PASS Information

Title	A Cohort Study to Assess Drug Utilisation and Long-Term Safety of Galcanezumab in US Patients in the Course of Routine Clinical Care
Study identifier	I5Q-MC-B001
Version identifier	Amendment(b)
Date of last version	23 July 2020
EU PAS Register No:	EUPAS27597
Active substance	Galcanezumab; ATC code: N02CX08 (N02CD02 as of year 2020)
Medicinal product(s):	Galcanezumab 120-mg solution and 100-mg solution
Product reference:	EU/1/18/1330
Procedure number:	EMEA/H/C/004648
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	This study aims to evaluate the utilisation and long-term safety of galcanezumab in terms of serious cardiovascular events, serious malignancies, and rates of serious hypersensitivity reactions in US routine clinical practice. The long-term 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, episodic cluster headache patients (as defined by receipt of an episodic or unspecified cluster headache diagnosis code) and patients with other indications, as well as 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 serious hypersensitivity reactions, serious cardiovascular events and malignancies excluding non-melanoma skin cancers (NMSC) among patients exposed to galcanezumab overall, in migraine patients, episodic cluster headache patients (as defined by receipt of an episodic or unspecified cluster headache diagnosis code) and patients with other indications, 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: 14-Dec-2020 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 corresponding incidence rates among migraine patients receiving other migraine prophylactic medication(s). 2) If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort during the five years of Phase 1, to conduct comparative analyses for serious cardiovascular events and malignancies (excluding NMSC) using migraine patients treated with other prophylactic medication(s) as the active comparator group. No formal comparative analyses are planned for serious hypersensitivity reactions; however, incidence rates for serious hypersensitivity reactions in a comparator cohort will be provided for context. Given the low prevalence of cluster headache, comparative analyses within the episodic cluster headache cohort are not expected to be feasible and will not be conducted.
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3. List of Abbreviations

Abbreviation	Term
AAN	American Academy of Neurology
ADIN	Action, Decision, Issue, Notification
AE	Adverse event
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-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
ICD-10	International Classification of Diseases, Tenth Revision
IHS	International Headache Society
Kg	Kilogram
M	Meter
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
PPV	Positive predictive value
PSUR	Periodic safety update reports
PTSD	Post-Traumatic Stress Disorder
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

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5. 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

Amendment(b)

PPD

Rationale and background

Galcanezumab is approved for the treatment of episodic cluster headache and 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 Medicines Agency (EMA). Certain aspects of the safety profile of continuous or intermittent long-term use of galcanezumab in routine clinical settings remain unclear. Although galcanezumab was generally well-tolerated in clinical trials, adverse events that have a longer latency period such as malignancy, and/or are infrequent, such as serious hypersensitivity reactions, could occur with the use of galcanezumab in routine clinical settings. Given the short follow-up in the trials, the implications of long-term inhibition of Calcitonin Gene-Related Peptide (CGRP) remain unknown, including the impact on long-term safety. Furthermore, patients 65 years of age or older, and patients with recent acute cardiovascular (CV) events and/or serious cardiovascular risks 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, serious malignancies, and rates of serious hypersensitivity reactions in US routine **c**linical practice. The long-term safety profile will be characterised through assessment of pertinent data for a period up to five years.

The primary objectives of this study are:

- To describe the utilisation of galcanezumab overall, in patients with migraine, patients with episodic cluster headache (as defined by receipt of an episodic or unspecified cluster headache diagnosis code) and patients

with other indications as well as in special populations of interest including patients at least 65 years of age, and patients with recent acute cardiovascular events and/or serious cardiovascular risks.

- To estimate unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding non-melanoma skin cancers (NMSC) among patients exposed to galcanezumab overall, in patients with migraine, episodic cluster headache (as defined by receipt of an episodic or unspecified cluster headache diagnosis code) and patients with other indications, as well as in the subgroups of patients aged 65 years or older, and patients with recent acute cardiovascular events and/or serious cardiovascular risks.

The secondary objectives of this study are:

- To provide context for unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among the galcanezumab-exposed migraine cohort by estimating the unadjusted incidence rates of these outcomes among migraine patients receiving another migraine prophylactic medication and in the subgroups of these patients aged 65 years or older, and patients with recent acute cardiovascular events and/or serious cardiovascular risks.
- If a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort during the five years of Phase 1, to conduct comparative analyses of serious cardiovascular events, and-malignancies excluding NMSC, using migraine patients treated with other prophylactic medication(s) as the active comparator group(s). Formal comparative analyses for serious hypersensitivity reactions will not be conducted. Additionally, given the low prevalence of cluster headache, comparative analyses within the episodic cluster headache cohort are not expected to be feasible and will not be conducted.

Study design

This will be a cohort study using data from a US administrative claims database and will include two phases. The first phase consists of; (1) monitoring the number of galcanezumab users, (2) describing the characteristics of galcanezumab and comparator medication users overall and in the identified subgroups, and (3) determining the unadjusted incidence rates of outcomes of interest for each group overall and in the identified subgroups. The second phase, if a sufficient number of serious cardiovascular events accrue in the galcanezumab migraine cohort during Phase 1, will consist of comparative analyses for serious cardiovascular events and malignancies (excluding NMSC) comparing galcanezumab to active comparator group(s).

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, episodic cluster headache (as defined by receipt of an episodic or unspecified cluster headache diagnosis code), and other indications (inclusive of patients that do not qualify for either the migraine nor the episodic cluster headache cohorts; Figure 1). The number of the safety outcomes from the galcanezumab cohorts and comparator drug cohorts 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 recent acute cardiovascular (CV) events and/or serious cardiovascular risk, will be monitored and described. The unadjusted incidence rates of the safety outcomes of interest in these cohorts and sub-cohorts will be estimated and stratified by duration of exposure. In addition, incidence rates for the safety outcomes of interest will be estimated for three comparators among those with migraine diagnosis codes: (1) topiramate, (2) oral prophylactic migraine medications other than CGRP, and (3) onabotulinumtoxinA injection (approved for chronic migraine prevention in North America and the European Union), to be included in interim and final reports. Additionally, within these migraine comparator cohorts, unadjusted incidence rates of safety outcomes of interest will be estimated for patients 65 years of age and older, and patients with recent acute cardiovascular (CV) events and/or serious cardiovascular risk.

Phase 2: Comparative Analyses

Upon accrual of sufficient number of serious cardiovascular events in the galcanezumab migraine cohort (see Section 10.6) and five years of database time (i.e., completion of Phase 1), 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. Unadjusted incidence rates for serious hypersensitivity reactions in patients receiving topiramate (oral) or onabotulinumtoxinA injection will be provided for context. Given the low prevalence of cluster headache, statistically meaningful comparative analyses within the episodic 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, episodic cluster headache, and other 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 episodic cluster headache will be defined by having a diagnosis of either episodic or unspecified cluster headache on or before the first galcanezumab dispensing or injection date. Galcanezumab-exposed cohorts are defined in detail in Section 10.2.1.1

In addition, uptake monitoring and estimation of unadjusted incidence rates for safety outcomes of interest will be performed for three comparators: (1) topiramate, (2) other oral non-CGRP migraine prophylactic medications, (3) and onabotulinumtoxinA injection. The comparator cohorts will consist of patients who have at least one pharmacy dispensing or injection procedure for (1) topiramate, (2) oral prophylactic migraine medications other than CGRP antagonists, or (3) onabotulinumtoxinA (see Section 10.2.1.2), and 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 comparator cohorts, 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 10.2.1.3).

Unadjusted incidence rates for serious cardiovascular events, serious hypersensitivity reactions, and malignancies other than NMSC will be estimated within the cohorts/sub-cohorts identified above. Follow-up of the cohorts starts on the day after the index date and ends at the earliest date of the events defined in Section 10.3. The index date is defined as the date of the first dispensing of galcanezumab or the comparator drug.

Phase 2: Comparative Analyses

Upon accrual of sufficient number of serious cardiovascular events in the galcanezumab migraine cohort (see Section 10.6) and 5 years of database time (i.e., completion of Phase 1), 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 cohorts will be subject to additional inclusion/exclusion criteria specific to each safety outcome and study design (See Section 10.2.1.4). 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 10.2.1.1) to minimise lag-time bias. Specifically, for serious cardiovascular events, topiramate is chosen as the primary comparator drug and Botox® (onabotulinumtoxinA injection) is chosen as the secondary comparator drug. For malignancies excluding NMSC, new users of oral, non-CGRP migraine prophylactic treatments is chosen as a primary comparator group (see Section 10.2.1.2). Formal comparative analyses for serious hypersensitivity reactions will not be conducted due to lack of an appropriate active comparator (oral comparators are not expected to produce serious hypersensitivity reactions, and onabotulinumtoxinA injection acts locally, whereas galcanezumab acts systemically). Unadjusted incidence rates for serious hypersensitivity reactions in patients receiving topiramate (oral) or onabotulinumtoxinA injection 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 eligible comparator migraine prophylactic medications will be ascertained from pharmacy claims and medical claims (See Section 10.4.1).
- **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 10.4.2). Serious cardiovascular events will be defined as a composite and individual outcomes. Malignancies excluding NMSC will be analysed overall and by organ system. In Phase 2, 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 10.4.3).

Data sources

This study will be conducted in the HealthCore Integrated Research Database (HIRD). The HIRD is a longitudinal medical and pharmacy claims database including approximately 48 million private commercially insured lives across the US. This study will seek medical records for safety outcome adjudication and NDI linkage for 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 24 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. Comparative analyses will not be initiated until accrual of five years of database time in addition to sufficient sample size in order to allow for assessment of long-term safety.

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 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 cohorts 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 risks within both the galcanezumab and comparator cohorts will also be determined and described, (See Section 10.2.1.3).

The unadjusted incidence rates of the safety outcomes of interest will be determined in the galcanezumab-exposed cohorts (see Section 10.2.1.1), the comparator drug migraine cohorts, and the special populations of interest within both the galcanezumab and comparator cohorts (see Section 10.2.1.3). The unadjusted incidence rates in all cohorts and in the special populations of interest (see Section 10.2.1.3) 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 10.4.2). The unadjusted incidence of serious hypersensitivity reactions will be presented overall. The incidence of malignancies excluding NMSC will be presented overall and by organ site.

Phase 2: Comparative Analysis

If a sufficient number of serious cardiovascular events accrue in the galcanezumab-exposed migraine cohort during the five years of Phase 1 (see Section 10.6), 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 or onabotulinumtoxinA injection 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.

Summary of Analyses

Outcome	Active Comparator	Secondary Comparator	Estimand(s)*
Serious CVE[†]	Topiramate	OnabotulinumtoxinA injection	IR, HR
Serious HSR[‡]	Topiramate	OnabotulinumtoxinA injection	IR
Malignancy[§]	Composite[‖]	OnabotulinumtoxinA injection	IR, HR

*That which is being estimated.

[†]Both new user and prevalent new user design.

[‡]Analyses for HSR will be limited to IRs by treatment group; no direct comparative analyses for HSR will be carried out.

[§]Excluding NMSC.

[‖]Composite comparator group of oral prophylactic migraine medications other than CGRPs including galcanezumab.

Abbreviations: CVE=cardiovascular event; HSR=hypersensitivity reactions; IR=incidence rate; HR=hazard ratio.

Milestones

Data collection will begin in 2020. Annual product uptake monitoring in Phase 1 will monitor galcanezumab uptake and is expected to last until Q4 2023. A Phase 1 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. The study will last for a total of seven years with the first five years for accrual of patients and five years of database time (for assessment of long-term safety), and the last year and a half for comparative analyses and development of the study report. 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 does 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 per commitments to European regulators.

6. Amendments and Updates

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	9 July 2020	Throughout	Phase 2 (comparative analyses) will not be initiated until accrual of 5 years of database time (not just sufficient sample size).	To allow for sufficient follow-up time for long term safety evaluation, particularly malignancy.
1	9 July 2020	Throughout	Addition of Botox comparator	Known utilization and strong potential as an active comparator
1	9 July 2020	Throughout; Figure 1	Exclusion of chronic cluster headaches from cluster headache cohort	Drug not indicated for chronic cluster headache
1	9 July 2020	Section 10.2.1.4 (page 31)	Exclusion of patients with prior cardiovascular events from cardiovascular events analysis	To prevent counting prevalent events as incident.
1	9 July 2020	Section 10.3.1	Addition of time window for hypersensitivity reactions	Outcome ascertainment for hypersensitivity reactions is needed and has implications for whether capture includes delayed reactions

1	9 July 2020	Section 10.4.3 (page 40)	Addition of structured EHR "lifestyle" factor variables	To supplement or improve covariate ascertainment
1	9 July 2020	Section 10.4.3 (pages 40-42)	Addition of sensitivity analyses to address chronic migraine indication for Botox, ascertainment of delayed hypersensitivity reactions, and concomitant medication use.	To address potential limitations.
1	9 July 2020	Throughout	Further refinements to improve upon existing language and figures	N/A
2	Please see approval on front page	Section 10.4.2 (page 41)	Remove epinephrine administration from definition of serious hypersensitivity reactions	Epinephrine administration is too non-specific to appropriately identify serious hypersensitivity reactions in the absence of a diagnosis code.
2	Please see approval on front page	Section 10.4.1 (pages 38-39)	Redefines the exposure windows for galcanezumab and the comparator medications	The exposure definitions were not consistent across the different groups. This could lead to biases in result interpretation.
2	Please see approval on front page	Section 10.4.1 (pages 38)	Redefines the exclusion window for previous use of the index drug to	This exclusion was not consistent across patients

			183 days pre-index.	with different lengths of baseline enrolment.
2	Please see approval on front page	Section 12.1 (page 52)	Clarifies how product complaints should be reported	To provide additional clarity.

7. Milestones

Milestone	Planned date
Registration in the EU PAS Register	17 January 2019
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
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 final analyses and development of the study report.

8. 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 three or more months, of which eight 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 treatments to relieve symptoms such as triptans or nonsteroidal anti-inflammatory drugs.

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 using the drug after six months and only 14% after 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 a male-to- female ratio of 4:3 (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 one to three 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 and the treatment of episodic cluster headache in adults and a marketing authorisation from the European Medicines Agency for migraine prophylaxis in adults who have at least four migraine days per month. Galcanezumab 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 65 years of age or older, 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 covariates, ascertainment of outcomes that are fatal without a healthcare encounter, 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 describes an observational study using claims data to evaluate the long-term safety of galcanezumab in routine practice in the US.

9. Research Question and Objectives

This study aims to evaluate the utilisation and long-term safety of galcanezumab in terms of serious cardiovascular events, serious malignancies, and rates of serious hypersensitivity reactions in 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 patients, episodic cluster headache patients (as defined by receipt of episodic or unspecified cluster headache diagnosis codes) and patients with other indications, as well as 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 unadjusted incidence rates of the safety outcomes of interest among galcanezumab-exposed patients overall, galcanezumab-exposed patients with migraine, episodic cluster headache (as defined by receipt of episodic or unspecified cluster headache diagnosis codes) or other indications, as well as 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 unadjusted incidence rates of the safety outcomes of interest among the galcanezumab-exposed patients with migraine by estimating the corresponding unadjusted 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 during the five years of Phase 1, to conduct comparative analyses for serious cardiovascular events, and malignancies excluding NMSC using migraine patients initiating another migraine prophylactic medication as the active comparator group(s). Given the low prevalence of cluster headache, comparative analyses within the episodic cluster headache cohort are not expected to be feasible and will not be executed.

10. Research Methods

10.1. Study Design

This 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

- **Number of Patients:** Monitor the number of patients exposed to galcanezumab overall and in patients with migraine, patients with episodic cluster headache (as defined by receipt of either an episodic or unspecified cluster headache diagnosis code) and patients with other indications (inclusive of patients that do not qualify for either the migraine or the episodic cluster headache cohorts; Figure 1), as well as the duration of galcanezumab use from these cohorts. Uptake monitoring will occur annually and will last for five years. This phase will facilitate sample size projections and the accrual of sufficient database time for the assessment of long-term safety.
- **Patient Characteristics:** 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 recent acute cardiovascular (CV) events and/or serious cardiovascular risk.
- **Incidence Rates:** In the interim report, estimate the unadjusted incidence rates for serious cardiovascular events, serious hypersensitivity reactions and malignancies (excluding NMSC) in these cohorts and sub-cohorts and outcome specific comparator drug cohorts. The unadjusted 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 (and/or recent acute cardiovascular events). For serious hypersensitivity reactions, incidence rates will be presented overall. 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 during the five years of Phase 1, 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.

- **Cardiovascular Outcomes:** For serious cardiovascular events, we will use both an incident new-user design (20) and a prevalent new-user design (21) with topiramate as the primary active comparator and onabotulinumtoxinA injection as the secondary active comparator.
- **Serious Hypersensitivity Reactions:** Formal comparative analyses for serious hypersensitivity reactions will not be conducted due to lack of an appropriate active comparator (oral comparators are not expected to produce hypersensitivity reactions, and onabotulinumtoxinA injection acts locally, whereas galcanezumab acts systemically). Unadjusted incidence rates for serious hypersensitivity reactions in the topiramate and onabotulinumtoxinA injection cohorts will be provided for context.
- **Malignancy Outcomes:** For malignancies excluding NMSC, we will use a new-user design (20) with a composite comparator group of oral prophylactic migraine medications other than CGRPs including galcanezumab. A secondary comparator, onabotulinumtoxinA injection will also be assessed.

The study will seek to validate selected safety outcomes using a sample of medical records. Among patients who leave 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.

10.2. Setting

The study will be conducted using the HIRD. The HIRD is a longitudinal claims database that includes 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 principal source for exposure status, safety outcomes and covariates. Structured clinical data extracted from medical records will be linked for lifestyle factors. Medical records will be sought for outcome adjudication and NDI will be used to identify deaths that occur outside of the health care system.

10.2.1. Study Population

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

10.2.1.1. Galcanezumab Cohort

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 code indicating a pharmacy dispensing or 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 dispensing date. This allows for sufficient look-back time to ascertain information on baseline covariates, prior index treatment, and prevalent safety outcomes. The index date is defined as the date of the first claim for dispensing or injection of galcanezumab appearing in the HIRD during the intake period.

Exclusion criteria:

- A dispensing or a procedure of injection of a non-galcanezumab CGRP antagonist on or before the 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.

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

- **Galcanezumab Migraine Cohort:**
  - No diagnosis of cluster headache (episodic, chronic or unspecified) 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 index date.
- **Galcanezumab Episodic Cluster Headache Cohort:**
  - A diagnosis of episodic or unspecified cluster headache on or before the index date.
  - No diagnosis of chronic cluster headache.
- **Galcanezumab Cohort with Other Indications:**
  - No diagnosis of cluster headache (episodic, chronic or unspecified) or migraine and no dispensing or injectionof triptans on or before the index date.

10.2.1.2. Comparator Drug Migraine Cohorts

To form the active comparator drug migraine cohorts, we will identify patients meeting all the following inclusion criteria and none of the exclusion criteria (Figure 1). The active comparator cohorts will consist of patients who have at least one pharmacy dispensing or injection procedure for (1) topiramate, (2) onabotulinumtoxinA, (3) non-CGRP oral prophylactic migraine medications (e.g., antiepileptics, beta-blockers, calcium channel blockers, antidepressants)and who meet the additional inclusion/exclusion criteria defined

below. For all cohorts, patients may have dispensings of more than one migraine prophylactic medication.

The non-CGRP oral prophylactic cohort will also include topiramate users and will be used for the malignancy analyses only. Comparator drugs for this cohort will include a range of medications that have shown to be efficacious or probably effective for migraine prophylaxis (American Academy of Neurology (AAN)/American Headache Society (AHS) 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.

Inclusion criteria:

- At least one pharmacy dispensing or injection procedure 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 index date (See Section 10.3).
- The index date is defined as the date of the first claim for dispensing or injection of a comparator drug appearing in the HIRD during the intake period

Exclusion criteria:

- A diagnosis of cluster headache (episodic, chronic or unspecified) on or before the index date.
- A dispensing/injection of a CGRP antagonist, including galcanezumab, on or before the index date.

10.2.1.3. Special Populations of Interest

Special populations of interest will be defined within each exposure cohort 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.

10.2.1.4. 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 during the five years of Phase 1, additional inclusion and exclusion criteria listed below will be applied to the **galcanezumab migraine cohort** and **active comparator drug migraine cohorts** based on safety outcomes and study designs.

Serious cardiovascular events

- New-user design with topiramate or onabotulinumtoxinA injection as the active comparator:

  Topiramate and onabotulinumtoxinA injection are chosen as separate comparators with topiramate being primary and onabotulinumtoxinA being secondary. They are chosen as the comparator drugs because they are indicated for migraine prophylaxis, and limited evidence exists for an association with cardiovascular diseases. In 2018, approximately 15% of migraine patients had at least one dispensing of topiramate, compared with approximately 3% for onabotulinumtoxinA injections based on a preliminary analysis in the HIRD. For each new galcanezumab exposure, we will separately identify a new topiramate exposure and a new onabotulinumtoxinA exposure with the same number of prior dispensings or injections of other migraine prophylactic medication(s).

Inclusion criteria:

- Age 18 years or older on the index date.

Exclusion criteria:

- Patients with prior cardiovascular events up to 12 months prior to index (except in the case of the serious cardiovascular risk subgroup analysis).

Comparator-specific exclusion criteria:

Primary active comparator – topiramate

- A dispensing of topiramate or a dispensing/injection of galcanezumab before the index date. This exclusion is to account for prevalent users and the related healthy users effect, whereby patients experiencing adverse effects may tend to discontinue and switch therapy, while patients doing well continue therapy. For example, patients who stay on topiramate may be less

susceptible to the safety outcome, and therefore potentially bias against galcanezumab.
    - A diagnosis ofepilepsy on or before the index date. This exclusion is to increase comparability of indications between comparison treatments as epilepsy has been reported to be associated with an increased risk of cardiovascular diseases (23), and topiramate is indicated for epilepsy.

Secondary active comparator – onabotulinumtoxinA injection

- An injection of onabotulinumtoxinA or a dispensing/injection of galcanezumab before the index date.
- An injection of onabotulinumtoxinA associated with (on the same claim as) a diagnosis of migraine on the index date.

- Prevalent new-user design with topiramate and onabotulinumtoxinA injection as separate active comparator groups:

  Topiramate and onabotulinumtoxinA are chosen as separate comparators with topiramate being primary and onabotulinumtoxinA being secondary. They are chosen as the comparator drug for the same reason as stated in the new-user design section above. The 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 or onabotulinumtoxinA based on our preliminary analyses. Potential biases if assumptions are violated are discussed in Section 10.10.

  Within each comparative analysis, for every new-user of galcanezumab from the galcanezumab migraine cohort, we will identify a patient from the relevant comparator 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 who is also a topiramate initiator at a similar time but remains on topiramate.

Serious hypersensitivity reactions

- Formal comparative analyses for serious hypersensitivity reactions will not be conducted. Unadjusted incidence rates for serious hypersensitivity reactions in patients receiving topiramate or onabotulinumtoxinA will be provided for context.

  Inclusion criteria:

    - Age 18 years of age or older on the index date.

Malignancies excluding NMSC

- New-user design with a composite comparator group consisting of oral, non-CGRPs as the primary active comparator and onabotulinumtoxinA injection as the secondary active comparator.

  The composite comparator group will consist of oral prophylactic medications other than CGRPs recommended by clinical guidelines. If there is reasonable evidence in the literature 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.

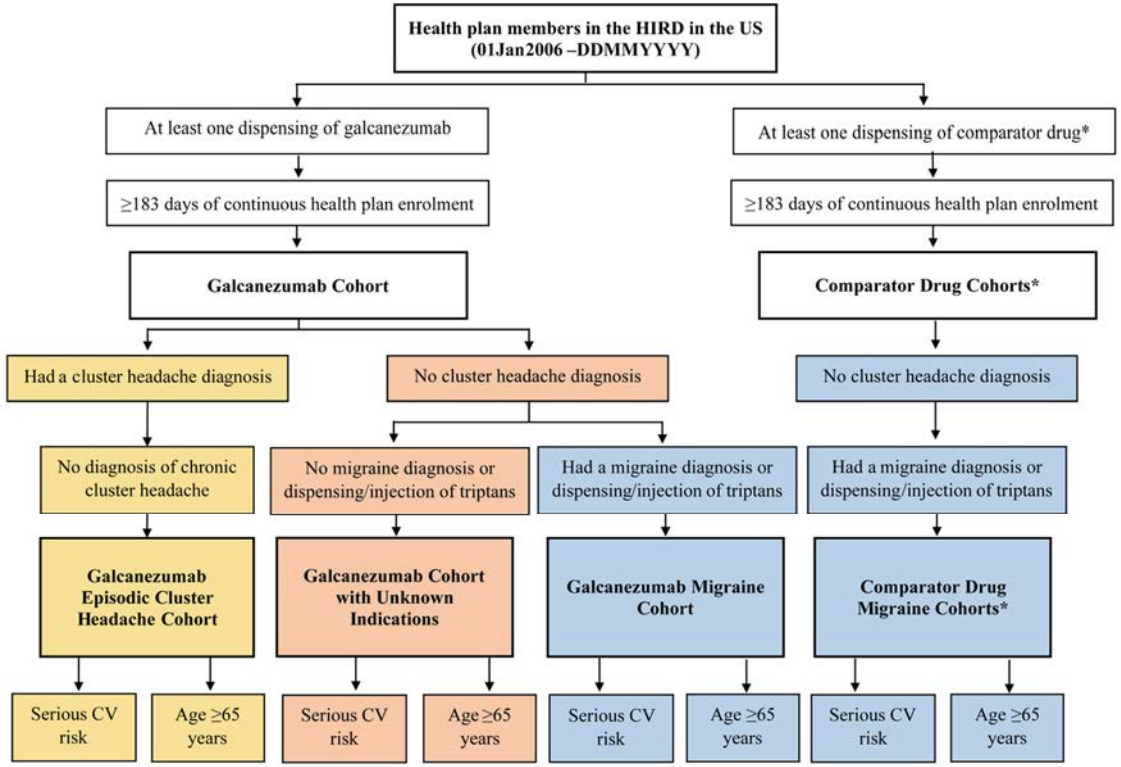
  Inclusion criteria:

  - Age 18 years or older on the index date.

  Exclusion criteria:

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

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

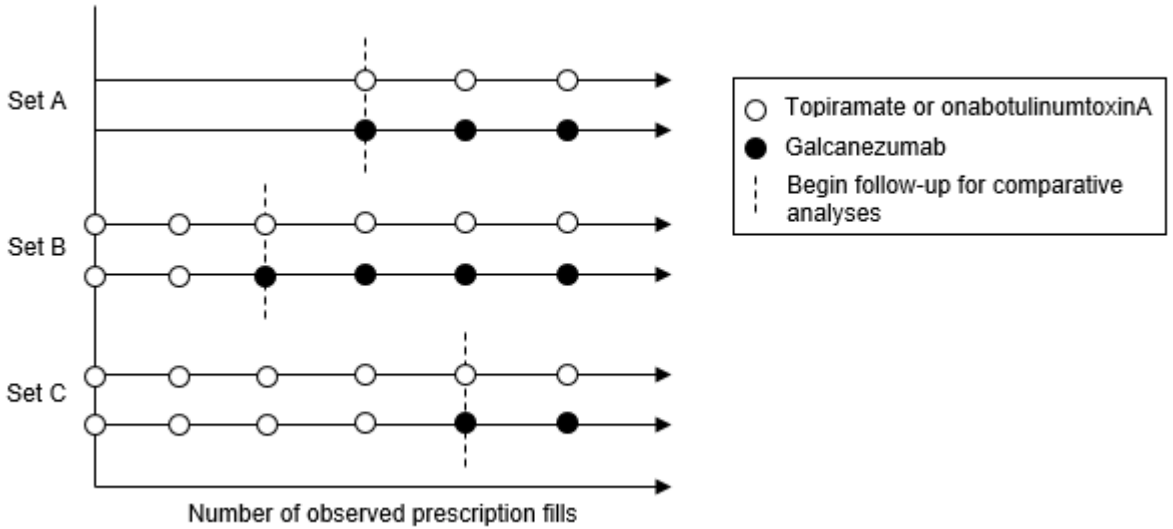


*Comparator drug cohorts include (1) topiramate, (2) oral prophylactic migraine medications other than CGRP, and (3) onabotulinumtoxinA. In Phase 1, a single patient may contribute person-time to multiple cohorts. In Phase 2, for the new-user design comparisons, patients will be censored upon switching from one study drug to another. For the prevalent new-user design comparisons, patients will be grouped according to the drug that they stayed on or switched to (see Figure 2).

Abbreviations: CV=cardiovascular; HIRD=HealthCore Integrated Research Database; US=United States.

Colors: Yellow, galcanezumab episodic cluster headache cohort; Orange, galcanezumab other indications cohort; Blue, migraine cohorts for Phase 2 comparative analyses.

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



Set A represents the frequently used "new-user, active comparator" design, where incident users of a new drug (e.g., galcanezumab) are compared to incident users of an older drug (e.g., topiramate or onabotulinumtoxinA). **Sets B-C** represent the "prevalent new-user" design in which prevalent users of an older drug who switched to a newer drug (e.g., galcanezumab) are compared to prevalent users of the older drug who did not switch. Each exposure set is defined by the number of observed prescription fills up to the point of switching (e.g., two fills for **Set B** and four fills for **Set C**). Note that patients are matched chronologically such that the second patient in **Set C** -- until they become a galcanezumab user -- could serve as a match for the second patient in **Set B**. Thus, a patient can contribute person-time to both the galcanezumab group and one or more comparator groups.

10.3. Study Period

Galcanezumab was approved by the FDA on 27 September 2018. Therefore, the planned intake period of the comparison treatments will start as early as 28 September 2018. Phase 1 uptake monitoring will start in 2020 and will last for five years. We anticipate accruing a sufficient number of serious cardiovascular events in the Galcanezumab Migraine Cohort by 2024 to execute comparative analyses (See Section 10.6). 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).

10.3.1. 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 during or closely following treatment. 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 or onabotulinumtoxinA as the active comparator:

The index date is defined as the first dispensing/injection of galcanezumab, the first dispensing of topiramate as the primary active comparator, or the first injection of onabotulinumtoxinA as the secondary active comparator. Topiramate and onabotulinumtoxinA patients will be sampled separately and are not interchangeable. Each patient will enter the cohort once, and only the first eligible index treatment episode will be used to capture new use.

- Prevalent new-user design with topiramate or onabotulinumtoxinA as the active comparator:

For the galcanezumab cohort, the index date is defined as the first dispensing/injection of galcanezumab or the date when topiramate or onabotulinumtoxinA users add or switch to galcanezumab. For the active comparator cohorts, the index date is defined as the corresponding dispensing date of topiramate or the injection date of onabotulinumtoxinA in the selected dispensing/injection-based exposure sets (Figure 2). Patients can enter multiple exposure sets and therefore have more than one index date.

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 antagonist.
- End of the continuous exposure episode (see Section 10.4.1).
- Health plan disenrolment.
- Death.
- End of the study period.

Serious hypersensitivity reactions

- Comparative analyses for serious hypersensitivity reactions will not be conducted due to lack of an appropriate active comparator. Unadjusted incidence rates for serious hypersensitivity reactions in patients receiving onabotulinumtoxinA injection or topiramate will be provided for context.

For the calculation of unadjusted incidence rates, the index date is defined as the first dispensing/injection of galcanezumab or the first dispensing/injection of topiramate or onabotulinumtoxinA.

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

- Occurrence of a serious hypersensitivity reaction.
- End of the day after an injection (or one half-life from the end of the days' supply for topiramate). A sensitivity analysis (Section 10.10) will be performed, expanding the risk window for hypersensitivity reactions to encompass the time from index through 30 days after the last exposure.
- Health plan disenrolment.
- Death.
- End of the study period.

10.3.2. 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, each with a potential cancer risk. To address this source of possible confounding, treatment histories will be matched between galcanezumab exposures and comparator drug exposures by identifying lines of therapy (Figure 3).

Person-time and events during follow-up will be classified according to three exposure groups: galcanezumab only, comparator drug only, and exposure to both. Follow-up will start with the dispensing of a qualifying medication, and end at the earliest date of the following events:

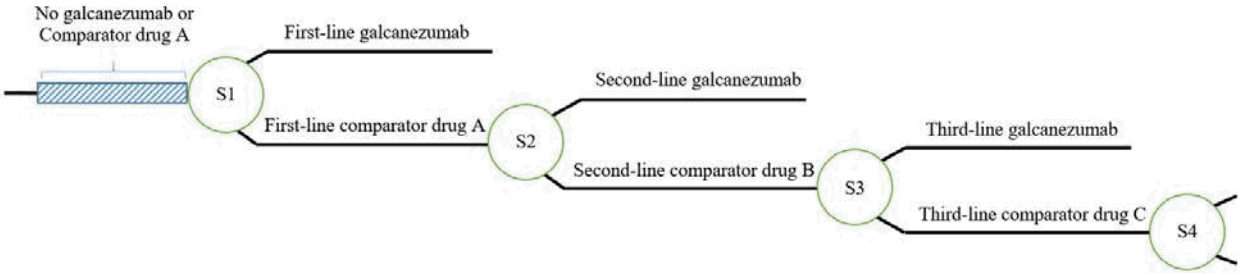
- Diagnosis of any cancer, excluding NMSC.
- Death.
- Health plan disenrollment.
- Calendar end of study.

In addition to the "as initiated" exposure classification, cancer outcome rates by cumulative exposure to galcanezumab will be examined. Cumulative exposure will be calculated as the cumulative dose of galcanezumab or the comparator medication that an individual receives during follow-up.

Because the empirical latency period of cancer after exposure to migraine prophylactic medications is unknown, we will implement sensitivity analyses in an attempt to account for

varying induction and latency periods (24) of malignancies corresponding to cancer initiation and promotion.

Figure 3. Schematic illustration of new-user design with a composite active comparator



10.4. Variables

10.4.1. Exposures

Exposure to galcanezumab and the eligible comparator medication(s) will be assessed using pharmacy and medical claims in the HIRD. New users are those patients without any recorded dispensing or injection for the index treatment in the 183 days prior to the index date (a sensitivity analysis will be executed with new users defined as without any recorded dispensing or injection for the index treatment based on all available data).

The following paragraphs define the first eligible index treatment episode for galcanezumab and the comparator medications. These definitions will be utilized for the cardiovascular outcomes analysis.

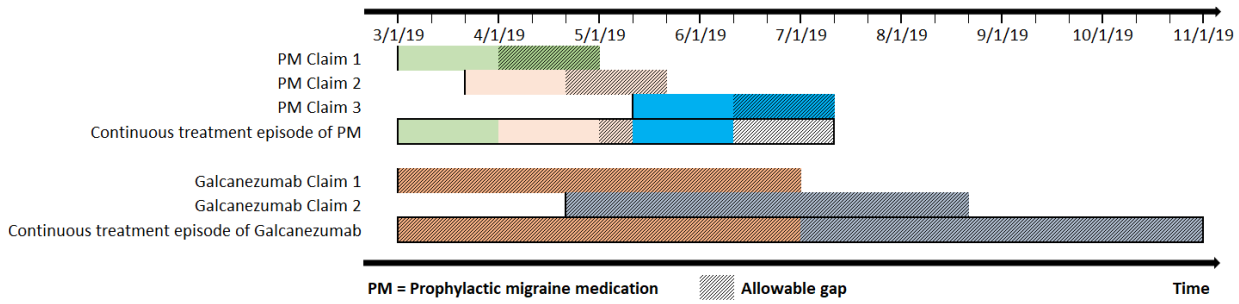
Because galcanezumab is administered as monthly injections and its elimination half-life is approximately 27 days (25), we will consider patients to be exposed to galcanezumab for four half-lives after the date of administration. An additional 30 days will be added beyond this window in order to capture delayed events and account for variations in patient adherence. Therefore, patients are allowed to have gaps of up to 138 (four half-lives + 30 additional days) days between galcanezumab administrations in the calculation of continuous treatment episode to galcanezumab. If there is more than one administration of galcanezumab separated by gaps of up to 138 days, the administrations will be concatenated into a single continuous treatment episode. A gap in treatment of more than 138 days will end the treatment episode. For administrations with overlapping days-supply, stockpiling will be assumed as shown in Figure 4.

OnabotulinumtoxinA is administered intramuscularly every three to six months. The continuous exposure period of onabotulinumtoxinA will be determined with an empirical data driven approach and will depend on the cohort mode of intervals between injections within the HIRD. An additional 30 days will be added beyond this window in order to capture delayed events and

account for variations in patient adherence. If there is more than one administration of onabotulinumtoxinA separated by gaps of up to the empirically determined window plus 30 days, the administrations will be concatenated into a single continuous treatment episode. Gaps in treatment longer than the empirically determined window plus 30 days will end the treatment episode. If there is more than one consecutive injection of onabotulinumtoxinA within the treatment episode, the subsequent injection will truncate the previous treatment episode and extend the episode by the associated exposure period of the subsequent injection (i.e. stockpiling will not be assumed).

The majority of other migraine prophylactic medications (e.g., topiramate) are taken orally. We will consider patients to be exposed to oral preventives for four half-lives after the days-supply ends. An additional 30 days will be added beyond this in order to capture delayed events and account for variations in patient adherence (10). If there is more than one consecutive dispensing of the index comparator drug separately by gaps of up to 4 half-lives post expiration of days-supply plus 30 days, the dispensings will be concatenated into a single continuous treatment episode. A gap in treatment of more than 4 half-lives post expiration of days-supply plus 30 days will end the treatment episode. For administrations with overlapping days-supply, stockpiling will be assumed as shown in Figure 4.

Figure 4. Schematic illustration of continuous treatment episode using stockpiling



10.4.2. Outcomes

The occurrence of the safety outcomes listed below will be identified the HIRD using claims-based coding algorithms. Incident events are of interest, so patients with a serious cardiovascular event in the 12 months 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). A random sample of medical records will be sought for selected claims-identified outcomes to validate the positive predictive value (PPV) on the algorithm. 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 occurring outside of the health care setting, we will link patients 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/overall outcome, and the following events are under consideration:
        - Anaphylaxis
        - Angioedema
        - Acute asthma or acute bronchospasm
        - Acute upper airway obstruction
        - 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, TenthRevision (ICD-10) hierarchy (e.g., bone, breast, urinary tract, etc.).

10.4.3. Covariates

Covariates including patient demographics, lifestyle factors, 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 10.8). All available data prior to the start of the treatment will be used to assess baseline demographics, lifestyle factors, 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
- Lifestyle factors:
    - Body mass index (kilogram[kg]/meters[m]^2)

  - Smoking status
  - Alcohol intake
- 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

10.5. 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 enrollment, 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. Structured clinical data, such as lifestyle factors, from medical records can be linked for a subset (estimated 65-75%) of patients.

Medical records will be used to validate algorithms for select outcomes.

Deaths occurring out of health care system and the underlying cause of death will be identified using the NDI. NDI is a national database of deaths dating back to 1979 and is maintained by the US National Center for Health Statistics (NCHS). Patients can be linked to NDI records using

patient characteristics such as full name, gender, date of birth, state of residence and (when available) social security number.

10.6. Study Size

The available number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in the US. 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 24 serious cardiovascular events from 5,099 patients newly initiating galcanezumab need to be accrued over the five years of Phase 1 to have an 80% power for a hazard ratio 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 four months of follow-up corresponding to duration the index treatment episode.

For malignancies excluding NMSC, we assume an average follow-up of three years. The minimum detectable hazard ratio 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). These calculations are for a study design with no prespecified latency period.

To conduct comparative analyses for onabotulinumtoxinA injection, approximately 48 serious cardiovascular events from 10,202 patients newly initiating galcanezumab need to be accrued during the five years of Phase 1 to have an 80% power to detect a hazard ratio of 2.0 (galcanezumab versus onabotulinumtoxinA injection) 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), an onabotulinumtoxinA-to-galcanezumab ratio of 1:1, 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 hazard ratio with 80% power at a significance level of 0.05 will approximately be 1.45, assuming 4.36 per 1,000 person-year background incidence of all cancer types (30), and an onabotulinumtoxinA-to-galcanezumab ratio of 1:1 among 10,202 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 hazard ratios 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 acknowledge the number of outcomes and lack of multiple comparison adjustment.

10.7. 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.

10.8. Data Analysis

10.8.1. 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, episodic cluster headache (as defined by receipt of an episodic or unspecified cluster headache diagnosis code), or other indications (neither migraine or episodic cluster headache; Figure 1), respectively, as well as the duration of galcanezumab exposure from these cohorts defined in Section 10.2.1.1 will be presented.

For the interim report, we will describe distributions of covariates including demographics, comorbidity, medications, and health care utilisation (See Section 10.4.3) overall, and separately stratified by cohorts as defined in Section 10.2.1.1 and Section 10.2.1.2, and special population as defined in Section 10.2.1.3. 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.

For the interim and final report, 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 10.3). 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.

Unadjusted incidence rates will be presented overall, and separately stratified by cohort/sub-cohort defined by diagnosis/treatment of migraine, episodic cluster headache or other indications (See Section 10.2.1.1 and Section 10.2.1.2), 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. Sensitivity analyses will be performed to assess outcome misclassification.

10.8.2. Phase 2: Comparative Analyses

In Phase 2, upon completion of five years of uptake monitoring in Phase 1, if a sufficient number of serious cardiovascular events have accrued 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 or prevalent users of the other prophylactic migraine treatment(s) 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 10.4.3) 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 or onabotulinumtoxinA as the reference group in 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 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.

10.9. 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.

10.10. Limitations of the Research Methods

- **Uncertainties common to new medications**

It is uncertain how many patients with migraine or episodic 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 us unable to draw formal aetiologic conclusions. 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 unadjusted incidence of safety outcomes among patients exposed to other prophylactic medication(s), interpretation of the unadjusted 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 (i.e., the minimum magnitude of the association between the confounder and the exposure and outcome needed to produce the observed exposure-outcome association) (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. Initial doses of drugs may be missed if they did not result in a claim (e.g., physician provides patient with a sample pack of the drug). Furthermore, in office administration of drugs for which there is no HCPCS code may also be missed. 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.

- **Chronic migraine indication for onabotulinumtoxinA injection**

OnabotulinumtoxinA injection is approved in the European Union and North America for the prevention of headaches in chronic migraine sufferers (as opposed to episodic migraine). As an additional analysis, we will report Phase 2 findings for the subgroup of patients with a chronic migraine diagnosis.

- **Delayed hypersensitivity reactions**

A sensitivity analysis will be performed extending the outcome ascertainment window for hypersensitivity reactions to include delayed hypersensitivity reactions. The time window for this sensitivity analysis will encompass the time from index through 30 days after last exposure.

- **Treatment switching and concomitant treatment use**

An internal study using MarketScan data found that concomitant use of multiple preventive migraine medications is not uncommon, with 18.8% of new galcanezumab users generating a claim for onabotulinumtoxinA injection during their first six months of galcanezumab use, and 53.8% generating a claim for an oral preventive agent during that same time. To address treatment switching and concomitant treatment use, a number of approaches will be employed. First, if a large number of patients are concomitant preventive migraine medication users, a sensitivity analysis will be conducted in which they form a distance cohort. Second, the prevalent new-user design proposed for the serious cardiovascular events analyses addresses treatment switching, allowing patients to contribute person-time to more than one cohort over the study period. Third, because cardiovascular and hypersensitivity events are acute outcomes attributed to a currently or recently used drug, events occurring during an exposure episode for a treatment will be attributed to that drug. For concomitant users, a sensitivity analysis will be performed stratifying patients by presence or absence of concomitant preventive medication(s). During Phase 1, we will explore additional, newer methods available to address time-varying treatments including drug switching and concomitant medication use.

10.11. Other Aspects

Not applicable.

11. 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.

12. 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 10.4. All protocol-defined AEs collected will be summarised in the interim and final study report. No other AEs will be collected.

12.1. 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.

Complaints related to comparator drugs or concomitant drug/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

Researchers are instructed to report product complaints as they would for products in the marketplace.

13. Plans for Communication and Dissemination of Study Results

This study will produce interim and final reports that will be delivered to the EMA.

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

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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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
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	☒	☐	☐	9.3 9.2.1
4.2.2 Age and sex	☒	☐	☐	9.2 9.2.1 9.3
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
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
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
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

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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
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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
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**
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**
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: _____