before the dispesing date. This allows for sufficient look-back time to ascertain information on baseline covariates, prior index treatment, and prevalent safety outcomes. The potential index date is defined as the date of the first dispensing or injection of galcanezumab during the intake period.

Exclusion criteria:

- A dispensing or a procedure of injection of a non-galcanezumab CGRP inhibitor on or before the potential index date. For individuals previously treated with medications that share a class with galcanezumab, the decision to initiate galcanezumab could depend on previous experience with a similar drug. If there were a negative effect of CGRP

inhibitors on the safety outcomes, galcanezumab-exposed patients with prior other CGRP inhibitors may be less susceptible to the safety outcomes, and therefore bias study results in favour of galcanezumab.

From the **Galcanezumab Cohort**, three additional cohorts meeting all the following inclusion criteria are created according to potential indications. They are depicted in Figure 1, and described further below.

- **Galcanezumab Migraine Cohort**:
  - No diagnosis of cluster headache on or before the index date.
  - At least one diagnosis of migraine or at least one dispensing/injection of triptans (i.e, a proxy for migraine diagnosis if not available) on or before the potential index date.
- **Galcanezumab Cluster Headache Cohort**:
  - A diagnosis of cluster headache on or before the potential index date.
- **Galcanezumab Cohort with Unknown Indications:**
  - No diagnosis of cluster headache or migraine and no dispensing or injection of triptans on or before the index date.

9.2.1.2. Base Comparator Drug Migraine Cohort

To form the **Comparator Drug Migraine Cohort**, we will identify patients meeting all the following inclusion criteria and none of the exclusion criteria (Figure 1). Comparator drugs include a range of medications that have shown efficacious or probably effective for migraine prophylaxis (American Academy of Neurology (AAN)/American Heart Association (AHA) 2012/2015, Level A and B evidence; Institute for Clinical Systems Improvement (ICSI) 2013, high quality evidence): antiepileptics (divalproex sodium, sodium valproate, topiramate, and gabapentin), beta-blockers (metoprolol, propranolol, oral timolol, nadolol, atenolol, and nebivolol), calcium channel blocker (verapamil), and antidepressants (amitriptyline and venlafaxine). The list of comparator drugs is subject to changes with modifications to clinical guidelines. For each safety outcome, different comparator drug(s) will be selected.

Inclusion criteria:

- At least one pharmacy dispensing for a comparator drug during the intake period.
- Continuous medical and pharmacy health plan coverage (i.e., gaps no longer than 30 days) for at least 183 days on or before the dispensing date.
- At least one migraine diagnosis or a dispensing/injection of triptans on or before the potential index date (See Section 9.3).

Exclusion criteria:

- A diagnosis of cluster headache on or before the potential index date.
- A dispensing/injection of CGRP inhibitors including galcanezumab on or before the potential index date.

9.2.1.3. Special Populations of Interest

Special populations of interest will be defined within the base cohorts and include the following:

- Patients who have a recent acute cardiovascular event (i.e., myocardial infarction [MI], transient ischaemic attack [TIA], ischaemic heart disease, angina, or stroke) or undergo coronary revascularisation (i.e., coronary artery bypass graft surgery [CABG] or percutaneous coronary intervention [PCI]) and/or serious cardiovascular risk within 183 days prior to the index date.
    - Patients who have serious cardiovascular risk within 183 days prior to the index date are operationally defined as patients who have a recent acute cardiovascular event defined above.
- Patients who are aged 65 years of age or older on the index date.

9.2.1.4. Outcome- and Study Design-Specific Inclusions/Exclusions to Migraine Cohorts

For comparative analyses, if a sufficient number of serious cardiovascular outcomes accrue in the Galcanezumab Migraine Cohort, additional inclusion and exclusion criteria listed below will be applied to the base **Galcanezumab Migraine Cohort** and base **Comparator Drug Migraine cohort** based on safety outcomes and study designs.

Serious cardiovascular events

- New user design with topiramate as the control

  Topiramate is chosen as the comparator drug because it is indicated for migraine prophylaxis, limited evidence exists for an association with cardiovascular diseases, and it is frequently used among migraine patients (approximately 15%) in the HIRD in 2018. For each new galcanezumab exposure, we will identify a new topiramate exposure with the same number of prior dispensing of other migraine prophylactic medication(s).

  Inclusion criteria:

    - Age 18 years or older on the potential index date.

  Exclusion criteria:

    - A dispensing of topiramate on or before the potential index date. This exclusion is to account for prevalent topiramate users and the related healthy users effect, whereby patients experiencing adverse effects discontinue and switch therapy, while patients doing well continue therapy. Patients who stay on topiramate may be less susceptible to the safety outcome, and therefore potentially bias against galcanezumab.
    - A diagnosis of epilepsy on or before the potential index date. This exclusion is to increase comparability of indications between comparison treatments and to reduce indication bias as epilepsy has been reported to be associated with an increased risk of cardiovascular diseases (23).

- Prevalent new user design with topiramate as the control

  Topiramate is chosen as the comparator drug for the same reason as the new user design above. Prevalent new user design is proposed as a complement to the new user design in order to preserve galcanezumab exposures because approximately 20% of galcanezumab users have used topiramate based on our preliminary analyses. Ppotential biases if assumptions are violated are discussed in Section 9.10.

  For every new user of galcanezumab from the base Galcanezumab Migraine Cohort, we will identify a patient from the base Comparator Drug Migraine Cohort who has the same number of prior dispensings of the comparator drug to form dispensing-based exposure sets (Figure 2). For example, for topiramate initiators who subsequently add or switch to galcanezumab as a second line treatment, we will identify a matched reference patient with a defined time interval who is also a topiramate initiator but remains on topiramate from the base cohort.

  Inclusion criteria:

  - Age 18 years or older on the potential index date.

Serious hypersensitivity reactions

Inclusion criteria:

- Age 18 years or older on the potential index date.

Malignancies excluding NMSC

- New user design with a composite comparator group as the control

  The composite comparator group will consist of prophylactic medications other than CGRPs recommended by clinical guidelines. If there is consistent evidence supporting an association between the prophylactic medication and the top five most frequently diagnosed cancers in the migraine patients, the prophylactic medication will be ineligible to be included in the composite comparator group.

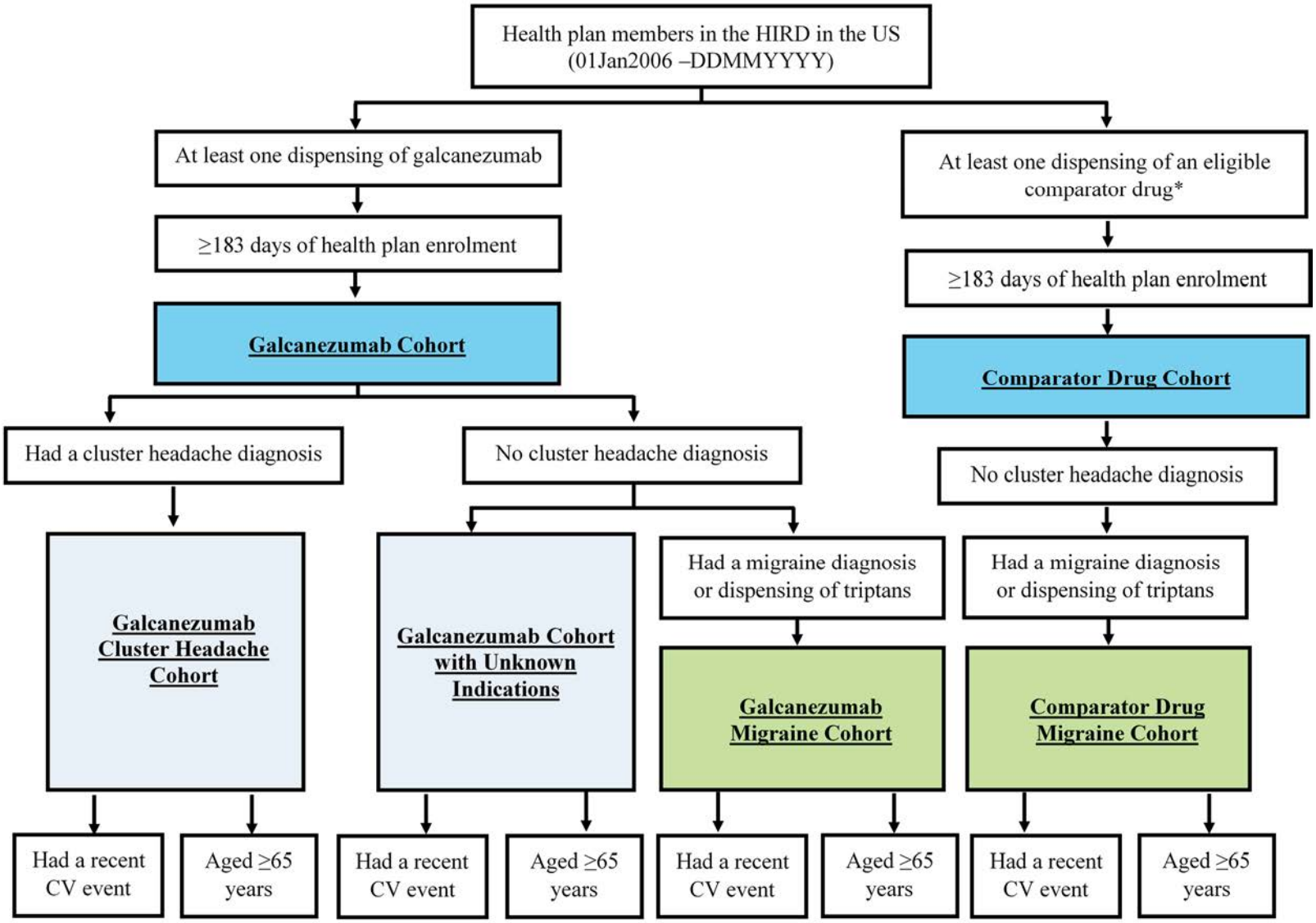
  Inclusion criteria:

  - Age 18 years or older on the potential index date.

  Exclusion criteria:

  - For **Comparator Drug Migraine Cohort** only, patients with a potential indication other than migraine on or before the potential index date. For example, patients with the treatment episode of topiramate and a prior diagnosis of epilepsy will be excluded.
  - Patients who have a diagnosis of any invasive cancer other than NMSC prior to the potential index date.

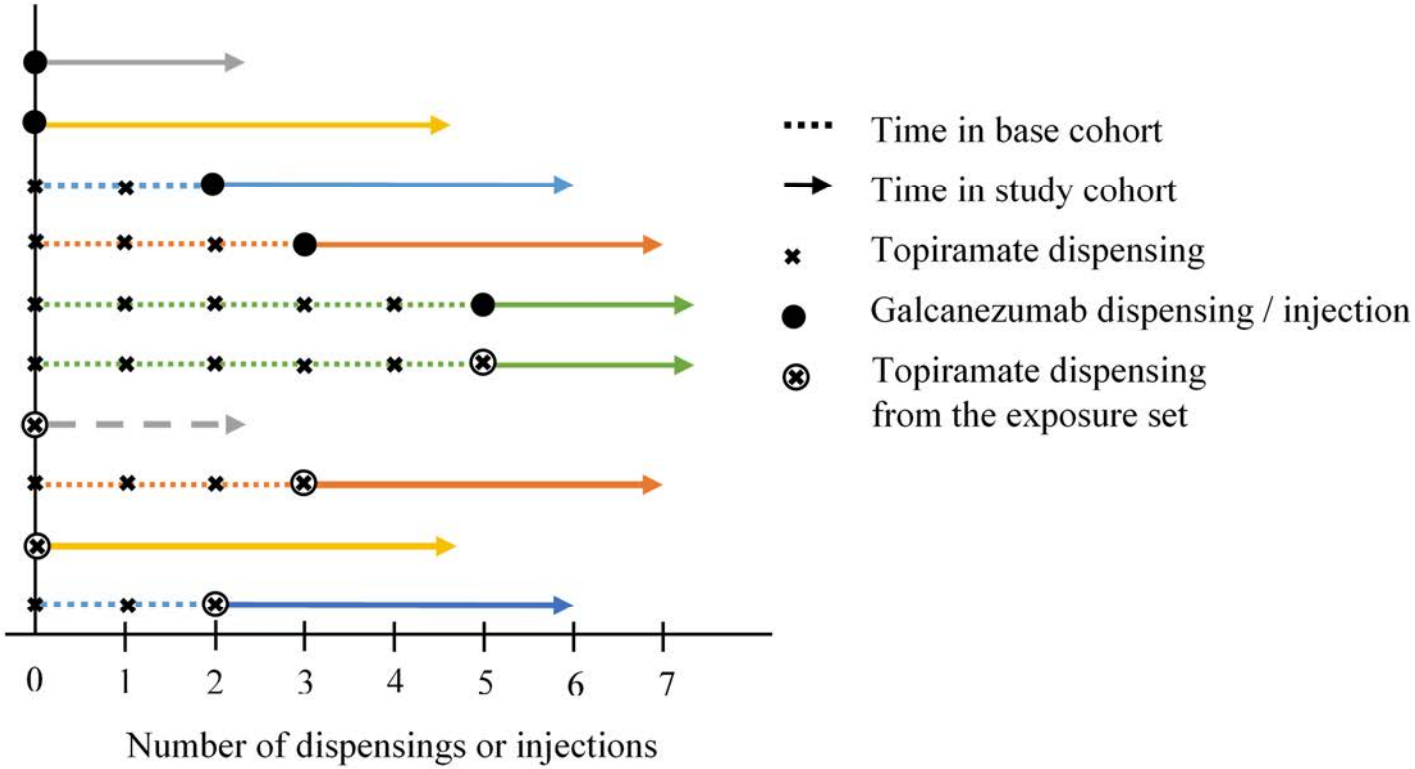
Figure 1. Flow diagram showing the composition of the base cohorts.



* Comparator drugs under consideration include a range of medications that have shown efficacious or probably effective for migraine prophylaxis other than CGRP inhibitors.

CV = Cardiovascular, HIRD = HealthCore Integrated Research Database, US = United States

Figure 2. Schematic illustration of the prevalent new user design*



* Initiators of topiramate who add or switch to galcanezumab are matched to initiators of topiramate who remain on topiramate on the number of topiramate dispensings before the first use of galcanezumab with the arrows indicating the index date and the follow-up period for safety outcomes.

9.3. Study Period

Galcanezumab was approved by the US FDA on 27 September 2018. Therefore, the planned intake period of the comparison treatments will start on 28 September 2018. The uptake monitoring will start in 2020 and will last for five years for Phase 1. We anticipate accruing a sufficient number of serious cardiovascular events in the Galcanezumab Migraine Cohort by 2024 to execute comparative analyses. The baseline period captures information collected for a patient on or before the index date with a minimum duration of 183 days and can date back to the earliest available data (01 January 2006 in the HIRD).

9.3.1. At-risk Period for Acute Outcomes

Acute outcomes include serious cardiovascular events and serious hypersensitivity reactions. We assume that any potential increased risk of acute outcomes related to medication use could occur at the beginning of the treatment, be maintained for the duration of treatment, and decrease gradually after treatment is stopped. The time window at risk for each index drug will be characterised as the index treatment episode.

Serious cardiovascular events

- New user design with topiramate as the control

The index date is defined as the first dispensing/injection of galcanezumab or the first dispensing of topiramate. Each patient will enter the cohort once, and only the first eligible index treatment episode will be used to capture new use. The analyses unit will be patient.

- Prevalent new user design with topiramate as the control

For the galcanezumab cohort, the index date is defined as the first dispensing/injection of galcanezumab or the date when topiramate users add or switch to galcanezumab. For the topiramate cohort, the index date is defined as the corresponding dispensing date of topiramate in the selected dispensing-based exposure sets (Figure 2). Comparator patients enter the multiple exposure sets and therefore could have more than one index date. The analysis unit will be the treatment episode. Follow-up of the index treatment episode for serious cardiovascular events will begin on the day after the index date, and continue until the earliest date of the following events:

- Occurrence of a serious cardiovascular event.
- Initiation of a non-galcanezumab CGRP inhibitor.
- End of the continuous exposure episode (see Section 9.4.1).
- The date of treatment switches: Patients have a dispensing of topiramate within the continuous exposure episode of galcanezumab, or patient have a dispensing or procedure of galcanezumab within the continuous exposure episode of topiramate.
- Health plan disenrolment.
- Death.
- End of the study period.

Serious hypersensitivity reactions

- New user, design without formal comparative analyses. Incidence rates in the topiramate cohort will be determined to provide context.

The index date is defined as the first dispensing/injection of galcanezumab or the first dispensing of other migraine prophylactic medications. The analyses unit will be patient.

Follow-up of the index treatment episode for serious hypersensitivity reactions will begin on the day after the index date, and continue until the earliest date of the following events:

- Occurrence of a serious hypersensitivity reaction.
- Initiation of a non-galcanezumab CGRP inhibitor.
- Health plan disenrolment.
- Death.
- End of the study period.

9.3.2. At-risk Period for Cancer Outcomes

Because galcanezumab is covered by commercial insurance as a third-line treatment for migraine prophylaxis in the US, patients receiving galcanezumab may have been exposed to other prophylactic migraine treatments. To preserve the advantages of the new user design, treatment histories will be matched between galcanezumab exposures and comparator drug exposures by identifying lines of therapy (Figure 3). Specifically, patients will enter the follow-up at the first treatment episode of galcanezumab or one eligible comparator drug corresponding to the first-line therapy. A new index date will be assigned among patients who have received a first-line comparator drug, if the patients switch to galcanezumab or another eligible comparator drug from the first-line comparator drug, corresponding to the second-line therapy. A third index date will be assigned among patients who have received first- and second-line comparator drugs, if the patients switch to galcanezumab or a third eligible comparator drug from the first- and second-line comparator drugs, corresponding to the third-line therapy. This identification of new switchers in later-line therapy will continue until no galcanezumab exposures are available. Therefore, comparisons between galcanezumab and comparator drugs are always within the same line of therapy with comparable treatment history.

The follow-up of patients will start from the index date of the first-line treatment and the exposure group will be updated when a new treatment on the drug substance level starts with an exception. If an eligible comparator drug initiated after the index treatment episode of galcanezumab, the follow-up will be censored at the dispensing date of the comparator drug. Person-time and events during follow-up will be attributed to three mutually exclusive exposure groups: galcanezumab only, comparator drug only, and the two combined. The combined exposure group is defined in the following three scenarios:

(1) If an eligible comparator drug has an earlier start date of the continuous treatment episode than galcanezumab, and its continuous treatment episode overlaps the continuous treatment episode of galcanezumab, the overlapping segment will start the next treatment line and the corresponding person-time and event will be attributed to the combined exposure group. The non-overlapping segment will be attributed to the comparator drug only group.
(2) If an eligible comparator drug has a later end date of the continuous treatment episode than galcanezumab, and its continuous treatment episode overlaps the continuous treatment episode of galcanezumab, the overlapping segment will remain in the same treatment line as galcanezumab and the corresponding person-time and event will be attributed to the combined exposure group. Follow-up will be censored at the end date of the continuous exposure episode of galcanezumab.
(3) If the continuous treatment episode of an eligible comparator drug is completely covered by the continuous treatment episode of galcanezumab, the overlapping segment will remain in the same treatment line as galcanezumab and the corresponding person-time and event will be attributed to the combined exposure group. The non-overlapping segment will be attributed to the galcanezumab only group.

Taken together, follow-up will end at the earliest date of the following events:

- Diagnosis of any cancer, excluding NMSC
- A dispensing of an eligible comparator drug with full or partial days supply occurring after the end date of the continuous treatment episode of galcanezumab.
    - The censoring date will be the date of the dispensing if no overlapping continuous treatment episode.
    - The censoring date will be the date of the end date of the continuous treatment episode of galcanezumab if overlapping continuous treatment episode.
- Death
- Health plan disenrolment
- End of study

Although the proposed method is un-biased, the "current" exposure approach limits the exposure time of galcanezumab. Given that the majority of solid tumours have a relatively long latency period after exposure to pharmacotherapy, we will attribute person-time and events following a galcanezumab initiation to galcanezumab. In other words, once patients initiate galcanezumab, they will be considered "ever-exposed" to galcanezumab. Evaluation of the incidence of cancer in relation to the cumulative exposure to galcanezumab is of greater interest than the "ever" exposure analysis. Therefore, in addition to the "as initiated" exposure classification, mutually exclusive categories of cumulative exposure to galcanezumab will be created for the galcanezumab cohort. Cumulative exposure will be calculated as the cumulative dose of galcanezumab that an individual receives during follow-up. Follow-up will end at the earliest date of the following events:

- Diagnosis of any cancer, excluding NMSC
- A dispensing of an eligible comparator drug with full or partial days supply occurring after the end date of the continuous treatment episode of galcanezumab.
- Death
- Health plan disenrolment
- End of study

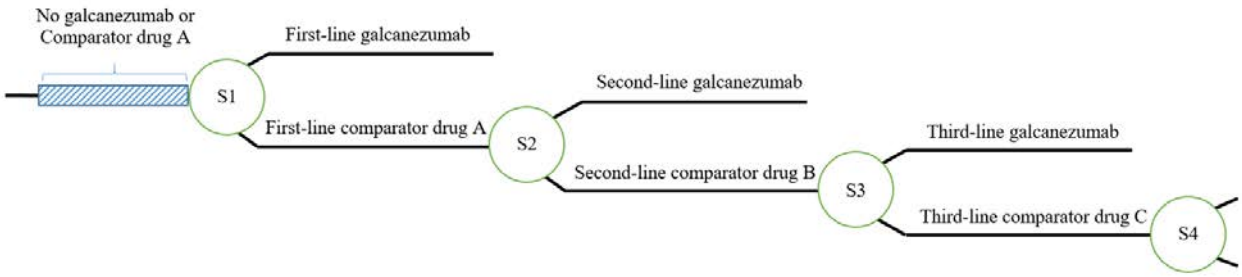
The advantage of the "ever" exposure analysis is that we could have longer galcanezumab exposure. However, this approach could also bias against galcanezumab as we will attribute events that could have been caused by the earlier exposure to comparator drugs to galcanezumab, if the long latency assumption holds. Meanwhile, this approach could also bias in favour of galcanezumab if the long latency assumption does not hold, whereby we attribute the later low-risk person-time to galcanezumab group.

Because the empirical latency period (i.e., induction period plus latency period) of cancer after exposure to migraine prophylactic medications are unknown, we will implement several sensitivity analyses in an attempt to account for varying induction and latency period of malignancies corresponding to cancer initiation and promotion:

1) To evaluate whether the hazard function is constant, we will visually inspect the cumulative incidence curve in relation to time since exposure.

2) To account for a meaningful biological effect on cancer initiation (24) and to screen out pre-existing latent cancers, we will require a 183-day lag period between the first fill and the beginning of follow-up, limiting the analysis to patients who are still on the index treatment after 183 days of initiation.

Figure 3. Schematic illustration of new user design with a composite comparator as the control.



9.4. Variables

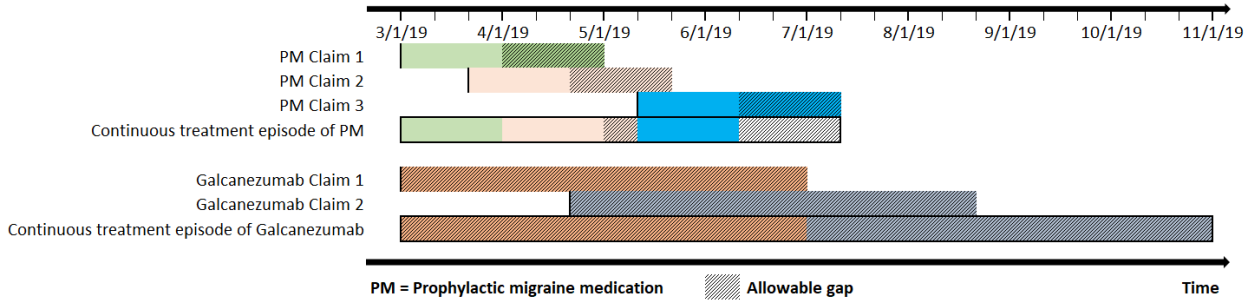
9.4.1. Exposures

Exposure to galcanezumab and the eligible comparator medication(s) will be assessed using the pharmacy and medical claims in the HIRD. New users (newly dispensed) are those patients without any recorded dispensing for the index treatment based on all available data prior to the index date with a minimum duration of 183 days.

Because galcanezumab is administered as monthly injections and its elimination half-life is approximately 27 days (25), we will consider patients to be exposed to galcanezumab for approximately 120 days after the date of administration. Therefore, patients are allowed to have gaps of up to 120 days between dispensing dates in the calculation of continuous treatment episode to galcanezumab. If there is more than one dispensing of galcanezumab separated by gaps of up to 120 days, the start date of subsequent dispensing will move forward to the day after the end date of the prior exposure period and all exposure periods will be added a single continuous treatment episode (i.e., stockpiling) (Figure 4).

The majority of other migraine prophylactic medications (e.g., Topiramate) are taken orally. Continuous exposure episodes for each eligible comparator medication will be created using dispensing date, plus the number of days supplied, plus 30 days to account for possible non-adherence and non-concordance of dispensing date and medication use (10). If there is more than one consecutive dispensing of the index comparator drug separately by gaps of 30 days or fewer, days of supply will be added in a stockpiling fashion to define a continuous treatment episode.

Figure 4. Schematic illustration of continuous treatment episode using stockpiling



9.4.2. Outcomes

The occurrence of the safety outcomes of interest listed below will be identified in the HIRD using claims-based coding algorithms. Incident events are of interest, so patients with a history of serious cardiovascular events anytime prior to the index date or with a history of invasive cancer diagnosis (excluding NMSC) at any time prior to the index date will be respectively excluded from the computation of incidence for that specific event. The coding algorithms (e.g., clinical settings, and combination of diagnosis, procedure, and medication codes) will be defined through literature review and expert consultation and will be detailed in a separate Statistical Analysis Plan (SAP). For the final report, a random sample of medical records will be sought for selected claims-identified outcomes to compute positive predicative value-adjusted incidence rates. Two clinicians will adjudicate case status according to clinical criteria. When there is disagreement, final case status will be decided by a committee with a third reviewer. Details of the clinical review and adjudication process for safety outcomes will be described in SAP. To ascertain acute deaths from ischaemic heart disease, ischaemic cerebrovascular disease or hypersensitivity occurring outside of health care settings, we will link patients who are disenroled from the health plan during follow-up and do not have any additional health plan enrolment segments between initial disenrolment and the end of the study period to the NDI.
Serious cardiovascular outcomes:

- Serious cardiovascular events will comprise the following events and will be reported as a composite outcome and as separate outcomes if the sample size of the event surpasses 10.
  - MI, TIA, ischaemic stroke, ischaemic heart disease, and angina
  - Coronary revascularisation: CABG or PCI
  - Deaths from ischaemic heart disease or ischaemic cerebrovascular disease

- Serious hypersensitivity reactions:
  - Serious hypersensitivity reactions will be reported as a composite outcome, and the following events are under consideration:
    - Anaphylaxis
    - Angioedema
    - Acute asthma or acute bronchospasm
    - Acute upper airway obstruction

        - Epinephrine administration
        - Deaths from hypersensitivity reactions
- Malignancies excluding NMSC:
    - Malignancies will be reported as a composite outcome overall and by organ system defined by the International Classification of Diseases, Tenth Revision (ICD-10) hierarchy (e.g., bone, breast, urinary tract, etc.).

9.4.3. Covariates

Covariates including patient demographics, comorbidities, medication use, and health care utilisation will be assessed in descriptive analyses and will be considered potential confounders to be included in the propensity score for comparative analyses (if feasible) (see Section 9.8). All available data prior to the start of the treatment will be used to assess baseline demographics and clinical covariates. The coding algorithms using diagnosis, procedure or drug codes for a subset of these covariates will be detailed in a separate SAP.

- Demographics:
    - Age (years) on the index date
    - Sex
    - US region of residence
    - Duration of continuous health plan enrolment on or before the index date
    - Calendar year of index date
    - Calendar month of index date
- Comorbidities:
    - Hypertension
    - Hyperlipidaemia
    - Type 1 diabetes
    - Type 2 diabetes
    - Overweight and obesity 183 days on or before index date as available in claims
    - Smoking as available in claims
    - History of cardiovascular diseases:
        - MI
        - TIA
        - Ischaemic stroke
        - Ischaemic heart disease
        - Angina
        - Heart failure
        - Cardiac arrhythmia
        - Haemorrhagic stroke
        - Peripheral vascular disease
        - Atherosclerosis
    - History of coronary revascularisation: CABG or PCI
    - History of malignancy excluding NMSC
    - History of serious hypersensitivity reactions

  - Epilepsy
  - Bipolar disorder
  - Alcohol dependence
  - Mood disorders
  - Post-Traumatic Stress Disorder (PTSD)
  - Major depressive disorders
  - Anxiety disorders
  - Migraine type (e.g., with vs. without aura) and severity (with vs. without intractable pain)
  - Cluster headache type and severity (with vs. without intractable pain)
  - Renal failure
  - Liver disease
  - 25 most frequently occurring diagnoses recorded
- Medication use:
  - Prophylactic migraine drugs
  - Prophylactic cluster headache drugs
  - Acute migraine drugs (e.g. triptans)
  - Analgesics (e.g. opioids, non-steroidal anti-inflammatory drugs [NSAIDs])
  - Acute cluster headache drugs
  - Antidepressants
  - Anti-epileptic medications
  - Antipsychotics
  - Anxiolytics/sedatives/hypnotics
  - Cholesterol-lowering medications
  - Antihypertensive medications
  - Antiplatelet agents
  - Anticoagulants
  - Antihistamines
  - Oral contraceptives for women
  - Postmenopausal hormone therapy for women
  - 25 most frequently dispensed medication classes
- Health care utilisation 183 days prior to and including index date
  - Count of office visits, emergency department visits, and hospitalisations
  - Specialty of index drug prescriber as available
- Galcanezumab and comparator drug treatment characterisation
  - Duration of exposure
  - Treatment lines (i.e., observed treatment sequences in claims)
  - Distribution of prior other migraine prophylactic treatments

9.5. Data Sources

This study will be conducted in the HIRD. The HIRD is a broad, clinically rich, and geographically diverse spectrum of longitudinal medical and pharmacy claims data from health plan members across the US. Member enrolment, medical care (professional and facility claims),

outpatient prescription drug use, outpatient laboratory test result data, and health care utilisation may be tracked for health plan members in the database dating back to January 2006. The HealthCore Integrated Research Environment (HIRE) has the ability to link the claims data in the HIRD to complementary data sources, such as inpatient and outpatient medical records as well as national vital statistics records.

In the HIRD, diagnoses and procedures will be identified using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision (ICD-10), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) codes, for both outpatient visits and inpatient stays. Pharmacy claims are captured by National Drug Codes (NDCs), which can then be translated to broader categories of Generic Product Identifier (GPI) codes. Information on physician specialty is also retained in the HIRD.

Medical records of coding algorithm identified safety outcomes will be retrieved via the linkage to the HIRD and available medical records will be adjudicated by clinical reviewers to minimise outcome misclassification.

Deaths occurring out of health care system and the underlying cause of death will be identified through a linkage of the HIRD to the US NDI using patient characteristics such as full name, gender, date of birth, state of residence and (when available) social security number. NDI is a centralised database of death information dating back to 1979 and is maintained by the US National Center for Health Statistics (NCHS). NDI data lags real-time by an average of 18-24 months and is updated once annually. Therefore, the capture of fatal events will lag behind that for nonfatal events.

9.6. Study Size

The available number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in the US. The Phase 1 of this study will monitor the uptake of galcanezumab in the study population against the target study size estimated for the primary safety outcome, the composite serious cardiovascular events. Approximately 71 serious cardiovascular events from 5,099 patients newly initiating galcanezumab need to be accrued to have an 80% power for a relative risk of 2.0 (galcanezumab versus comparators) at a significance level of 0.05 in a two-sided log-rank test (26), with a background rate of approximately 7.0 per 1,000 person-years among migraine patients (27, 28), a comparator-to-galcanezumab ratio of 4:1, an average of approximately four months of each index treatment episode (i.e., follow-up on treatment).

For malignancies excluding NMSC, we assume an average follow-up of three years in the HIRD. The minimum detectable relative risk with 80% power at a significance level of 0.05 will approximately be 1.40, assuming 4.36 per 1,000 person-year background incidence of all cancer types (30), and a comparator-to-galcanezumab ratio of 4:1 among 5,099 galcanezumab-exposed patients, using a two-sided log-rank test (26).

This study also includes other individual outcomes that comprise specific composite outcomes. Depending on the incidence or prevalence of those events, the minimum detectable relative risks vary. Given a large number of outcomes, some outcomes may be significantly different between

new users of galcanezumab and the eligible comparator drug by chance alone. Multiple comparisons will not be addressed in these analyses (31). However, the interpretation of the results will note this study as hypothesis generating with acknowledgment of the number of outcomes and lack of multiple comparison adjustment.

9.7. Data Management

All data management and analyses will be conducted by HealthCore in accordance with their standard operating procedures (SOPs) and guidelines. The study records including study database, analytic files, and statistical programming will be documented, stored electronically, and archived on a secure server, for a minimum of 15 years after completion or discontinuation of the study, or as required by applicable local regulations. The investigator must obtain Lilly's written permission before disposing of any records, even if retention requirements have been met. De-identified and aggregated results will be reported to Lilly. All counts ≤10 will reported as "≤10" according to HealthCore/Anthem guidelines.

9.8. Data Analysis

9.8.1. Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drugs

For uptake monitoring, the number and percentage of patients exposed to galcanezumab overall and in patients with migraine, cluster headache, or neither, respectively, as well as the duration of galcanezumab exposure and the number of safety outcomes from these cohorts defined in Section 9.2.1.1 will be presented.

For the interim report, we will describe distributions of covariates including demographics, comorbidity, medications, and health care utilisation (See Section 9.4.3) overall, and separately stratified by cohorts as defined in Section 9.2.1.1 and Section 9.2.1.2, and special population as defined in Section 9.2.1.3. The number of observations, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables, and the number and percent of patients in each category will be presented for categorical variables.

Unadjusted incidence rates of the safety outcomes will be computed by dividing the total number of the events by the total at-risk person-time accumulated for all cohort members during the follow-up (See Section 9.3). Confidence intervals for the incidence estimates will be computed using methods based on the Poisson distribution. Incidence rates will be estimated only among individuals who do not have a diagnosis of the outcome of interest recorded at baseline. Incidence rates will be presented overall, and separately stratified by cohort/sub-cohort defined by diagnosis/treatment of migraine or cluster headache (See Section 9.2.1.1 and Section 9.2.1.2), patients with a recent (≤183 days) history of acute cardiovascular events, and duration of galcanezumab use. The incidence of serious cardiovascular events will be presented as a composite outcome and individual outcomes. The incidence of malignancies excluding NMSC will be presented overall and by organ site. Incidence rates will be adjusted based on predictive positive values from outcome adjudication and additional safety outcomes via NDI linkage to

identify additional fatal events missed by the administrative claims where healthcare was not accessed.

9.8.2. Phase 2: Comparative Analyses

In Phase 2, if a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort, we will estimate hazard ratios and 95% confidence intervals for safety outcomes among patients with migraine comparing propensity score-matched new users of galcanezumab with new users of the other prophylactic migraine treatment in Cox proportional hazards regression models for serious cardiovascular events and malignancies excluding NMSC. Galcanezumab exposures will be matched on treatment lines with the comparator drug(s) exposures to minimise lag-time bias.

To control for measured confounding factors, we will construct propensity scores from baseline covariates. The propensity score is the predicted probability of being assigned to galcanezumab conditional on a set of observed covariates and will be estimated in logistic regression models. The general rule of covariates selection is to select variables that both related to the exposure and the outcome for confounding adjustment, and variables that are related to the outcome but not to the exposure to for precision improvement of the estimates without introducing bias (32). Covariates including demographics, comorbidities, medications, and health care utilisation (see Section 9.4.3) will be considered for propensity score creation.

For composite serious cardiovascular events using new user design, propensity score will be generated for the first index treatment episode using patients initiating topiramate as the reference group in conditional logistic regression models. For composite serious cardiovascular events using prevalent new user design, time-conditional propensity scores will be generated using all the exposure sets in logistic regression models. For composite malignancies excluding NMSC, propensity score will be generated for each index treatment episode at imitation or switch in unconditional logistic regression models.

Distributions of covariates will be assessed within exposure groups before and after propensity score matching to assess the balance of baseline patient characteristics and potential residual confounding. Absolute standardised differences (33), the difference in means or proportions divided by the pooled standard deviation, will be computed for each covariate to check its distribution balance within exposure groups.

Covariates with an absolute standardised difference greater than 0.10 residual differences will be further controlled in the analysis by including the specific variables in the proportional hazards model. Hazard ratios will be adjusted based on results from outcome adjudication and NDI linkage.

For serious hypersensitivity reactions no formal comparative analyses will not be conducted due uncertainty in the ability to accurately identify serious hypersensitivity events in secondary data and lack of an appropriate comparison group; however, incidence rates for hypersensitivity reactions in a comparator cohort will be provided for context.The unadjusted incidence rates will be determined as described in Section 9.8.1.

9.9. Quality Control

The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

- Role-Based Control Checks: Each member of the team is responsible for performing thorough quality control checks on their work; also, the Principal Investigator and Research Project Manager are also accountable for the quality of all deliverables.
- Quality Check Points: Centralised "checkpoints" have been implemented during the data management cycle to help ensure accurate translation of programming requests.
- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project lifecycle.
- Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

HealthCore's research team documents study progress and scientific and quality review of all study activities and deliverables (e.g., protocol, data management, data analysis, reports, manuscripts, etc.) in an ADIN (Action, Decision, Issue, Notification) log and in a Quality Control (QC) Log. The ADIN Log provides documentation of study progress, action items, issues/issue resolution, and notifications, and is updated weekly during internal project team meetings. Also, the QC Log documents the quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed by HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore SOPs and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that Protocol criteria were met. If validation checks are not satisfied, then an examination of the problem will be performed on the dataset or datasets in question and the problem resolved.

9.10. Limitations of the Research Methods

- **Uncertainties common to new medications**

It is uncertain how many patients with migraine or cluster headache will use galcanezumab, as galcanezumab is a new medication for migraine prophylaxis, and only a small proportion of migraine patients require prevention treatments. The accrual galcanezumab-exposed patients will be monitored during Phase 1 of this study, and we anticipate to accrue a sufficient number of serious cardiovascular events in five years. However, if the target event size cannot be reached, comparative analyses will not be implemented. Without the comparative analyses, the primary

analyses are descriptive, rendering uncertainty to draw aetiologic attribution of galcanezumab exposure to the safety outcomes. While the study will explore for potential dose-response relationship using duration of galcanezumab exposure as proxy and the incidence rates of the safety outcomes in the galcanezumab exposed patients will be compared to crude incidence of safety outcomes among patients exposed to other prophylactic medication(s), interpretation of the crude estimates requires caution.

- **Indication bias**

The study might not be able to determine the precise indication for the use of other comparator migraine prophylactic medications. For example, some patients might not have received topiramate for migraine prophylaxis, as it is also indicated for the treatment of epilepsy which may be associated with the risk of MI and stroke (34). To reduce the potential for this indication bias, we will exclude patients who are diagnosed with other indications for the comparator migraine prophylactic medications on or before the index date.

- **Unmeasured confounding**

As is the case with all observational studies, the potential for residual confounding in this observational study cannot be ruled out. In addition, although propensity scores will be estimated based on measured covariates during the baseline period to ensure adequate balance of the baseline covariates, we are not able to fully capture important prognostic factors related to ischaemic heart diseases such as smoking (35), body mass index (36), and migraine severity (37) in claims data. Although using baseline patient characteristics as proxies for unmeasured variables may improve adjustment and there are some diagnosis codes for these conditions, residual confounding cannot be completely ruled out. To evaluate the extent of unmeasured confounding, we will use E-values (38) that are assumption-free and measure the magnitude of the association between the confounding factor and the exposure to explain away the observed association.

- **Measurement errors**

Claims data are collected administratively for billing purpose and are subject to inaccuracies. In the clinical setting, some diagnoses may be missed, different professional types may have different coding patterns, and not all coding may be accurate. To minimise misclassification of safety outcomes, we will obtain a random sample of medical records and link claims data to the NDI for adjudication of selected outcomes, increasing the validity of case status and adjusting risk estimates and hazard ratios in comparative analyses.

- **Selection bias due to prevalent users**

Prevalent new user design compares new users of galcanezumab including new switchers from the comparator drug with prevalent users of the comparator drug. The underlying assumption for valid result estimates is that switching is unrelated to the outcome. The violation of this assumption could result in selection bias, whereby patients who stay on the comparator drugs are less susceptible to have the safety events (“depletion of susceptibles”) or have better control of migraine or a less severe migraine, rendering a lower risk of serious cardiovascular events and

biasing against galcanezumab. To explore the differences between switchers and adherers, we will evaluate the distributions of the baseline characteristics, incidence rates of safety outcomes, and cumulative incidence curves between switchers and adherers. However, similarities do not necessarily mean there is no survival bias due to prevalent users because of unmeasured confounding. To a lesser extent of importance, covariates for drug users at the study entry are often plausibly affected by the drug itself, and adjustment for such covariates on the causal pathway may introduce collider bias (a type of selection bias). However, a simulation study (39) demonstrated that if a collider is an important confounder, controlling for confounding would take precedence over avoiding collider bias.

- **Informative censoring**

For acute outcomes, galcanezumab discontinuation or switching might be related to early cardiovascular or hypersensitivity symptoms or signs. This could have made discontinuation or switching a predictor for serious cardiovascular events or serious hypersensitivity reactions, leading to informative censoring or reverse causation. To minimise this potential bias, we will consider extending the exposure risk window by 30 and 90 days after drug discontinuation or switches, or carry the first exposure forward, similar to an intention-to-treat analysis, without considering either drug discontinuation or switching in sensitivity analyses.

- **Generalisation**

Because the HIRD contains only commercially-insured patients, there are limits to the generalisability of study findings to the broader population. For example, patients with low socioeconomic status, including those that are insured through US Medicaid programs, are not included. In so far as their patterns of care and disease incidence and prevalence may differ from that seen in our study population, results from this study may not hold true in that group.

9.11. Other Aspects

Not applicable.

10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

11. Management and Reporting of Adverse Events (AE) /Adverse Reactions (AR)

This is a non-interventional study based on secondary data use, and therefore no individual case safety report reporting is required. The protocol-defined AEs are specified in Section 9.4. All protocol-defined AEs collected will be summarised in the interim and final study report. No other AEs will be collected.

11.1. Product Complaints

When a condition related to the pre-filled syringe, pen, or autoinjector necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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12. Plans for Disseminating and Communicating Study Results

This study will produce interim and final reports that will be delivered to the European Union European Medicines Agency (EU EMA).

Results from Phase 2 may be disseminated via presentations at scientific conferences and/or publication in peer-reviewed journals.

13. References

1. Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018;17(11):954-76.
2. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Current pain and headache reports. 2012;16(1):86-92.
3. Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache. 2012;52(10):1456-70.
4. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.
5. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. The Lancet Neurology. 2017;16(1):76-87.
6. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ (Clinical research ed). 2009;339:b3914.
7. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. BMJ open. 2018;8(3):e020498-e.
8. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007;47(3):355-63.
9. Rizzoli P. Preventive pharmacotherapy in migraine. Headache. 2014;54(2):364-9.
10. Berger A, Bloudek LM, Varon SF, Oster G. Adherence with migraine prophylaxis in clinical practice. Pain practice : the official journal of World Institute of Pain. 2012;12(7):541-9.
11. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. Journal of managed care pharmacy : JMCP. 2014;20(1):22-33.
12. Hepp Z, Dodick DW, Varon SF, Chia J, Matthew N, Gillard P, et al. Persistence and switching patterns of oral migraine prophylactic medications among patients with chronic migraine: A retrospective claims analysis. Cephalalgia : an international journal of headache. 2017;37(5):470-85.
13. Ashkenazi A, Schwedt T. Cluster headache--acute and prophylactic therapy. Headache. 2011;51(2):272-86.
14. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia : an international journal of headache. 2018;38(1):1-211.
15. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia : an international journal of headache. 2008;28(6):614-8.
16. Manzoni GC, Taga A, Russo M, Torelli P. Age of onset of episodic and chronic cluster headache - a review of a large case series from a single headache centre. The journal of headache and pain. 2016;17:44-.

17. Durham PL. Inhibition of calcitonin gene-related peptide function: a promising strategy for treating migraine. Headache. 2008;48(8):1269-75.
18. Forderreuther S, Zhang Q, Stauffer VL, Aurora SK, Lainez MJA. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. The journal of headache and pain. 2018;19(1):121.
19. Martinez J, editor Study CGAL: A phase 3 placebo-controlled study of galcanezumab in patients with episodic cluster headache: Results from the 8-week double-blind treatment phase. 60th Annual Scientific Meeting American Headache Society; 2018; Marquis San Francisco, CA: Headache: The Journal of Head and Face Pain. 2018;58 (8):289-290.
20. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Current epidemiology reports. 2015;2(4):221-8.
21. Suissa S, Moodie EE, Dell'Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiology and drug safety. 2017;26(4):459-68.
22. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ (Clinical research ed). 2016;354:i4515.
23. Shmuely S, van der Lende M, Lamberts RJ, Sander JW, Thijs RD. The heart of epilepsy: Current views and future concepts. Seizure. 2017;44:176-83.
24. Pottegård A, Friis S, Stürmer T, Hallas J, Bahmanyar S. Considerations for Pharmacoepidemiological Studies of Drug–Cancer Associations. Basic & Clinical Pharmacology & Toxicology. 2018;122(5):451-9.
25. Emgality Prescribing Information [Internet]. 2018 Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761063s000lbl.pdf, accessed on 28 January 2019. .
26. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Statistics in medicine. 1982;1(2):121-9.
27. Adelborg K, Szepligeti SK, Holland-Bill L, Ehrenstein V, Horvath-Puho E, Henderson VW, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ (Clinical research ed). 2018;360:k96.
28. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. Jama. 2006;296(3):283-91.
29. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Current opinion in allergy and clinical immunology. 2005;5(4):309-16.
30. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2017 Sub (1973-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. [Internet].
31. Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology (Cambridge, Mass). 1990;1(1):43-6.
32. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol. 2006;163(12):1149-56.

33. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in medicine. 2009;28(25):3083-107.
34. Olesen JB, Abildstrom SZ, Erdal J, Gislason GH, Weeke P, Andersson C, et al. Effects of epilepsy and selected antiepileptic drugs on risk of myocardial infarction, stroke, and death in patients with or without previous stroke: a nationwide cohort study. Pharmacoepidemiology and drug safety. 2011;20(9):964-71.
35. Desai RJ, Solomon DH, Shadick N, Iannaccone C, Kim SC. Identification of smoking using Medicare data--a validation study of claims-based algorithms. Pharmacoepidemiology and drug safety. 2016;25(4):472-5.
36. Ammann EM, Kalsekar I, Yoo A, Johnston SS. Validation of body mass index (BMI)-related ICD-9-CM and ICD-10-CM administrative diagnosis codes recorded in US claims data. Pharmacoepidemiology and drug safety. 2018;27(10):1092-100.
37. Kurth T, Schürks M, Logroscino G, Buring JE. Migraine frequency and risk of cardiovascular disease in women. Neurology. 2009;73(8):581-8.
38. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-ValueIntroducing the E-Value. Annals of Internal Medicine. 2017;167(4):268-74.
39. Liu W, Brookhart MA, Schneeweiss S, Mi X, Setoguchi S. Implications of M bias in epidemiologic studies: a simulation study. Am J Epidemiol. 2012;176(10):938-48.

Annex 1. ENCePP Checklist for Study Protocols

Study title: A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients in the Course of Routine Clinical Care

EU PAS Register® number: EUPAS27597

Study reference number (if applicable): I5Q-MC-B001

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
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	☒	☐	☐	7

[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 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

The protocol discusses research questions and study objectives. A full discussion of statistical methods, including formal hypothesis testing as applicable, will be included in the Statistical Analysis Plan.

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 & 9.5
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	9.8
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))	☒	☐	☐	9.8
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period				
4.2.2 Age and sex	☒	☐	☐	9.3
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
	☒	☐	☐	9.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

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)	☒	☐	☐	9.4.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1.2 & 9.2.1.4

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?	☒	☐	☐	9.4.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.4.2
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)	☒	☐	☐	9.4.2
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)	☒	☐	☐	9.4.3

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)	☒	☐	☐	9.10
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.1.1, 9.2.2.2, & 9.10
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10

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)	☒	☐	☐	9.2.1.3 & 9.8

Comments:

Full details of these analyses will be included in the Statistical Analysis Plan.

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)	☒	☐	☐	9.4.1 & 9.5
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4.2 & 9.5

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4.3 & 9.5
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)	☒	☐	☐	9.5
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.5
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.5
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.5
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.5
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.5

Comments:

Specific coding algorithm and NDI linage will be described in the Statistical Analysis Plan.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.6

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	9.8.1
10.4 Are stratified analyses included?	☒	☐	☐	9.8.1
10.5 Does the plan describe methods for analytical control of confounding?	☒	☐	☐	9.8.2
10.6 Does the plan describe methods for analytical control of outcome misclassification?	☒	☐	☐	9.8.1
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.3.1.2 & 9.10

Comments:

Detailed description on missing data handling and discussion on potential biases will be included in the Statistical Analysis Plan.

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)	☒	☐	☐	9.7
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**

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?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
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).	☒	☐	☐	9.10
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)	☒	☐	☐	

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?	☐	☒	☐	

Comments:

Full details of data protection requirements will be described in a separate Statistical Analysis Plan.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**

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: _____

Date: / /

Signature: _____