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
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Research question and objectives	This study aims to evaluate the utilisation and long-term safety of galcanezumab in terms of serious cardiovascular events, malignancies other than non-melanoma skin cancer (NMSC), 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 5 years. The primary objectives of this study are: 1) To describe the utilisation of galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of 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 serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients exposed to galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only).

	The secondary objectives of this study are: 1) To estimate the unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients with migraine receiving other prophylactic migraine medications, as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only). 2) To conduct comparative analyses of serious cardiovascular events, and malignancies excluding NMSC, comparing migraine patients treated with galcanezumab to migraine patients treated with other prophylactic medication(s) as the active comparator group(s). This objective is contingent upon meeting the target study size for the serious cardiovascular events incident new-user analysis with topiramate as the comparator during the 5 years of uptake monitoring (Phase 1). 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.
Country(-ies) of study	United States
Authors	

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3. List of Abbreviations

Abbreviation	Term
ADIN	Action, Decision, Issue, Notification
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CABG	Coronary artery bypass graft surgery
CGRP	Calcitonin Gene-Related Peptide
CPT	Current Procedural Terminology
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
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
MAH	Marketing authorisation holder

Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NDC	National Drug Codes
NDI	National Death Index
NMSC	Non-melanoma skin cancers
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
UMR	Uptake Monitoring Report
US	United States
WHO	World Health Organization

4. Responsible Parties

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

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). 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. Furthermore, patients 65 years of age or older, and patients with recent acute cardiovascular events and/or serious cardiovascular risk were not included in the clinical trials, yet the use of galcanezumab in these populations may occur in routine clinical practice. 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, malignancies other than non-melanoma skin cancers (NMSC), 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 5 years.

The primary objectives of this study are:

- To describe the utilisation of galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of patients 65 years of age or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk.
- To estimate unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients exposed to galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only).

The secondary objectives of this study are:

- To estimate the unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients with migraine receiving other prophylactic migraine medications, as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with

recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only).

- To conduct comparative analyses of serious cardiovascular events, and malignancies excluding NMSC, comparing migraine patients treated with galcanezumab to migraine patients treated with other prophylactic medication(s) as the active comparator group(s). This objective is contingent upon meeting the target study size for the serious cardiovascular events incident new-user analysis with topiramate as the comparator during the 5 years of uptake monitoring (Phase 1). 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 health insurance claims database and will include two phases. Phase 1 will monitor the number of galcanezumab users, describe the characteristics of galcanezumab and comparator users, and determine the unadjusted incidence rates of outcomes in galcanezumab and comparator users. Phase 2 will be executed upon meeting the target study size for the serious cardiovascular events incident new-user analysis with topiramate as the comparator. Comparative analyses will examine serious cardiovascular events and malignancies (excluding NMSC), comparing patients with migraine treated with galcanezumab to migraine patients treated with active comparators. A second comparative analysis will be conducted for serious cardiovascular events employing a prevalent new-user design to allow for inclusion of galcanezumab users with prior use of comparators.

Summary of Study Designs

Outcome	Primary Comparator	Secondary Comparator	Phase 1 Design	Phase 2 Design
Serious cardiovascular events	Topiramate	OnabotulinumtoxinA injection	Incident new-user	**(1)** Incident new-user (primary analysis) **(2)** Prevalent new-user (secondary analysis)
Serious hypersensitivity reactions*	Topiramate	OnabotulinumtoxinA injection	Incident new-user	None*
Malignancy†	Composite‡	OnabotulinumtoxinA injection	Incident new-user	Incident new-user

*Analyses for serious hypersensitivity reactions will be limited to incidence rates by treatment group; no comparative analyses for serious hypersensitivity reactions will be carried out.

†Excluding non-melanoma skin cancer (NMSC).

‡Composite comparator group of oral prophylactic migraine medications other than calcitonin gene-related peptides (CGRPs) including galcanezumab.

Data Sources

This study will be conducted using data from the HealthCore Integrated Research Database® (HIRD), a longitudinal medical and pharmacy insurance claims database including >62.2 million private commercially insured patients with medical and pharmacy coverage across the US. This study will seek medical records for safety outcome adjudication and National Death Index linkage for death ascertainment.

Study Size

The available number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in HIRD plan members. Comparative analyses will be executed if there is an adequate number of patients qualifying for the incident new-user comparison of galcanezumab with topiramate. Approximately 10,900 study eligible galcanezumab users and 43,600 study eligible topiramate users must be accrued in order to obtain an expected upper 95% confidence limit less than 2.00 when the true risk ratio for serious cardiovascular events is 1.00.

Data Analysis

Phase 1: Galcanezumab Uptake Monitoring and Utilisation of Study Drugs

The number of patients exposed to galcanezumab overall and by indication will be monitored and described along with patients' demographic characteristics, comorbidities, concomitant medications, and health care utilisation. The distribution of covariates in the special populations of interest, in other words, patients 65 years of age or older, and patients with serious cardiovascular risk, will also be determined and described. Additionally, the interim report will provide these figures for qualifying comparator users along with unadjusted incidence rates of the safety outcomes of interest (in other words, serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC).

Phase 2: Comparative Analysis

If a sufficient number of serious cardiovascular events accrue in the galcanezumab-exposed migraine cohort for comparison with topiramate, the study team will initiate Phase 2 (comparative) analyses. In this phase, we will estimate risk ratios and 95% confidence intervals for serious cardiovascular events and malignancies excluding NMSC, comparing migraine patients treated with galcanezumab to propensity-score-matched migraine patients treated with other prophylactic medication(s). The primary analysis will consist of an incident new-user analysis of serious cardiovascular events, comparing migraine patients treated with galcanezumab to propensity-score-matched migraine patients treated with topiramate. Additional analyses are planned as described in the table below.

Summary of Analyses

Outcome	Primary Comparator*	Secondary Comparator*	Phase 1 Estimates	Phase 2 Estimates*
Serious cardiovascular events†	Topiramate	OnabotulinumtoxinA injection	Incidence ate	Incidence rate risk ratio
Serious hypersensitivity reactions‡	Topiramate	OnabotulinumtoxinA injection	Incidence rate	Incidence rate
Malignancy§	Composite¶	OnabotulinumtoxinA injection	Incidence rate	Incidence rate risk ratio

*The comparator groups are only used for comparisons during comparative analyses (Phase 2) pending sufficient sample size for Phase 2 execution. During Phase 1, they are enumerated and described.

†Both new-user and prevalent new-user design.

‡Analyses for serious hypersensitivity reactions will be limited to incidence rates by treatment group; no comparative analyses for serious hypersensitivity reactions will be carried out.

§Excluding non-melanoma skin cancer (NMSC).

¶Composite comparator group of oral prophylactic migraine medications other than calcitonin gene-related peptides (CGRPs) including galcanezumab.

Milestones

Data collection began in 2020. Annual product uptake monitoring, which will be described in the uptake monitoring reports 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 galcanezumab users to determine the feasibility of comparative analyses for serious cardiovascular events. The study will encompass 5 years of patient accrual time and 2 additional years for analysis. The end of data collection is anticipated to be Q2 2025. The final study report will be submitted with the periodic safety update report (PSUR)/Risk Management Plan (RMP) within 12 months of study completion. If a sufficient number of galcanezumab-exposed patients 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.

Study Deliverables

Study deliverables will include uptake monitoring reports, an interim report, and a final report. The uptake monitoring reports will include Phase 1 (descriptive) analyses of galcanezumab users and monitor the sample size for the main comparative analysis. The interim and final reports will include descriptive analyses of galcanezumab users and will also include unadjusted (unmatched) incidence rates for serious cardiovascular events, serious hypersensitivity reactions, and malignancies other than NMSC. If sample size is sufficient, then the interim and/or final report(s) will contain Phase 2 (comparative) analyses for serious cardiovascular events, and malignancies other than NMSC.

Summary of Study Deliverables

Study Element	UMR	Interim Report	Final Report
Cohorts Included			
• Descriptive galcanezumab cohorts: migraine, cluster, unknown indications	Yes	Yes	Yes
• Cohort of galcanezumab users meeting criterion for primary comparative analysis*	Yes†	Yes	Yes
• Other drug cohorts (topiramate, onabotulinumtoxinA, composite oral migraine prophylaxis)	No	Yes	Yes
Estimates Reported			
• Descriptive analyses of demographics and clinical characteristics	Yes	Yes	Yes
• Unmatched/unadjusted incidence rates	No	Yes	Yes
• Matched incidence rates	No	If sample size met	If sample size met
• Comparative analyses (risk ratios)	No	If sample size met	If sample size met

Abbreviation: UMR, uptake monitoring report.
*Primary comparative analysis is the comparison of serious cardiovascular event incidence in migraine patients using galcanezumab versus topiramate.
†For sample size monitoring only

6. Amendments and Updates

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
A	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). **Note**: this amendment applies to the malignancy analyses only.	To allow for sufficient follow-up time for long term safety evaluation, particularly malignancy.
A	9 July 2020	Throughout	Addition of Botox comparator	Known utilization and strong potential as an active comparator
A	9 July 2020	Throughout; Figure 1	Exclusion of chronic cluster headaches from cluster headache cohort	Drug not indicated for chronic cluster headache
A	9 July 2020	Section 10.2.1.4	Exclusion of patients with prior cardiovascular events from cardiovascular events analysis	To prevent counting prevalent events as incident.
A	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
A	9 July 2020	Section 10.4.3	Addition of structured electronic health record "lifestyle" factor variables	To supplement or improve covariate ascertainment

A	9 July 2020	Section 10.4.3	Addition of sensitivity analyses to address chronic migraine indication for Botox, ascertainment of delayed hypersensitivity reactions, and concomitant medication use.	To address potential limitations.
A	9 July 2020	Throughout	Further refinements to improve upon existing language and figures	N/A
B	3 Nov 2020	Section 10.4.2	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.
B	3 Nov 2020	Section 10.4.1	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.
B	3 Nov 2020	Section 10.4.1	Redefines the exclusion window for previous use of the index drug to 183 days pre-index **Note:** This is a minimum.	This exclusion was not consistent across patients with different lengths of baseline enrolment.
B	3 Nov 2020	Section 12.1	Clarifies how product complaints should be reported	To provide additional clarity

C	Please see approval on front page	Section 3 List of Abbreviations	Updated list to be inclusive of any new abbreviations used; removed abbreviations that were no longer used.	Increase clarity
C	Please see approval on front page	Throughout	Removed language that suggested looking at serious cardiovascular event count during Phase 1 as a threshold for sample size and execution of comparative analysis	Sample size threshold will rely on number of patients, not number of events; concerns regarding scientific appropriateness of looking at events in Phase 1
C	Please see approval on front page	Throughout	Removed statements implying sampling with replacement in prevalent new-user design	Sampling without replacement will be conducted to aid in feasibility
C	Please see approval on front page	Throughout	Certain sections needed to be moved due to restructuring. GVP requirements on section headings have been maintained.	Increase clarity
C	Please see approval on front page	Throughout	Clarified that the recent acute cardiovascular events or serious cardiovascular risk subgroup analysis will only apply to the serious cardiovascular events outcome and not to malignancy or serious hypersensitivity reactions.	To provide clarification and align with RMP.

C	Please see approval on front page	Section 5 Abstract	Shortened to 3 pages	Shortened to facilitate clear understanding of the goal of the protocol, to describe key elements for reader convenience.
C	Please see approval on front page	Section 10.4.1 Exposures	Updated figure	To reflect changes introduced in prior amendments.
C	Please see approval on front page	Section 10.6	Revised sample size section to replace HR with RR, updated background rate	Risk ratio will be estimated directly through Kaplan-Meier approach rather than indirectly as a hazard ratio; background rate from original version was prior to full operationalisation of serious cardiovascular events which will include hospitalisations only, and background rates cited were from less comparable populations than in other available literature
C	Please see approval on front page	Section 10.6; Section 10.8 Study Population	Added criterion requiring loading dose appears in claims	Free medication samples provided by physicians are not captured in claims. This leads to missed exposures to the drug and misclassification bias and impacts the validity of the study.
C	Please see approval on front page	Section 10.8 Data Analysis	Updated analysis section to assess risk ratios instead of hazard ratios	Risk ratio will be estimated directly through Kaplan-Meier approach rather than indirectly as a hazard ratio.

C	Please see approval on front page	Section 10.8.2	Updated comparator selection for prevalent new-user design	Selection of comparator patients for the prevalent new-user design will be without replacement to aid in feasibility and interpretability of study.
C	Please see approval on front page	Section 10.8 Data Analysis	Deleted sentence about covariate imbalance	To remove unnecessary detail from Protocol and allow for greater flexibility regarding how covariate imbalance will be handled
C	Please see approval on front page	Section 10.8	Added gepants and ditans to "triptans" for definition of migraine indication cohorts	These new drug classes are now available in addition to triptans and are exclusively for migraine and thus can be used to identify migraine patients similar to triptans
C	Please see approval on front page	Section 10.10 Limitations	Replaced e-values with more informative bias analyses	E-values do not adjust estimates and adjusted estimates are preferred for their end utility and informativeness
C	Please see approval on front page	Section 10.8 Study inclusion criteria (originally Study Population Section; now in Analysis section subsection for descriptive cohort inclusion criteria)	Removed epilepsy exclusion from descriptive cohorts' entry criteria.	The epilepsy exclusion only pertains to comparative analysis cohorts where epilepsy is an indication for the comparator drug.

C	Please see approval on front page	Section 10.8 Data Analysis	Moved inclusion/exclusion criteria into separate subsections within each study design/analysis; separated out the criteria by study design; deleted population figure.	Upon implementing the study and drafting the comparative analysis SAP, the study team found that the Protocol as written incorrectly implied a central cohort and study design when in fact there are several distinct studies within the Protocol; for proper implementation and clear documentation to avoid errors, these needed to be described separately. Because the Protocol template guidelines within Eli Lilly and Company did not allow for separating the Protocol into separate chapters or documents for these different studies, as level 1 and 2 subheadings could not be modified due to standard operating procedures, the study team decided to create a subheadings scheme within the Analysis section that would allow for description of the separate designs and population/study entry criteria for each study within this project.
C	Please see approval on front page	Section 14 References	Updated reference list; removed references that were	Increase clarity

	no longer used; updated citation numbers accordingly.

7. Milestones

Milestone	Planned date
Overall	
Registration in the EU PAS Register	17 January 2019
Start of data collection	31 December 2020*
End of data collection	30 June 2025
Progress Reports[†]	
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 & Final Reports[‡]	
Interim report	31 December 2024
Final report of study results	31 December 2026[§]

Abbreviations: EMA, European Medicines Agency; EU, European Union; PSUR, periodic safety update report.

*Reflects the date of first data extraction.

[†]Study progress reports are delivered annually to EMA in EU Appendix 4 of the PSUR. These study progress reports utilise a subset of information from the study's annual Uptake Monitoring Reports (UMRs).

[‡]Will include Phase 2 (comparative) analyses if sufficient sample size is achieved.

[§]The study will encompass 5 years of patient accrual time and 2 additional 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 3 or more months, of which 8 or more days meet criteria for migraine without aura and/or respond to migraine-specific treatment (2) and is much less common than episodic migraine (3, 4). Migraine is two to three times more prevalent in women than men (5) and its prevalence peaks in the middle of life in both sexes (1). Migraine has been consistently associated with increased risk of ischaemic stroke and myocardial infarction, with a significantly higher risk among patients who had migraine with aura versus without, and among women compared with men (6, 7). The majority of migraine patients use 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 6 months and only 14% after 12 months (10, 11).

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 (12). A cluster period generally lasts from 2 weeks to 3 months and a single attack typically lasts between 15 minutes and three hours. The International Headache Society (IHS) classified cluster headache into two major types: episodic (85–90%) and chronic (10–15%) (13). The lifetime prevalence of cluster headache overall is approximately 0.12% and it mostly affects men with a male-to-female ratio of 4 to 1 (14). The mean age of onset is approximately 30 years old (15).

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 (16). 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) (17). Another placebo-controlled phase-III study of patients with episodic cluster headache has also shown a significant reduction of weekly cluster headache attacks from baseline across weeks 1 to 3 comparing galcanezumab with placebo (18). 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 4 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. 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. 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 and can be investigated using real-world data. Because real-world data are not collected for research purposes, defining serious cardiovascular risk is more challenging. In lieu of direct clinical assessment, diagnosis codes in administrative claims data can be used as a surrogate for increased cardiovascular risk.

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 can be used to investigate potential safety signals and include patients who were not able to participate in the clinical trials. 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. To potentially 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 if sufficient sample size is achieved.

9. Research Question and Objectives

This study aims to evaluate the utilisation and long-term safety of galcanezumab in terms of serious cardiovascular events, malignancies other than non-melanoma skin cancer (NMSC), 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 5 years.

The primary objectives of this study are:

1) To describe the utilisation of galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of 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 serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients exposed to galcanezumab, both overall and by indication (in other words, migraine, episodic cluster headache, unknown), as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only).

The secondary objectives of this study are:

1) To estimate the unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and malignancies excluding NMSC among patients with migraine receiving other prophylactic migraine medications, as well as in the subgroups of patients 65 years of age or older (for all outcomes) and patients with recent acute cardiovascular events and/or serious cardiovascular risk (for serious cardiovascular events outcome only).

2) To conduct comparative analyses of serious cardiovascular events, and malignancies excluding NMSC, comparing migraine patients treated with galcanezumab to migraine patients treated with other prophylactic medication(s) as the active comparator group(s). This objective is contingent upon meeting the target study size for the serious cardiovascular events incident new-user analysis with topiramate as the comparator during the 5 years of uptake monitoring (Phase 1). 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.

10. Research Methods

10.1. Study Design

This cohort study will use data from the HealthCore Integrated Research Database® (HIRD), a US commercial administrative claims database and will be conducted in two phases:

Phase 1: Galcanezumab Uptake Monitoring, Utilisation, and Crude Incidence Rates

- **Number of Patients:** Monitor the number of patients exposed to galcanezumab overall and in patients with migraine, episodic cluster headache (as defined by receipt of either an episodic or unspecified cluster headache diagnosis code) and unknown indications (inclusive of patients that do not qualify for either the migraine or the episodic cluster headache cohorts), as well as the duration of galcanezumab use from these cohorts.
- **Patient Characteristics:** 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 events and/or serious cardiovascular risk.
- **Incidence Rates:** Estimate the unadjusted incidence rates for serious cardiovascular events, serious hypersensitivity reactions, and malignancies other than NMSC in these cohorts and outcome-specific comparator drug cohorts. For serious cardiovascular events, the incidence rates will be presented for a composite outcome and individual outcomes and will be presented for the subgroups of patients 65 years of age or older and patients with recent acute cardiovascular events and/or serious cardiovascular risk. For serious hypersensitivity reactions, incidence rates will be presented overall and for the subgroup of patients 65 years of age or older. The incidence of malignancies will be presented overall and by organ site and for the subgroup of patients 65 years of age or older.

Phase 2: Comparative Analyses

- We will conduct comparative analyses among migraine patients for serious cardiovascular events and malignancies excluding NMSC, comparing new users of galcanezumab with propensity score-matched patients treated with other prophylactic migraine medications. This objective is contingent upon meeting the target study size for the serious cardiovascular events incident new-user analysis with topiramate as the comparator.
- **Cardiovascular Outcomes:** For serious cardiovascular events, we will use both an incident new-user design (19) and a prevalent new-user design

(20) 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 since galcanezumab and biologics in general are known to cause serious hypersensitivity reactions; cases of serious hypersensitivity reactions shortly after galcanezumab exposure will be assumed to be caused by galcanezumab and therefore no comparative analyses will be conducted. Unadjusted incidence rates for serious hypersensitivity reactions in the topiramate and onabotulinumtoxinA injection cohorts will be reported.
- **Malignancy Outcomes:** For malignancies excluding NMSC, we will use an incident new-user design (19) with a composite comparator group of oral prophylactic migraine medications other than CGRPs including galcanezumab. A secondary comparator, onabotulinumtoxinA injection will also be assessed.

10.2. Setting

This study will be conducted using data from the HIRD, a longitudinal medical and pharmacy insurance claims database including >62.2 million private commercially insured patients with medical and pharmacy coverage 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 the National Death Index will be used to identify deaths that were not recorded in claims or medical records.

This study comprises both descriptive objectives and comparative objectives (comparative objectives contingent on sample size), each with their own inclusion and exclusion criteria. Section 10.8.1 describes the descriptive (Phase 1) analyses cohorts, while Section 10.8.2 describes the comparative (Phase 2) analyses cohorts.

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 27 September 2018. Phase 1 uptake monitoring was started in 2020 and will last for 5 years. We anticipate accruing a sufficient number of patients in the Galcanezumab Migraine Cohort by 2024 to execute comparative analyses (see Section 10.6).

The baseline period captures information collected for a patient before the index date with a minimum duration of 183 days and can date back to the earliest available data (01 January 2006).

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 patients without a baseline dispensing or injection for the index treatment prior to the index date based on all available data with a minimum lookback period of 183 days.

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

Because galcanezumab is administered as monthly injections and its elimination half-life is approximately 27 days (23), we will consider patients to be exposed to galcanezumab for approximately four half-lives after the date of administration. An additional 30 days will be added beyond this window in order to account for possible non-adherence and non-concordance of dispensing date and medication use (10). Therefore, patients are allowed to have gaps of up to 138 (in other words, 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 galcanezumab fill separated by gaps of up to 138 days (in other words, four half-lives plus 30 days), the start date of the subsequent pharmacy dispensing will move forward to the day after the end date of the prior exposure period and all exposure periods will be added to form a single continuous treatment episode (in other words, stockpiling; Figure 1). Medical claims for galcanezumab will not be eligible for stockpiling as they indicate in-office administration occurring on that date.

OnabotulinumtoxinA is administered intramuscularly every 3 to 6 months. The continuous exposure period of onabotulinumtoxinA will be determined with an empirical data-driven approach and will depend on the mode (in other words, most frequently occurring value) of time between injections among patients with more than one claim for this drug. An additional 30 days will be added beyond this window in order to account for variations in patient adherence. Gaps in treatment longer than the empirically determined window plus 30 days will end the treatment episode. If there is more than one administration of onabotulinumtoxinA separated by gaps of up to the empirically determined window plus 30 days, the subsequent injection will truncate the previous treatment episode and extend the episode by the associated exposure period of the subsequent injection (in other words, stockpiling will not be assumed). A truncation approach is taken instead of a stockpiling approach since this drug is not filled in a pharmacy and self-administered, thus the date of the claim is the date of administration of the drug, and stockpiling is not possible.

The majority of other migraine prophylactic medications (for example, topiramate) are taken orally. Continuous exposure episodes for each eligible comparator medication will be created using dispensing date, plus the number of days supplied, plus four half-lives, plus 30 days to account for possible non-adherence and non-concordance of dispensing date and medication use (10). If there is more than one consecutive dispensing of the index comparator drug separated by

gaps less than the sum of the days supplied plus four half-lives plus 30 days, days of supply will be added in a stockpiling fashion to define a continuous treatment episode.

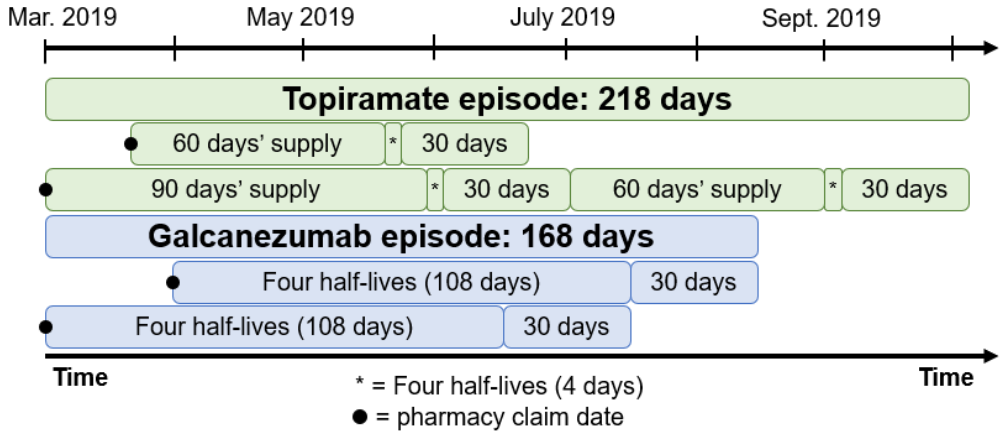

Figure 1. Schematic illustration of continuous treatment episodes.

Note: Galcanezumab pharmacy claim is assumed to be for one syringe in this example. It is assumed that the patient will self-inject on this date. Days' supply is not shown for galcanezumab, because the last exposure date to which four half-lives are added is the date of self-injection.

10.4.2. Outcomes

The occurrence of the safety outcomes listed below will be identified using claims-based coding algorithms. Incident events are of interest, so patients with a history of the event of interest will be excluded from the computation of incidence for that specific event as described in the inclusion/exclusion criteria listed for each analysis is Section 10.8. The coding algorithms (for example, 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). To ascertain deaths occurring outside of the health care setting, patients will be linked to the National Death Index.

In addition, a random sample of medical records will be sought for cases according to selected algorithms to estimate the positive predictive value (PPV) of the algorithm. Two clinicians will adjudicate case status according to clinical criteria. When there is disagreement, final case status will be decided by either a committee consensus or with a third reviewer. Details of the clinical review and adjudication process for safety outcomes will be described in the SAP.

Definitions:

- Serious cardiovascular events:
  - Serious cardiovascular events will comprise the following events and will be reported as a composite outcome and as separate outcomes if the number of events for a particular outcome surpasses 10.
    - Myocardial infarction (MI), transient ischaemic attack (TIA), ischaemic stroke, ischaemic heart disease, and angina

        - Coronary revascularisation: coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI), and
        - Deaths from ischaemic heart disease or ischaemic cerebrovascular disease.
- Serious hypersensitivity reactions:
    - Serious hypersensitivity reactions will be reported as a composite outcome:
        - Anaphylaxis
        - Angioedema
        - Acute asthma or acute bronchospasm
        - Acute upper airway obstruction, or
        - Deaths from hypersensitivity reactions.
- Malignancies excluding NMSC:
    - Malignancies will be reported as a composite outcome overall and by organ system defined by the International Classification of Diseases, Tenth Revision (ICD-10) hierarchy (for example, bone, breast, urinary tract, and so on).

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, as 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 the SAP. Covariates will be assessed for all available lookback before the index date unless otherwise specified.

- Demographics:
    - Age (years) on the index date
    - Sex
    - US region of residence
    - Duration of continuous health plan enrolment on or before the index date
    - Calendar year of index date
    - Calendar month of index date
- Comorbidities:
    - Hypertension
    - Hyperlipidaemia
    - Type 1 diabetes
    - Type 2 diabetes
    - Overweight and obesity 183 days on or before index date as available in claims
    - Smoking as available in claims
    - Cardiovascular diseases:
        - MI
        - TIA
        - Ischaemic stroke
        - Ischaemic heart disease

        - Angina
        - Heart failure
        - Cardiac arrhythmia
        - Haemorrhagic stroke
        - Peripheral vascular disease
        - Atherosclerosis
    - Coronary revascularisation: CABG or PCI
    - Malignancy excluding NMSC
    - Serious hypersensitivity reactions
    - Epilepsy
    - Bipolar disorder
    - Alcohol dependence
    - Mood disorders
    - Post-traumatic stress disorder (PTSD)
    - Major depressive disorders
    - Anxiety disorders
    - Migraine type (for example, 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 (before index date):
    - Prophylactic migraine drugs
    - Prophylactic cluster headache drugs
    - Acute migraine drugs (for example, triptans)
    - Analgesics (for example, 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 in the 183 days before the 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 treatment episode
    - Treatment lines (in other words, observed treatment sequences in claims), and
    - 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, with data dating back to January 2006. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilisation are included for health plan members in the database. The claims data in the HIRD can be linked to complementary data sources, such as inpatient and outpatient medical records as well as national vital statistics records through the HealthCore Integrated Research Environment.

Diagnoses and procedures in the HIRD 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 the serious cardiovascular events outcome.

Deaths occurring out of health care system and the underlying cause of death will be identified using the National Death Index. The National Death Index is a national database of deaths dating back to 1979 and is maintained by the US National Center for Health Statistics. Patients can be linked to National Death Index 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, serious cardiovascular events, with topiramate as the comparator.

Serious Cardiovascular Events, Topiramate Comparison

The decision to execute comparative analyses will be based upon accrual of an adequate number of galcanezumab incident new users to obtain an expected upper 95% confidence limit less than 2.00 when the true risk ratio of serious cardiovascular events is 1.00. Assuming a background risk of 365 acute myocardial infarction and cerebral infarction hospitalizations per 100,000 US population in 2018 (24) and the median first treatment episode duration of 188 days as seen to date in the HIRD (data on file), approximately 10,900 incident galcanezumab users with an identifiable loading dose qualifying for the comparative analysis must be accrued in order to obtain an expected upper 95% confidence limit less than 2.00 when the true risk ratio of serious cardiovascular events is 1.00.

Serious Cardiovascular Events, OnabotulinumtoxinA Comparison

As stated above, the minimum sample size required to execute comparative analyses is 10,900 qualifying incident galcanezumab users. During uptake monitoring, we expect to accrue approximately equal numbers of incident galcanezumab and onabotulinumtoxinA users. With 10,900 incident galcanezumab users and 10,900 incident onabotulinumtoxinA users, the expected upper 95% confidence limit would be less than 2.40 when the true risk ratio is 1.00.

Malignancy Outcome

As stated above, the minimum sample size required to execute comparative analyses is 10,900 qualifying incident galcanezumab users. During uptake monitoring, we expect to accrue galcanezumab and composite oral comparator users at a 1:4 ratio. Given a background risk of 436 new cancer cases per 100,000 US population in 2018 (25), and the median time in database post-index of approximately 1 year as reported in Uptake Monitoring Report (UMR) 2, with 10,900 incident galcanezumab users and 43,600 incident composite oral comparator users, the expected upper 95% confidence limit would be less than 1.58 when the true risk ratio is 1.00.

Update(s) to Sample Size Calculations

If the risks observed in the interim report are substantially different from the background risks described above, sample size may be recalculated. Differences in patient population and methodology could result in observed risks for comparators in this study that are higher or lower than the US population used to estimate precision. The risk of serious cardiovascular events depends on the demographic and clinical composition of the population. Differences between the background risks used for sample size calculation and the risks in the study population could lead to over- or under-estimation of the sample size requirements for the comparative analysis. Underestimation of required sample size could lead to comparative analyses with inadequate precision to draw conclusions from the available data. To ensure the accuracy of target study size estimation, the study team will examine the risk of serious cardiovascular events reported in the Interim Report. If the risk of serious cardiovascular events is lower than the US population risk mentioned above, then the sample size necessary to obtain an expected upper 95% confidence limit less than 2.00 when the true risk ratio is 1.00 will be recalculated.

Multiple Comparisons

Multiple comparisons will not be addressed in these analyses (26). 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 be reported as "≤10" according to HealthCore guidelines.

10.8. Data Analysis

This study comprises both descriptive and comparative objectives. For this reason, we have broken this section into two broader sections, with subsections pertaining to each distinct analysis. Section 10.8.1 describes the descriptive (Phase 1) analyses, while Section 10.8.2 describes the comparative (Phase 2) analyses.

10.8.1. Phase 1 (Descriptive) Analyses

Descriptive analyses will be carried out to both characterise galcanezumab utilisation and to estimate the unadjusted incidence rates for serious cardiovascular events, serious hypersensitivity reactions, and malignancies other than NMSC, among users of galcanezumab and other migraine prophylactic medications. Because the utilisation objective requires a broader subset of patients and different analytic techniques than the incidence rates objectives, the study design, population, and analyses for Phase 1 are presented in two separate sections: Section 10.8.1.1 for utilisation and Section 10.8.1.2 for unadjusted incidence rates.

10.8.1.1. Phase 1: Drug Utilisation Objective

10.8.1.1.1. Study Design

The first primary objective of this study is to describe the utilisation of galcanezumab (Section 9). In this descriptive analysis, we will describe the utilisation of galcanezumab overall, in patients with migraine, episodic cluster headache, and unknown 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.

For each cohort and special population, we will describe both the number of galcanezumab users and their characteristics, including demographics, comorbidities, concomitant medication use, total time in database, duration of use, healthcare utilisation in the 183 days prior to index, and length of pre-index continuous enrollment. Duration of use will be defined as the length of the first continuous treatment episode as defined in Section 10.4.1.

10.8.1.1.2. Setting

Phase 1 will take place exclusively in the HIRD. Further description of the HIRD can be found in Section 10.2. Medical records and National Death Index data will not be introduced until Phase 2 (comparative analyses; execution contingent upon reaching minimum sample size).

10.8.1.1.3. Study Population

The utilisation analyses will describe galcanezumab users overall as well as galcanezumab users meeting the following cohort entry criteria:

1. Galcanezumab treatment: At least one dispensing of galcanezumab on or after 27 September 2018. The first dispensing during this period will serve as the **index date**.
2. Age: At least 18 years of age on the date of the first qualifying dispensing or injection.
3. Continuous enrollment requirement: At least 183 days of continuous medical and prescription enrollment in the HIRD on or before the first qualifying dispensing or injection. A 30-day gap in enrollment will be permitted.
4. New user: No dispensing of galcanezumab prior to the index date.
5. Patients will be classified into one of four possible cohorts:
    a) **Galcanezumab episodic cluster headache cohort**:
        i. A diagnosis of episodic or unspecified cluster headache on or before galcanezumab initiation.
        ii. No diagnosis of chronic cluster headache on or before galcanezumab initiation.
        iii. Patients whose index fill is for a galcanezumab migraine dose will be excluded.
    b) **Galcanezumab cohort with unknown indications**:
        i. No cluster headache diagnosis on or before the index date.
        ii. No migraine diagnosis or dispensing/injection of triptans, ditans, or gepants.
    c) **Galcanezumab migraine cohort**:
        i. No cluster headache diagnosis on or before the index date.
        ii. At least one diagnosis code for migraine or at least one dispensing/injection of triptans, ditans, or gepants prior to or on the index date.
    d) **Galcanezumab migraine cohort for comparative analysis of serious cardiovascular events:** Implement criterion from Section 10.8.2.1.3.

10.8.1.1.3.1. Special Populations

Special populations of interest within each exposure cohort include the following:

- Patients 65 years of age or older on the index date.
- Recent acute cardiovascular events and/or serious cardiovascular risk: Patients who have a recent acute cardiovascular event (in other words, MI, TIA, ischaemic heart disease, angina, or stroke) or undergo coronary revascularisation (in other words,

CABG or PCI) and/or serious cardiovascular risk (for example, diabetes mellitus, obesity, hypertension, and so on; list further defined in SAP) within 183 days prior to the index date.

- Note: Because this subgroup is relevant to the serious cardiovascular events outcome only, it will not be constructed for the composite oral prophylactic migraine cohort which is intended for the malignancy outcome analyses.

10.8.1.1.4. Study Period

For each patient, the date of the first dispensing or administration of galcanezumab or comparator during the intake period (in other words, 28 September 2018 through end of available data period) will constitute the index date with follow-up beginning on that day.

10.8.1.1.5. Data Analyses

For each cohort and special population, the number of patients exposed to galcanezumab will be presented, as well as the duration of galcanezumab exposure and total post-index time in database. The number of galcanezumab users qualifying for the primary serious cardiovascular events comparative analysis will also be reported in order to assess sample size (Section 10.6).

For each cohort and special population, we will describe distributions of covariates including demographics, comorbidities, medications, and health care utilisation. 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.

10.8.1.2. Phase 1: Unadjusted Incidence Rates

10.8.1.2.1. Study Design

The second primary objective of this study is to estimate unadjusted incidence rates of serious cardiovascular events, serious hypersensitivity reactions, and non-NMSC malignancies in galcanezumab users. A secondary objective is to estimate the same incidence rates in patients taking other migraine prophylactic medications (Section 9). This analysis will include the galcanezumab cohorts and special populations from the utilisation objective (Section 10.8.1.1.3), and introduce three additional cohorts: topiramate, onabotulinumtoxinA, and composite oral migraine prophylaxis treatments (inclusive of topiramate). All cohorts will be composed of incident new users of the respective drug(s).

For each cohort and special population, we will describe both the number of patients and their characteristics, including demographics, comorbidities, concomitant medication use, total time in database, duration of use, healthcare utilisation in the 183 days prior to index, and length of pre-index continuous enrollment. Duration of use will be defined as the length of the first continuous treatment episode as defined in Section 10.4.1.

We will estimate the unadjusted incidence rates for serious cardiovascular events, serious hypersensitivity reactions, and malignancies (excluding NMSC) in each cohort and special population. Incidence rates for serious hypersensitivity reactions and malignancies (excluding

NMSC) will not be estimated for the recent acute cardiovascular events and/or serious cardiovascular risk special population.

10.8.1.2.2. Setting

Unadjusted incidence rates will be calculated using data from the HIRD. Further description of the HIRD can be found in Section 10.2. Medical records and National Death Index data will not be used in the fulfillment of the unadjusted incidence rates objectives.

10.8.1.2.3. Study Population

Incidence rates will be reported for the utilisation cohorts and special populations described in Section 10.8.1.1.3. In addition, incidence rates will be reported for patients with migraine using other migraine prophylactic drugs, who meet the following study entry criteria. Separate cohorts will be created corresponding to topiramate, onabotulinumtoxinA, and other non-CGRP oral prophylactic migraine medications (which will include topiramate) and attrition will be shown for each cohort:

1. Prophylactic migraine treatment: At least one dispensing of one of the following medications on or after 27 September 2018.
    a. Topiramate
    b. OnabotulinumtoxinA
    c. Oral prophylactic migraine medication(s) other than CGRP antagonists (for the composite oral prophylactic migraine cohort):
        i. Antiepileptics:
            - Divalproex sodium
            - Sodium valproate
            - Topiramate
            - Gabapentin
        ii. Beta-blockers:
            - Metoprolol
            - Propranolol
            - Oral timolol
            - Nadolol
            - Atenolol
            - Nebivolol
        iii. Calcium channel blocker:
            - Verapamil
        iv. Antidepressants:
            - Amitriptyline, and
            - Venlafaxine.
2. Age: At least 18 years of age on the date of the first qualifying dispensing or injection.
3. Continuous enrollment requirement: At least 183 days of continuous medical and prescription enrollment in the HIRD on or before the first qualifying dispensing or injection. A 30-day gap in enrollment will be permitted.

4. New user: No dispensing of the index medication prior to the index date.
5. Cluster headache exclusion: No cluster headache diagnosis
6. Migraine requirement: At least one diagnosis code for migraine or at least one dispensing/injection of triptans, ditans, or gepants prior to or on the index date.

The following additional criteria will be applied to the utilisation migraine cohorts (Section 10.8.1.1.3) to ensure that follow-up begins at the first galcanezumab dose (loading dose):

a) First fill or administration was for migraine dose rather than cluster headache dose.
b) First claim was pharmacy claim with ≤30 days' supply and syringe quantity of 2.0, or a medical claim indicating office administration.

Finally, incidence will be estimated only among individuals who do not have a diagnosis of the outcome of interest recorded before the index date (with the exception of the estimation of the incidence of serious cardiovascular events in the recent acute cardiovascular events and/or serious cardiovascular risk special population defined in Section 10.8.1.1.3.1). This will result in different cohorts for each outcome, representing different denominators for each:

- **Serious cardiovascular events**: Patients with acute cardiovascular events up to 12 months prior to index will be excluded. However, this criterion will not apply to patients in the recent acute cardiovascular events and/or serious cardiovascular risk special population.
- **Serious hypersensitivity reactions**: Patients with a diagnosis of serious hypersensitivity reaction prior to the index date will be excluded.
- **Malignancies other than NMSC**: Patients with a diagnosis of malignancy other than NMSC prior to the index date will be excluded.

10.8.1.2.4. Study Period

For each patient the date of the first dispensing or administration of galcanezumab or comparator during the intake period (in other words, 28 September 2018 through end of available data period) will constitute the index date with follow-up beginning on that day.

Follow-up for serious cardiovascular events will begin on 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 first continuous exposure episode, as defined in Section 10.4.1
- Health plan disenrollment
- Death, or
- End of data availability.

Follow-up 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 the dispensing
- Health plan disenrollment
- Death, or
- End of data availability.

Follow-up for malignancies will begin on the day after the index date, and continue until the earliest date of the following events:

- Diagnosis of any cancer, excluding NMSC
- Health plan disenrollment
- Death, or
- End of data availability.

10.8.1.2.5. Data Analyses

For each cohort and special population, 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 (Section 10.8.1.2.4). Confidence intervals for the incidence estimates will be computed using methods based on the Poisson distribution, noting that the methods used in this analysis are not controlling for confounding and that the confidence intervals reported assume no systematic error.

The incidence of malignancies excluding NMSC will be presented overall and by organ site.

10.8.1.2.5.1. Sensitivity Analyses

The following sensitivity analyses will be performed in addition to the main analysis:

- The time window for serious hypersensitivity reactions will be expanded to 30 days after index in order to capture delayed hypersensitivity reactions (for example, reactions taking longer than 48 hours to develop, which would not be captured in the main analysis) as described in Section 10.10.
- The outcome definition for malignancies includes any diagnosis, including diagnoses in an outpatient setting and/or in any position which may represent rule-out diagnoses. To address the potential for counting non-cases as cases, the malignancies excluding NMSC outcome will be redefined, restricting the definition to require at least one inpatient admission or 2 outpatient visits at least 2 weeks apart.
- Exposure misclassification is possible when using claims data to assess drug exposure, particularly for pharmacy dispensed drugs which may not be used consistently or at all. Specifically, patients who receive multiple pharmacy dispensings are likely to be consistent users, but patients who obtain only one dispensing might have used only some or even none of the dispensed medication. For the serious cardiovascular events outcome, will conduct a sensitivity analysis excluding galcanezumab or oral comparator users who did not have a second fill. We will start follow-up at the first fill, consistent with the main analysis. However, starting follow-up at the first fill while requiring a second fill induces immortal person-time between the first and second fill. To address this, we will include patients who did not have a second fill but did have an event. This

analysis will assume that patients who filled galcanezumab or an oral comparator once and did not go on to develop an event or fill the drug again did not take the drug and were never exposed.

10.8.2. Phase 2 (Comparative) Analyses

Comparative analyses will be executed upon meeting the target study size for the incident new-user analyses of serious cardiovascular events comparing galcanezumab to topiramate (Section 10.6). There are three separate comparative analyses, each with distinct study populations, designs, and analytic approaches. The approaches used for serious cardiovascular events with an incident new-user design are described in Section 10.8.2.1, while methods for the prevalent new-user design are described in Section 10.8.2.2. Finally, Section 10.8.2.3 describes the methods for the comparative analyses of malignancies other than NMSC.

10.8.2.1. Phase 2: Comparative Analysis of Serious Cardiovascular Events, Incident New-User Design

10.8.2.1.1. Study Design

For the primary comparative analysis of serious cardiovascular events, we will use an incident new-user design (19) with topiramate as the primary active comparator and onabotulinumtoxinA injection as the secondary active comparator.

10.8.2.1.2. Setting

Qualifying patients, their treatment group assignment, and their outcome status will be identified in the HIRD. Further description of the HIRD can be found in Section 10.2. Medical records and National Death Index data will be used to verify outcome status as described in Section 10.4.2 and Section 10.5.

10.8.2.1.3. Study Population

The incident new-user comparative analysis for serious cardiovascular events will include patients meeting the following study entry criteria which will result in the construction of four distinct cohorts: (1) galcanezumab users for comparison to topiramate users, (2) topiramate users, (3) galcanezumab users for comparison to onabotulinumtoxinA users, and (4) onabotulinumtoxinA users. Study attrition will be reported for each step for each of the four cohorts.

1. Prophylactic migraine treatment: At least one dispensing of one of the following medications on or after 27 September 2018:
    a. Galcanezumab
    b. Topiramate, or
    c. OnabotulinumtoxinA.
2. Migraine loading dose (applies to galcanezumab users only):
    a. First fill or administration was for migraine dose rather than cluster headache dose.
    b. First claim was pharmacy claim with ≤30 days' supply and syringe quantity of 2.0, or a medical claim indicating office administration.

3. Age: At least 18 years of age on the date of the first qualifying dispensing or injection.
4. Continuous enrollment requirement: At least 183 days of continuous medical and prescription enrollment in the HIRD on or before the first qualifying dispensing or injection (index date). A 30-day gap in enrollment will be permitted.
5. Incident new user: No dispensing of galcanezumab or the comparator of interest (for example, topiramate for the comparison of galcanezumab to topiramate) prior to the index date.
6. Multiple index drugs: Patients with a fill for both galcanezumab and the comparator of interest (for example, topiramate for the comparison of galcanezumab to topiramate) on the index date will be excluded.
7. Cluster exclusion: Patients with any cluster headache diagnosis on or before the index date will be excluded.
8. Migraine diagnosis or acute migraine treatment: Patients with at least one diagnosis code for migraine or at least one dispensing/injection of triptans, ditans, or gepants prior to or on the index date.
9. CGRP exclusion: Patients with a dispensing/injection of a non-galcanezumab CGRP antagonist on or before the index date will be excluded.
10. Cardiovascular events exclusion: Patients with acute cardiovascular events up to 12 months prior to index will be excluded. However, this criterion will not apply to patients in the recent acute cardiovascular events and/or serious cardiovascular risk special population.
11. Epilepsy exclusion for topiramate comparison (applies to both galcanezumab users and topiramate users): Patients with an epilepsy diagnosis code on or before treatment initiation (index) will be excluded from analyses comparing galcanezumab to topiramate.

10.8.2.1.4. Study Period

In the analysis comparing galcanezumab to topiramate, the index date will be defined as the patient's first dispensing of galcanezumab or topiramate. In the analysis comparing galcanezumab to onabotulinumtoxinA, the index date will be defined as the patient's first dispensing of galcanezumab or onabotulinumtoxinA.

Follow-up of the index treatment episode for serious cardiovascular events will begin on 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
- Initiation of the contrasting agent (in other words, comparator user initiates galcanezumab or galcanezumab user initiates the comparator)
- End of the first continuous exposure episode, as defined in Section 10.4.1
- Health plan disenrollment

- Death, or
- End of data availability.

10.8.2.1.5. Data Analyses

If a sufficient number of patients have accrued, we will estimate risk ratios and 95% confidence intervals for serious cardiovascular events, comparing qualifying galcanezumab users to qualifying comparator users according to the study entry criteria stated in Section 10.8.2.1.3. Kaplan-Meier analysis will be used to compute cumulative incidence proportions ("risk"), risk ratios, and risk differences for different points in time after treatment initiation. Follow-up will be limited to first-treatment episode (Section 10.4.1).

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 for precision improvement of the estimates without introducing bias (27). Covariates (Section 10.4.3) including demographics, comorbidities, medications, and health care utilisation will be considered for propensity score creation.

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 (28), the difference in means or proportions divided by the pooled standard deviation, will be computed for each covariate to check its balance between exposure groups. If balance is not achieved, then the propensity score model and weight distributions will be revisited to explore different ways of modeling the imbalanced covariates or of addressing the imbalance (for example, different cut points for the covariate, interaction terms, trimming, truncation, and so on). Risk ratios will be adjusted based on results from outcome adjudication and National Death Index linkage.

10.8.2.1.5.1. Sensitivity Analyses

Sensitivity analyses will be carried out to address residual confounding by smoking, body mass index, and migraine severity, and will also address measurement error (outcome misclassification), informative censoring, and concomitant medication use (Section 10.10). In an additional sensitivity analysis, comparisons of galcanezumab to onabotulinumtoxinA will be restricted to patients with a chronic migraine diagnosis as described in Section 10.10.

10.8.2.2. Phase 2: Comparative Analysis of Serious Cardiovascular Events, Prevalent New-User Design

10.8.2.2.1. Study Design

For secondary comparative analysis of serious cardiovascular events, we will use a prevalent new-user design (20) with topiramate as the primary active comparator and onabotulinumtoxinA injection as the secondary active comparator.

10.8.2.2.2. Setting

Qualifying patients, their treatment group assignment, and their outcome status will be identified in the HIRD and National Death Index. Further description of the HIRD can be found in Section 10.2.

10.8.2.2.3. Study Population

The prevalent new-user comparative analysis for serious cardiovascular events will include patients meeting the following study entry criteria which will result in the construction of four distinct cohorts: (1) galcanezumab users for comparison to topiramate users, (2) topiramate users, (3) galcanezumab users for comparison to onabotulinumtoxinA users, and (4) onabotulinumtoxinA users. Study attrition will be reported for each step for each of the four cohorts.

Treatment assignment will take place chronologically such that for each calendar date starting 28 September 2018, for each new initiator of galcanezumab we will select users of comparator drugs with a similar history of comparator use. For example, for a patient who initiated galcanezumab on 28 September 2018 who had used topiramate for 6 months prior, we will select (matching without replacement) as comparators topiramate users who are continuing topiramate use on that day who also had 6 months of prior topiramate use. If data are insufficient to select comparator patients with similar treatment history by day, a broader unit of calendar time may be used for comparator selection. As a result of this chronological approach, galcanezumab users who initiated galcanezumab later in time may serve as matches for earlier galcanezumab users.

For patients in the galcanezumab treatment group, the index date will be defined as the first galcanezumab fill during the intake period. For patients selected into the comparator group, the index date will be the closest fill date to the galcanezumab index date.

Inclusion and exclusion criteria are as follows:

1. Prophylactic migraine treatment: At least one dispensing of one of the following medications on or after 27 September 2018:
    a) Galcanezumab
    b) Topiramate, or
    c) OnabotulinumtoxinA.
2. Matches to a galcanezumab user: For each qualifying galcanezumab user, a matching comparator user with a similar treatment history will be selected. Treatment history will be defined by length of exposure episode in discrete 30-day units rounded to the nearest whole number, with exposure episodes calculated as described in Section 10.4.1.
3. Not already serving as a match for another galcanezumab user: This study will use a matching without replacement approach. Galcanezumab users who previously used the comparator of interest and served as a match to an earlier galcanezumab user will not contribute to the study as galcanezumab users once they switch.
4. Migraine loading dose (applies to galcanezumab users only):
    a) First fill or administration was for migraine dose rather than cluster

headache dose.

b) First claim was pharmacy claim with ≤30 days' supply and syringe quantity of 2.0, or a medical claim indicating office administration.

5. Age: At least 18 years of age on the date of the first qualifying dispensing or injection.
6. Continuous enrollment requirement: At least 183 days of continuous medical and prescription enrollment in the HIRD on or before the first qualifying dispensing or injection (index date). A 30-day gap in enrollment will be permitted.
7. New user (meets one of the following criteria):
    a. Incident new user: No dispensing of galcanezumab or the comparator of interest (for example, topiramate for the comparison of galcanezumab to topiramate) in the 183 days prior to the index date or with a days' supply extending into the 183 days prior to the index date, OR
    b. Prevalent new user:
        i. No dispensing of galcanezumab in the 183 days prior to the index date or with a days' supply extending into the 183 days prior to the index date.
        ii. A dispensing of the comparator of interest in the 183 days prior to the index date or with a days' supply extending into the 183 days prior to the index date.
8. Cluster exclusion: Patients with a cluster headache diagnosis on or before the index date will be excluded.
9. Migraine diagnosis or as-needed migraine treatment: At least one diagnosis code for migraine or at least one dispensing/injection of triptans, ditans, or gepants prior to or on the index date.
10. CGRP exclusion: No dispensing/injection of a CGRP antagonist (**including galcanezumab**) on or before the index date. Eventual use of galcanezumab does not prevent assignment to the comparator group.
11. Cardiovascular events exclusion: Patients with acute cardiovascular events up to 12 months prior to index will be excluded. However, this criterion will not apply to patients in the recent acute cardiovascular events and/or serious cardiovascular risk special population.
12. Epilepsy exclusion for topiramate comparison (applies to both galcanezumab users and topiramate users): Patients with an epilepsy diagnosis code on or before treatment initiation (index) will be excluded from analyses comparing galcanezumab to topiramate.

10.8.2.2.4. Study Period

The index date for the prevalent new-user analysis of serious cardiovascular events is defined in Section 10.8.2.2.3.

Follow-up of the index treatment episode for serious cardiovascular events will begin on 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
- Initiation of the contrasting agent (in other words, comparator user initiates galcanezumab or galcanezumab user initiates the comparator)
- End of the first continuous exposure episode, as defined in Section 10.4.1
- Health plan disenrollment
- Death, or
- End of data availability.

10.8.2.2.5. Data Analyses

If a sufficient number of patients have accrued for the comparison of serious cardiovascular events in incident galcanezumab and topiramate users, we will estimate risk ratios and 95% confidence intervals for serious cardiovascular events, comparing qualifying galcanezumab users to qualifying comparator users according to the study entry criteria stated in Section 10.8.2.1.3. Kaplan-Meier analysis will be used to compute cumulative incidence proportions ("risk"), risk ratios, and risk differences for different points in time after treatment initiation. Follow-up will be limited to first-treatment episode (Section 10.4.1).

To control for measured confounding factors, we will construct propensity scores from baseline covariates as described in Section 10.8.2.1.5. Covariates (Section 10.4.3) including demographics, comorbidities, medications, and health care utilisation will be considered for propensity score creation. 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 as described in Section 10.8.2.1.5.

10.8.2.2.5.1. Sensitivity Analyses

Sensitivity analyses will be carried out to address selection bias due to prevalent users (Section 10.10).

10.8.2.3. Phase 2: Comparative Analysis of Malignancies

10.8.2.3.1. Study Design

For malignancies excluding NMSC, we will use an incident new-user design (19) with a composite comparator group of oral prophylactic migraine medications other than CGRPs including galcanezumab. A secondary comparator, onabotulinumtoxinA injection will also be assessed.

10.8.2.3.2. Setting

Qualifying patients, their treatment group assignment, and their outcome status will be identified in the HIRD. Further description of the HIRD can be found in Section 10.2. Medical records will not be used in this analysis. National Death Index data will be used to verify outcome status as described in Section 10.4.2 and Section 10.5.

10.8.2.3.3. Study Population

The incident new-user comparative analysis for malignancy excluding NMSC will include patients meeting the following study entry criteria which will result in the construction of four distinct cohorts: (1) galcanezumab users for comparison to oral migraine prophylaxis comparator users, (2) topiramate users, (3) galcanezumab users for comparison to onabotulinumtoxinA users, and (4) onabotulinumtoxinA users. Study attrition will be reported for each step for each of the four cohorts.

1. Prophylactic migraine treatment: At least one dispensing of one of the following medications on or after 27 September 2018:
    a. Galcanezumab
    b. Oral prophylactic migraine medication(s) other than CGRP antagonists:
        i. Antiepileptics:
            - Divalproex sodium
            - Sodium valproate
            - Topiramate
            - Gabapentin
        ii. Beta-blockers:
            - Metoprolol
            - Propranolol
            - Oral timolol
            - Nadolol
            - Atenolol
            - Nebivolol
        iii. Calcium channel blocker:
            - Verapamil
        iv. Antidepressants:
            - Amitriptyline
            - Venlafaxine, or
    c. OnabotulinumtoxinA.
2. Migraine loading dose (applies to galcanezumab users only):
    a. First fill or administration was for migraine dose rather than cluster headache dose.
    b. First claim was pharmacy claim with ≤30 days' supply and syringe quantity of 2.0, or a medical claim indicating office administration.
3. Age: At least 18 years of age on the date of the first qualifying dispensing or injection.
4. Continuous enrollment requirement: At least 183 days of continuous medical and prescription enrollment in the HIRD on or before the first qualifying dispensing or injection (index date). A 30-day gap in enrollment will be permitted.
5. Incident new user: No dispensing of galcanezumab or the comparator of interest (for example, onabotulinumtoxinA for the comparison of galcanezumab to onabotulinumtoxinA) in the 183 days prior to the index date, and no dispensing of

galcanezumab or the comparator of interest with a days' supply extending into the 183 days prior to the index date.

6. Multiple index drugs: Patients with a fill for both galcanezumab and the comparator of interest (for example, onabotulinumtoxinA for the comparison of galcanezumab to onabotulinumtoxinA) on the index date will be excluded.
7. Cluster exclusion: Patients with any cluster headache diagnosis on or before the index date will be excluded.
8. Migraine diagnosis or acute migraine treatment: Patients with at least one diagnosis code for migraine or at least one dispensing/injection of triptans, ditans, or gepants prior to or on the index date.
9. CGRP exclusion: Patients with a dispensing/injection of a non-galcanezumab CGRP antagonist on or before the index date will be excluded.
10. Prior malignancies exclusion: Patients with a diagnosis of malignancy other than NMSC prior to the index date will be excluded.
11. Drug-specific exclusion for composite oral migraine prophylaxis comparison: Patients with a diagnosis code on or before treatment initiation (index) for a non-migraine indication for their qualifying drug will be excluded from analyses comparing galcanezumab to non-CGRP oral migraine prophylaxis drugs. The following list of drug-indication pairs will be further refined in the SAP, by individual drug. Briefly, by class:
    a. Antiepileptics: index medication is an antiepileptic, and patient has diagnosis of epilepsy on or before index
    b. Beta-blockers: index drug is a beta-blocker, and patient has a diagnosis of hypertension, angina, coronary atherosclerosis, atrial fibrillation, myocardial infarction, essential tremor, hypertrophic subaortic stenosis, or pheochromocytoma on or before index
    c. Calcium-channel blockers: index drug is a calcium-channel blocker, and patient has a diagnosis of hypertension on or before index, and
    d. Antidepressants: index drug is an antidepressant, and patient has a diagnosis of depression on or before index.

10.8.2.3.4. Study Period

In the analysis comparing galcanezumab to an oral migraine prophylaxis comparator, the index date is defined as the patient's first dispensing of galcanezumab or an oral migraine prophylaxis comparator. In the analysis comparing galcanezumab to onabotulinumtoxinA, the index date is defined as the patient's first dispensing of galcanezumab or onabotulinumtoxinA.

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, or
- End of data availability.

10.8.2.3.5. Data Analyses

If a sufficient number of patients have accrued for the comparison of serious cardiovascular events in incident galcanezumab and topiramate users, we will estimate risk ratios and 95% confidence intervals for malignancies excluding NMSC, comparing qualifying galcanezumab users to qualifying comparator users according to the study entry criteria stated in Section 10.8.2.1.3. Kaplan-Meier analysis will be used to compute cumulative incidence proportions ("risk"), risk ratios, and risk differences for different points in time after treatment initiation. Follow-up will be limited to first-treatment episode (Section 10.4.1). Risk ratios and differences will be presented overall and by organ site. Risk ratios will also be adjusted based on results from outcome adjudication and National Death Index linkage.

To control for measured confounding factors, we will construct propensity scores from baseline covariates as described in Section 10.8.2.1.5. Covariates (Section 10.4.3) including demographics, comorbidities (including the indications for which some comparator users were excluded in step 11 in Section 10.8.2.3.3), medications, and health care utilisation will be considered for propensity score creation. 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 as described in Section 10.8.2.1.5.

10.8.2.3.5.1. Sensitivity Analyses

A sensitivity analysis will be carried to re-include the comparator users excluded in step 11 in Section 10.8.2.3.3. Non-migraine indication diagnoses will be included in the propensity score model and balanced between treatment groups as described above for the main analysis. Additional sensitivity analyses will address residual confounding by smoking and body mass index, and will also address concomitant medication use, and cancer latency (Section 10.10).

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.

10.9.1. HealthCore Quality Control Procedures

To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

Protocols, Statistical Analysis Plans, and Reports: Deliverable documents are drafted by the Principal Investigator and then reviewed by the Principal Scientist and Project Manager. After the review by the Principal Scientist and Project Manager, the document is returned to the Principal Investigator for editing and finalisation of the document for delivery to Eli Lilly and Company. Prior to delivery, a standard scientific quality check log is filled out by the Principal Investigator and a standard project management quality control log is filled out by the Project Manager. Upon receipt of feedback from Eli Lilly and Company, the Principal Investigator

revises the document and additional rounds of internal review are conducted by the Principal Scientist and Project Manager, and the quality control logs are filled out prior to delivery of the subsequent draft to Eli Lilly and Company. Analysts may also review documents, or flagged aspects of documents, when their insight is needed. This process includes all items accompanying document deliverables, including table shells, populated tables, and code lists.

Populated tables, data analyses: Analysts complete all data management and analyses and populate the table shells accompanying each report. The Principal Investigator conducts quality control reviews of analysts' data management and analyses across platforms (for example, Instant Health Data, SAS). When an analysis is particularly complex or unusual, the Principal Investigator or another HealthCore Analyst independently carries out some or all aspects of the analysis ("double coding") to ensure accurate data management and results. The Principal Investigator, Principal Scientist, and Project Manager each review all populated tables for internal consistency, plausibility, and formatting as part of the document deliverable quality control process described above.

Documentation: HealthCore's research team documents study progress and scientific and quality review of all study activities and deliverables (for example, protocol, data management, data analysis, reports, manuscripts, and so on) 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.

10.10. Limitations of the Research Methods

Uncertainties Related to Medication Sampling

Free medication samples are frequently distributed as part of a new drug's marketing approach and are not captured in healthcare claims because they do not produce costs for the provider or patient. As a result, a patient whose first exposure to galcanezumab was through sample receipt would not have their first exposure captured in claims. To address the resulting potential for exposure misclassification and prevalent user bias, our comparative analyses are restricted to the subgroup of galcanezumab patients with two syringes (the amount expected for a loading dose) in their first galcanezumab claim, thus generalisability to the entire galcanezumab user population may be affected. We will conduct sensitivity analyses including patients with only one syringe in their first galcanezumab claim and set their index date back 30 days to account for possible exposure due to sample receipt in the previous month.

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. If the target study size cannot be reached, comparative analyses will not be implemented. Without the comparative analyses, the

primary analyses will be descriptive, and comparisons across drug treatment groups should not be attempted given a likely imbalance of confounders.

Confounding by Indication

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 (29). To reduce the potential for this indication bias, we will exclude patients with non-migraine indications on or before the index date as described in the inclusion/exclusion criteria provided for each analysis in Section 10.8. For the malignancies outcome, a sensitivity analysis will be carried out to re-include the comparator users with non-migraine indications; we will then use propensity score matching to balance the frequency of these indications between galcanezumab and comparator users.

Residual 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, administrative claims do not include all the important prognostic factors related to ischaemic heart diseases such as smoking (30), body mass index (31), and migraine severity (32). 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.

We will conduct sensitivity analyses to address residual confounding by smoking status and body mass index (BMI). Preliminary analyses demonstrate that BMI is available for approximately 28% of galcanezumab users meeting study entry criteria for this analysis, and smoking status is documented for ~12%. Given that these variables are non-missing for at least 10% of the cohort, and this comprises thousands of galcanezumab users, we will re-run our risk ratio analyses among patients for whom all data are available, restricting to patients for whom BMI or smoking status are available. To address migraine severity, an unmeasured confounder, we will conduct a bias analysis to recalculate our risk ratios for relevant outcomes adjusting for migraine headache days, informed by external data from the literature. Further details of these sensitivity analysis are provided in the SAP.

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 (for example, 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 to examine the potential for outcome misclassification, and

link claims data to the National Death Index to ascertain additional cases, increasing the validity of case status. We will adjust risk estimates and risk ratios in the comparative analyses accordingly.

Selection Bias Due to Prevalent Users

The prevalent new-user design compares new users of galcanezumab – including new switchers from the comparator drug, with new or prevalent users of the comparator drug. An underlying assumption for a valid effect estimate is that the decision to switch from the comparator to galcanezumab 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 bias due to prevalent users because of unmeasured confounding.

Informative Censoring

For serious cardiovascular events, galcanezumab discontinuation or switching might be related to early cardiovascular symptoms or signs. This could have made discontinuation or switching a predictor for serious cardiovascular events, 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.

Generalisability

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 comparative analysis findings for the subgroup of patients in each cohort 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 6 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 distinct cohort. Second, the prevalent new-user design proposed for the serious cardiovascular events analyses addresses treatment switching by including patients who switched from the comparator to galcanezumab. 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.

Latency Period of Malignancy Diseases

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 (22) of malignancies corresponding to cancer initiation and promotion. In addition, cancer outcome rates by cumulative exposure 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.

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/Adverse Reactions

This is a non-interventional study based on secondary data use, and therefore no individual case safety report reporting is required. The protocol-defined adverse events (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.

13. Plans for Communication and Dissemination of Study Results

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

If sufficient sample size is achieved to conduct Phase 2 (comparative) analyses, results from Phase 2 will 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:

[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**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	9.8
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.8
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

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

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.4.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3
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: _____

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Approval	PPD 26-Oct-2022 15:56:10 GMT+0000

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