1. Protocol I5Q-MC-B004: preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH)

GPORWE-2016-4215

Confidential Information

galcanezumab (LY2951742)

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2. Abstract

- Title: Protocol I5Q-MC-B004: preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH)
- Rationale and background: Monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or the CGRP receptor have recently been demonstrated to be efficacious in clinical trials in the prevention of migraine, with galcanezumab, erenumab, and fremanezumab receiving approval in the United States and European Union. These new medications are specifically designed to target migraine pathophysiology. Observational studies are needed to confirm real-world effectiveness.
- Research question and objectives: The overall aim is to estimate real-world effectiveness and associated outcomes, as well as describe treatment patterns, in patients with migraine in routine clinical care who are switching or initiating pharmacologic treatment for migraine prevention. The primary comparison of interest will be between galcanezumab and oral standard of care. However, patients who are initiating other CGRP antagonists or botulinum toxin A or B will also be eligible to participate in the study and included in descriptive and statistical comparisons as sample sizes permit.
- Study design: Prospective, multicenter, international, 2-stage noninterventional study. Stage 1 is a cross-sectional, single-day assessment which can be office-, phone-, or web-based. Stage 2 is a 24-month longitudinal assessment. Entry into Stage 2 is dependent on which preventive treatment the patient is initiating. During Stage 2:
    - Postbaseline visits will occur at Months 3, 6, 12, 18, and 24, and can be office-, phone-, or web-based. Additional office visits are allowed as this is an observational study.
    - Patients will enter headache information into a personal electronic device each time they experience a headache throughout the longitudinal assessment.
    - Healthcare resource utilization will be collected monthly via personal electronic device.
- Population: Adult patients with migraine who are switching or initiating new preventive treatment in clinical practice settings in multiple countries.
- Variables:
    - demographics
    - concomitant medications
    - medical history and comorbidities
    - migraine history, migraine treatment history, and current disease state
    - preventive and acute treatment use and rationale for changes
    - migraine headache days and headache days, headache hours, severity, and symptoms

  - health-related quality of life
  - migraine-related burden and disability
  - healthcare resource utilization
  - work productivity and activity impairment
  - acute treatment outcomes
  - medication adherence, persistence, and satisfaction

- Data sources/Data collection: electronic data capture system with electronic clinical outcome assessment
- Study size: Stage 1 will include a sufficient number of patients to achieve approximately 4100 total patients entering Stage 2. The study will enroll patients from multiple sites and countries, with enrollment targets stratified by country.
- Data analysis: Stage 1 assessments will be descriptive. Stage 2 will include both descriptive and statistical comparisons. Treatment comparisons of galcanezumab to other migraine preventive treatments will be conducted by drug class or individually based on the sample sizes available. The primary comparison will be to oral standard of care overall.
- Milestones (anticipated):
  - Study start: 2020
  - Observation period: 2 years
  - Study report: Aimed to be provided within participating countries' required reporting period, but at least within 6 months of the end of data collection.

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4. Background and Rationale

Migraine Disease State

Migraine is a common disabling primary headache disorder (AHS 2019). In addition to the pain of migraine attacks and burdensome symptoms, migraine has a significant impact on patient's health-related quality of life, including physical, emotional, and social aspects of daily living, and effects on family, work, and social relationships (Chaushev and Milanov 2009; Abu Bakar et al. 2016). Globally, migraine is ranked second as a cause of disability expressed as years lived with disability (GBD 2017).

The etiology of migraine is not clear, but likely includes both genetic and environmental components (Magis and Schoenen 2012).

A recent global review has estimated that the global prevalence of migraine is 11.6%, with regional values including 9.7% in North America, 10.1% in Asia, and 11.4% in Europe (Woldeamanuel and Cowan 2017). The prevalence of migraine appears to be higher in females and in mid-life (Buse et al. 2012, 2013; Woldeamanuel and Cowan 2017).

The clinical presentation of migraine varies widely between patients, including the intensity of headache attack pain, and the pattern of associated symptoms, such as photophobia, phonophobia, nausea, vomiting, osmophobia, and movement sensitivity (Lipton and Silberstein 2015). Auras are present in about one-quarter of adults with migraine (Merikangas 2013).

Migraine is associated with a number of comorbidities, including psychiatric disorders, sleep disorders, fatigue, cardiovascular risk factors, and cardiovascular and cerebrovascular disease (Merikangas 2013; Schwedt 2014; Diener et al. 2015). The presence of comorbidities can impact migraine prognosis, treatment, and clinical outcomes (Silberstein et al. 2007; Jette et al. 2008; Merikangas 2013). In addition, comorbidities may impact patients' health-related quality of life and disability (Merikangas 2013).

Patients with migraine can experience a progression of increasing headache frequency over time, which can ultimately result in a transformation from episodic to chronic migraine (Turner et al. 2013; Schwedt 2014).

Form of Migraine	Frequency of Headache and Migraine Headache per Month
Episodic	Fewer than 15 migraine days or less than 15 headache days per month[a]
Chronic	At least 15 headache days per month, of which at least 8 are migraine[b]

[a] AHS 2019.
[b] ICHD-3 2018.

Among the most important factors that increase the risk of progression are attack frequency, overuse of acute medications for migraine, ineffective acute therapy, obesity, depression, and stressful life events (Schwedt 2014; Lipton and Silberstein 2015; May and Schulte 2016).

Migraine Treatment

Therapeutic management of migraine in current evidence-based guidelines recommend individualized pharmacological management of acute attacks, generally using specific migraine

medications including triptans and ergotamine, and non-specific medications including non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and combination analgesic/NSAIDs (Loder et al. 2012; Marmura et al. 2015). Preventive therapy is generally recommended for patients who have at least 4 migraine headache days per month or significant impairment due to their migraine attacks. The American Headache Society (AHS)/American Academy of Neurology (AAN) Guidelines for migraine prevention include several classes of medication with highest level (Level A) of evidence supporting their safety and efficacy, such as divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol, and botulinum toxin for chronic migraine (Loder et al. 2012; Simpson et al. 2016). However, treatment guidelines as well as approved preventive therapies vary by geography.

Recently, monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) or the CGRP receptor have been widely explored and shown to be efficacious in clinical trials in the prevention of migraine. Among these, galcanezumab, erenumab, (1-3), and eptinezumab have received approval in the United States (US) and European Union (EU). Additionally, small-molecule CGRP antagonists are currently available for the acute treatment of migraine and are being studied for the prevention of migraine. This new therapeutic approach, with a novel mechanism specifically designed to target migraine pathophysiology, provides an additional and much needed treatment option for patients with migraine.

Consequently, updated recommendations on migraine treatment have recently been published. Both the AHS and European Headache Federation (EHF) note these new CGRP antagonists are effective in migraine prevention based on the available clinical trial data, but that real-world data are needed (AHS 2019; Sacco et al. 2019). AHS also states that there is a need to achieve cost-effective care while ensuring access to those most appropriate for initiating treatment with these new monoclonal antibodies.

Observational Studies and Registries

Observational studies can be used to examine real-world use of treatments in routine clinical practice and in a real-world patient population. While such studies can be conducted to confirm the efficacy of drugs demonstrated in clinical trials, the large migraine observational studies conducted to date were not focused on evaluating effectiveness of migraine treatments (Buse et al. 2010; Blumenfeld et al. 2011; Katsarava et al. 2011, 2012; Lipton et al. 2016). Moreover, while these studies have provided valuable information regarding patients with migraine, they were conducted prior to the approval of the new CGRP antagonists and have other limitations, such as method of data collection and conduct in a single country.

Registries can also provide valuable real-world information regarding diseases and treatments. For example, the American Migraine Foundation (AMF) has launched a registry which will allow collection of long-term information regarding changes in headache patterns, healthcare resource utilization, diagnostic and management strategies, development of comorbidities, and responses to therapies in patients with migraine and other types of headaches (AMF [WWW]). Although the information collected through this registry is anticipated to provide valuable

insights regarding migraine, its purpose is not specifically to provide a comparison of effectiveness and outcomes data between preventive treatments.

Purpose and Overview of Study B004

Given the recent changes in treatment landscape for migraine prevention, Study I5Q-MC-B004 (B004) is being conducted to estimate real-world effectiveness and associated outcomes, as well as describe treatment patterns, in patients with migraine in routine clinical care who are switching or initiating pharmacologic treatment for migraine prevention.

The 3-month time point is of interest in this study. The EHF guideline notes that it is reasonable not to stop treatment with a CGRP antagonist prior to 3 months, even in the absence of a clinical response, as clinical trial data indicate some patients may see improvement with continuation of treatment (Nichols et al. 2019; Sacco et al. 2019).

Later time points are also of interest as recommendations regarding duration of treatment with monoclonal antibodies are evolving. The EHF guideline recommends considering discontinuation of CGRP antagonists after 6 to 12 months of treatment (Sacco et al. 2019). AHS (2019) recommends reassessing the benefits of monoclonal antibodies after the first 3 to 6 months of treatment, depending on dosing frequency, and continuing treatment only if a benefit has been demonstrated.

5. Objectives

This study will enroll patients with migraine in routine clinical care who are switching or initiating pharmacologic treatment for migraine prevention. The treatments of interest for the primary objective are patients initiating galcanezumab or oral standard of care. However, for secondary and exploratory objectives, additional treatment comparisons may be conducted as sample sizes permit, including comparisons to other CGRP antagonists or botulinum toxin A or B.

5.1. Primary Objective

The primary objective of this multi-country noninterventional study is to compare the effectiveness of galcanezumab to oral migraine preventive standard of care overall in adult patients with migraine who are switching or initiating preventive treatment in clinical practice settings. Specifically, this will estimate the proportion of patients in the longitudinal follow-up who achieve a clinically meaningful reduction from baseline in monthly migraine headache days at Month 3. Migraine headache days will be determined from patient responses in the electronic case report form (eCRF) at the 3-month visit. Clinically meaningful will be defined as

- ≥50% reduction from baseline at Month 3 for episodic migraine
- ≥30% reduction from baseline at Month 3 for chronic migraine

5.2. Secondary Objectives

Secondary objectives include those for the cross-sectional assessment (Stage 1) and those for longitudinal follow-up (Stage 2).

5.2.1. Cross-Sectional Assessment (Stage 1)

Secondary objectives for the cross-sectional assessment are to:

- Describe the patient demographics and disease characteristics, including symptoms, severity, migraine history, and migraine-specific disability
- Describe the baseline migraine-specific treatment patterns, including treatment choice and physician-reported rationale for migraine preventive drug initiation or switching, as well as treatment patterns related to acute medications for the treatment of migraine
- Describe acute treatment outcomes using the Migraine Treatment Optimization Questionnaire 6-item version (mTOQ-6)
- Describe historical migraine-specific treatment patterns for preventive and acute medications
- Describe medical history and comorbidities

5.2.2. Longitudinal Follow-up (Stage 2)

Stage 2 evaluations will include both descriptive and statistical comparisons over a 24-month period based on the timelines in the data collection schedule in Attachment 1. Treatment

comparisons of galcanezumab to other migraine preventive treatments will be conducted by drug classes or individually based on the sample sizes available.

Secondary objectives for the longitudinal follow-up are to:

- Compare the long-term, real-world effectiveness of galcanezumab to other migraine preventive treatments on reductions in monthly migraine headache days as collected from the CRF, including:
    - for episodic migraine, the proportion of patients with reduction from baseline ≥50%, ≥75%, and 100% in monthly migraine headache days
    - for chronic migraine, the proportion of patients with reduction from baseline ≥30%, ≥50%, ≥75%, and 100% in monthly migraine headache days
    - mean change from baseline in number of monthly migraine headache days
- Compare treatment discontinuation rates, all-cause time-to-treatment-discontinuation, and time-to-treatment-discontinuation for negative reasons (lack of effectiveness, intolerance to medication, lack of medication availability) between galcanezumab and other migraine preventive treatments initiated at baseline
- Describe treatment patterns specific to migraine preventive medication use over the 24-month follow-up period, including persistence, number of switches, proportion of patients switching from one class to another, physician-reported rationale for discontinuations (switches), and treatment choices (or terminal discontinuation). This includes switching patterns between CGRP antagonists.
- Describe treatment patterns specific to the acute treatment of migraine attacks, including switching or initiating new acute treatment, as well as reasons for treatment discontinuation.
    - compare changes in acute medication use for galcanezumab to other migraine preventive treatments with respect to mean change from baseline in the number of monthly days with acute headache medication use
- Assess acute treatment outcomes using the mTOQ-6
- Assess symptoms associated with migraine and attack characteristics
- time between headache attacks and interictal burden using the Migraine Interictal Burden Scale (MIBS-4)
- impact of headache on daily life using the Headache Impact Test-6 (HIT-6)
- physical and emotional impact on functioning using the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1)

  - compare changes in functioning for galcanezumab to other migraine preventive treatments with respect to mean changes in the Role Function-Restrictive Domain of the MSQ v2.1

- headache-related disability using the Migraine Disability Assessment (MIDAS)
- patient global impression of the severity of migraine using the Patient Global Impression of Severity (PGI-S) scale
- Assess migraine-specific economic burden, including:
  - work productivity and regular activities using the Work Productivity and Activity Impairment Questionnaire (WPAI)
  - healthcare resource utilization and employment status using the Health Care Resource Utilization questionnaire (HCRU) (US Food and Drug Administration Modernization Act [FDAMA] Objective)
    - US FDAMA Objective: compare the reduction of healthcare resource utilization between galcanezumab and oral migraine preventive standard of care
  - estimates of the total cost burden, including direct healthcare expenditures estimated from the HCRU questionnaire, costs associated with resource used taken from country-specific references, and indirect costs associated with work absenteeism and lost work productivity estimated from the MIDAS (US FDAMA Objective)
    - US FDAMA Objective: compare the reduction of total cost burden between galcanezumab and oral migraine preventive standard of care
- Assess other outcomes, including:
  - patient satisfaction with medication using the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M)

5.3. Exploratory

- Describe the proportion of patients using opioids or barbiturates where these are approved treatment choices.
- Describe migraine disease characteristics, including clinical features and symptoms, collected by headache diaries.

The protocol was amended to shorten the duration of PROs collected in the study, so the following questionnaires were collected only for the patients enrolled prior to the implementation of this amendment:

- Assess general health, including:
  - depression symptomatology using the Patient Health Questionnaire-8 (PHQ-8)

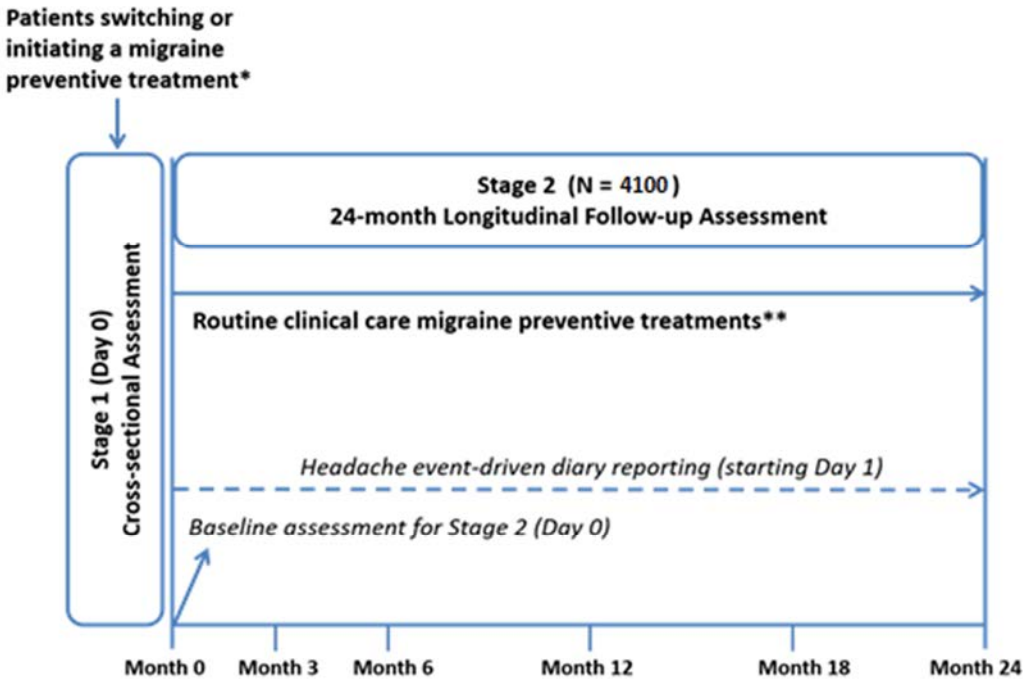
  - anxiety symptomatology using the 7-item Generalized Anxiety Disorder Scale (GAD-7)
  - presence and severity of allodynia using the Allodynia Symptom Checklist (ASC-12).

- Assess migraine preventive treatment adherence using the Medication Adherence Reporting Scale (MARS-5).

6. Research Design

6.1. Summary of Research Design

This study is a 24-month prospective, multicenter, international, 2-stage noninterventional study reflecting treatment within real-world settings of patients with migraine who are switching or initiating pharmacologic treatment for migraine prevention. The study design is illustrated in Figure 1.



* All patients must meet the study selection criteria listed in Section 6.3.1 to participate in the study.
** Patients who are receiving one of the migraine preventive treatments/classes listed in Section 6.3.2 in routine clinical care at Month 0 will be eligible to participate in Stage 2.

Figure 1. Study design.

Stage 1 will be a cross-sectional, single-day assessment of demographics, disease characteristics, and baseline and historical migraine treatment patterns, including preventive and acute treatments, of patients who qualify for the study. All patients must meet the study selection criteria listed in Section 6.3.1 to participate in the study.

The purpose of Stage 1 is two-fold. It will be used to capture important real-world information in qualified patients. Additionally, Stage 1 will be used to generate a pool of patients, from

which patients eligible for Stage 2 will be identified. A sufficient number of patients will be enrolled into Stage 1 to achieve approximately 4100 total patients entering Stage 2. In order to evaluate the study objectives in additional geographies, the number of patients in Stages 1 and 2 may be increased and their proportion is flexible, based on operational needs.

Stage 2 will be a 24-month longitudinal follow-up assessment. Patients who are receiving one of the migraine preventive treatments/classes listed in Section 6.3.2 in routine clinical care on Day 0 will be eligible to participate in Stage 2. Enrollment of eligible patients into Stage 2 will be consecutive unless certain imbalances are observed. In this scenario, capping enrollment in a particular treatment group may be considered in order to achieve the sample size estimates and treatment group allocation described in Section 7.1.

At Month 0 (Day 0), Stage 1 cross-sectional assessments will be collected, as well as baseline measures for those patients entering Stage 2. Migraine characteristics, including frequency of headache days and migraine headache days, will be collected by the investigator on Day 0 and will be based on the prior 30 days. If a patient does not initiate the index preventive treatment within 14 days of the baseline visit, they will be offered the opportunity to provide updated responses to the relevant variables for baseline migraine characteristics at the time that they initiate the first preventive treatment administration. If the patient does not provide updated responses to the relevant variables for baseline migraine characteristics, they will be excluded from the study. A maximum of 56 days will be allowed between treatment assignment and first dose; patients whose first dose occurs 57 or more days after treatment assignment will be excluded from the study. Baseline measures including PROs should be completed prior to initiating the first preventive treatment. However, patients who complete baseline measures including PROs in the 3 days after initiating the first preventive treatment will still be allowed to remain in the study.

Subsequent data collection for patients in Stage 2 will occur post-baseline at Month 3, Month 6, and every 6 months thereafter through Month 24, with the exception of data to be collected in the patient headache diary and the HCRU. For data collection in the diary, patients will be instructed to make event-driven entries (within 48 hours of the onset of a headache). Reminders will be sent instructing patients to review entries for accuracy, or to provide responses for any headaches that were not previously recorded. Data collection for the HCRU will occur monthly via an electronic device.

Multiple sites and countries will participate in this study; enrollment targets will be stratified by country.

Site selection will include representation of facilities that diagnose and treat migraine within each country. Patient stipends will be available for the completion of questionnaires, where allowable, per local regulations.

6.2. Data Collection

This study will use an electronic data capture (eDC) system. The site maintains a separate source for the data entered by the site into the eDC system.

The investigator or designated site personnel will transfer data from the patient's medical record into electronic case report forms (eCRF) within the eDC system directly at the site for collection of patient characteristics at baseline, as well as recording details related to treatment patterns and disease status throughout the study.

In addition, an electronic device will be used in this study to collect electronic clinical outcomes assessment (eCOA) measures at the Stage 1 (cross-sectional) visit and Stage 2 Month 0, Month 3, Month 6, Month 12, Month 18 and Month 24 (longitudinal) visits. For eCOA data where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

- For remote visits, patient headache diary entries, and monthly HCRU entries, eCOA data will be entered by the patient into a personal electronic device. Web-based data entry will also be available.
- For office visits, eCOA data will be entered directly by the patient on either their personal electronic device or using an electronic device at the site, such as a tablet. The eCOA data entries do not need to be completed at the office.

If eCOA records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Site personnel will be trained on the eDC and eCOA technologies.

Data verification will take place and any data verification activities will be executed in compliance with a Data Management Plan (including electronic edit checks). If medical coding is required, this has to be reviewed by qualified personnel. Data verification requirements might need to be amended based on any observed data trends.

Details regarding treatment changes, such as discontinuations, switches, augmentation, and initiation of new therapies, following the start of Stage 2 will be recorded.

Patients with treatment changes, including treatment discontinuation, can remain in the study.

Patients who are lost to follow-up or who withdraw from the study will be terminated from study participation following confirmation from the site and a reason for withdrawal will be collected when available. If a patient is identified as being inadvertently enrolled, a discussion must occur between the medical monitor and the investigator to determine if the patient may continue in the study. If it is agreed that the patient should not continue in the study, the patient will be terminated from study participation and will not be eligible for analysis. Patients who are terminated from study participation cannot be re-enrolled in the study.

6.3. Study Population

This study will enroll patients with migraine in routine clinical care who are switching or initiating pharmacologic treatment for migraine prevention; refer to Section 6.3.1 for study selection criteria for all patients and Section 6.3.2 for criteria specific to Stage 2.

Patients can be included in the study if they are followed in a registry.

6.3.1. Selection Criteria

Inclusion criteria for this study are the following:

1. A diagnosis of migraine, with or without aura, or chronic migraine, as determined by the study investigator and in consideration of International Headache Society International Classification of Headache Disorders – 3rd edition guidelines (ICHD-3 2018).
2. Under the care of the study investigator prior to entering the study or the study investigator will be providing routine migraine care throughout the duration of the study.
3. Able to reliably report on historical details regarding frequency of monthly migraine headache days during the past month, in the opinion of the study investigator.
4. Switching or initiating a new pharmacologic migraine preventive treatment within the usual course of care and according to the approved label in the respective country. Note that:
    a. The initiating treatment cannot be one that has been taken by the patient in the prior 12 months.
    b. Concurrent migraine preventive treatment, including pharmacological, nonpharmacological, and any over-the-counter supplement taken specifically for migraine prevention, is allowed, provided the existing treatment(s) has (have) been at a stable dose for at least 3 months prior to entry. For concurrent nonpharmacological treatment, the regimen must have been stable for at least 3 months prior to entry.
5. Adult patients ≥18 years of age and in accordance with country-specific requirements.
6. Able to provide written informed consent as approved by Eli Lilly and Company (Lilly) or its designee, and the Investigational Review Board/Ethical Review Board governing the site and/or study.
7. Sufficient literacy in the local language and cognitively able to understand and complete patient self-rated questionnaires.
8. Access to internet or personal device for completion of patient self-rated questionnaires and diary. The personal device must meet requirements for the eCOA platform.

Exclusion criteria for this study are the following:

9. Are investigator site personnel directly affiliated with the study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
10. Are Lilly employees.
11. Are terminally ill.

12. Are participating in another study that includes treatment with an investigational drug and/or intervention at the same time as enrollment in the current study.
13. Do not initiate the index preventive treatment within 56 days of the baseline visit or treatment assignment.

6.3.2. Patient Groups

The following migraine preventive treatments will be evaluated in Stage 2. Patients will be eligible to enter Stage 2 if they are initiating one of the following treatments in routine clinical care on Day 0.

- CGRP antagonists, including galcanezumab
- beta blockers
- anticonvulsants
- tricyclic antidepressants
- calcium channel blockers
- angiotensin II receptor antagonists
- botulinum toxin A or B, or
- a medication locally approved for the prevention of migraine.

From these treatments, the following treatment groups are of primary interest in this study.

- galcanezumab, and
- oral migraine preventive standard of care overall (will be defined in the statistical analysis plan [SAP] based on the classes of beta blockers, anticonvulsants, tricyclic antidepressants, calcium channel blockers, and angiotensin II receptor antagonists).

Additional treatment groups will be described by drug classes or individually and additional statistical comparisons will be based on the sample sizes available, including botulinum toxin A or B and other CGRP antagonists.

Any new preventive treatments that become available during the time period of the study and are reimbursed will be allowed in the study but will not be considered an oral migraine preventive standard of care for the primary objective.

Patients may terminate study participation at any time and at their own discretion by informing the appropriate study personnel of their desire to not be contacted again. If a patient enrolls in a study involving an investigational product, the patient is to be terminated from study participation. Patients can also be terminated from study participation if the investigator decides the patient should be discontinued.

6.4. Study Therapies

Treatment pattern and treatment initiation or changes are solely at the discretion of the investigator and the patient. There will be no attempt to influence the prescribing patterns of any individual investigator. Treatment for migraine will be prescribed in the usual standard of care and will not be provided by the study sponsor. Accordingly, treatment switches, augmentation,

dose adjustments, and the initiation of new therapies are permitted following the start of Stage 2. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study.

Patients who discontinue the initiating migraine preventive treatment can remain in the study and subsequent treatments will continue to be prescribed in the usual standard of care.

6.5. Variables/Measures

Details of the questionnaires for the secondary objectives are provided below. The timing of each assessment is provided in Attachment 1. It is anticipated that the total time to complete these questionnaires at each visit would be approximately 20 minutes.

Headache Impact Test-6: The HIT-6 is a patient-rated scale consisting of 6 questions. The questions assess impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress. There is also a question measuring the severity of headache pain (Kosinski et al. 2003; Yang et al. 2011). The recall period is 4 weeks, and response options include: never; rarely; sometimes; very often; and always. Each response option has an associated numerical score, with the summation across all 6 questions resulting in a total score ranging from 36 to 78. Higher scores indicate greater negative impact.

Migraine Disability Assessment: The MIDAS is a patient-rated scale which was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses. A higher value is indicative of more disability (Stewart et al. 1999, 2001). This instrument is considered highly reliable and valid and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999, 2001). For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability; Grade II (6 to 10) is for mild disability; Grade III (11 to 20) is for moderate disability; and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]) because a high proportion of patients with chronic migraine are in Grade IV (Blumenfeld et al. 2011).

Migraine-Specific Quality of Life Questionnaire version 2.1: The MSQ v2.1 is a self-administered health status instrument that was developed to address the physical and emotional impact on functioning that is of specific concern to individuals with migraine. The instrument consists of 14 items that address 3 domains: (1) Role Function-Restrictive; (2) Role Function-Preventive; and (3) Emotional Function (Jhingran et al. 1998b). The restrictive domain specifically measures disability as related to the impact on performance of normal activities, with the preventive domain addressing complete functional impairment and the emotional domain assessing the feelings related to disabling monthly migraine headache days. Responses are given using a 6-point Likert-type scale, ranging from “none of the time” to “all of the time.” Raw scores for each domain are computed as a sum of item responses, with the collective sum

providing a total raw score that is then converted to a 0 to 100 scale, with higher scores indicating a better health status, and a positive change in scores reflecting functional improvement (Jhingran et al. 1998a; Martin et al. 2000). The instrument was designed with a 4-week recall period and is considered reliable, valid, and sensitive to change in functional impairment due to migraine (Jhingran et al. 1998b; Bagley et al. 2012).

Patient Satisfaction with Medication Questionnaire-Modified: The PSMQ-M is a self-rated scale which measures patients' level of satisfaction with medication (Kalali 1999). The scale will be modified for use in this study, assessing 3 items related to the preventive treatment over the past 4 weeks: satisfaction; preference; and side effects. Satisfaction responses ranged from "very unsatisfied" to "very satisfied" with the current treatment. Preference compared the current medication to previous medications, with responses that ranged from "much rather prefer my previous medication" to "much rather prefer my current migraine preventive medication."

Migraine Interictal Burden Scale: The MIBS-4 measures the burden related to headache in the time between attacks. The self-administered instrument consists of 4 items that address disruption at work and school, diminished family and social life, difficulty planning, and emotional difficulty. The questionnaire specifically asks about the effect of the disease over the past 4 weeks on days without a headache attack. Response options include: don't know/not applicable; never; rarely; some of the time; much of the time; or most or all of the time. Each response has an associated numerical score, with the summation across all 4 items resulting in a total score ranging from 0 to 12, and the level of interictal burden being categorized into the following: 0 for none; 1-2 mild; 3-4 moderate; and $\geq$5 severe (Buse et al. 2007, 2009).

Work Productivity and Activity Impairment Questionnaire: The WPAI is a patient-reported instrument developed to measure the impact on work productivity and regular activities attributable to a specific health problem (Reilly et al. 1993); for this study, the questions are specific to migraine. Recall period is the past 7 days. The scale contains 6 items that measure: 1) employment status; 2) hours missed from work due to the specific health problem; 3) hours missed from work for other reasons; 4) hours actually worked; 5) degree health affected productivity while working; and 6) degree health affected productivity in regular unpaid activities. Four scores are calculated from the responses to these 6 items: absenteeism; presenteeism; work productivity loss; and activity impairment. Scores are calculated as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes.

Health Care Resource Utilization and Employment Status: The HCRU will be patient-reported and consists of 3 questions, asking about the number of hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred over the past month, outside of visits associated with their participation in the study. Patients are also specifically asked about the number of healthcare events that are related to migraine headaches. The baseline visit will include the same questions, however with the frame of reference being over the last 6 months. A question on employment status will also be solicited, given the correlation and potential confounding with health outcomes measures.

Migraine Treatment Optimization Questionnaire: The mTOQ is a validated, self-administered questionnaire that assesses the efficacy of current acute treatment and is demonstrated to measure an autonomous outcome domain related to, but distinct from, functioning and health-related quality of life over a 4-week period (Lipton et al. 2009). The items assess the domains of functioning, rapid relief, consistency, recurrence, and side effects (Serrano et al. 2015). This study will use the 6-item version (mTOQ-6) with Likert type response options of: never (0 points); rarely (0 points); less than half the time (1 point); and half the time or more (2 points). A total score from 0 to 8 is calculated by summing the points from 4 of the items (2-hour pain free; sustained 24-hour pain relief; comfortable to make plans; and perceived control) which define categories of acute treatment response: very poor (0); poor (1 to 5); moderate (6 to 7); and maximum (8) treatment efficacy (Lipton et al. 2015).

Patient Global Impression of Severity Scale: The PGI-S scale (Guy 1976) is a patient-rated instrument that measures illness severity. For this study, the patient will be instructed as follows: "Considering migraine as a chronic condition, how would you rate your level of illness?" The PGI-S includes a range of possible responses, from 1 ("normal, not at all ill") to 7 ("extremely ill").

6.5.1. Exploratory Variables/Measurements

Patient Headache Diary: Headache event-driven diary reporting will begin on or after Day 1. Patients will be asked to record headache information via headache diary entries using their personal electronic device or web portal. Study investigators should encourage patients to complete the diary each time they experience a headache, within 48 hours of onset. Patients will receive a reminder to go into the diary to either verify all headache information has been entered or, if necessary, to update the diary.

The diary will be used by the patient to report:

- headaches, including duration and severity
- migraine-associated symptoms, and
- use of any acute medication, by medication class.

The protocol was amended to shorten the duration of PROs collected in the study, so the following questionnaires were collected only for the patients enrolled prior to the implementation of this amendment:

Patient Health Questionnaire-8: The PHQ-8 is an 8-item patient-completed instrument used to detect depression and measure the severity of depressive symptoms (Kroenke and Spitzer 2002; Kroenke et al. 2009). The 8 items pertain to: anhedonia; depressed mood; trouble sleeping; feeling tired; change in appetite; guilt, self-blame, or worthlessness; trouble concentrating; and feeling slowed down or restless. Each item is rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), based on symptoms over the past 2 weeks. The overall score ranges from 0 to 24, with the levels of depression severity defined as follows: 0-4 no significant depressive symptoms; 5-9 mild; 10-14 moderate; 15-19 moderately severe; and 20-24 severe. The full instrument (PHQ-9, which includes a ninth item specific to

suicide) is considered reliable and valid for use in research and clinical settings (Kroenke et al. 2001), including in patients with migraine (Seo and Park 2015a).

7-Item Generalized Anxiety Disorder Scale: The GAD-7 is a patient-completed questionnaire that was designed to screen for GAD and for measuring the severity of anxiety symptoms (Spitzer et al. 2006). The tool was developed based on symptom criteria for GAD in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (still applicable for the fifth edition), as well as review of existing anxiety scales, with items addressing the following: feelings of nervousness; uncontrollable worrying; excessive worrying; trouble relaxing; restlessness; irritability; and fearfulness. The patient identifies how much they have been bothered by these symptoms over the past 2 weeks. Each of the 7 items is rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), with total score ranging from 0 to 21. The levels of anxiety severity are defined as follows: 0-4 minimal; 5-9 mild; 10-14 moderate; and 15-21 severe. The instrument is considered reliable and valid for use in research and clinical settings (Spitzer et al. 2006), including in patients with migraine (Seo and Park 2015b).

Medication Adherence Reporting Scale: The MARS-5 is a patient-reported measure that consists of 5 common patterns of nonadherent behavior that respondents score on a 5-point Likert scale, with: 1 = always; 2 = often; 3 = sometimes; 4 = rarely; and 5 = never. Scores are summed and totals range from 5 to 25, with higher scores indicating higher self-reported adherence (Mahler et al. 2010).

Allodynia Symptom Checklist (ASC-12): The ASC-12 is a 12-item validated, quantitative, and patient-completed instrument to measure the presence and severity of cutaneous allodynia in association with headache attacks. The tool was developed to provide graded responses rather than dichotomous (present/absent) responses. The ASC-12 asks how often the patient experiences increased pain or an unpleasant sensation on the skin during the most severe type of headache when engaging in each of 12 items, such as combing hair, wearing eyeglasses, and exposure to heat or cold. Each of the 12 items has the following response options: does not apply to me (0 points); never (0 points); rarely (0 points); less than half the time (1 point); and half the time or more (2 points). The total score ranges from 0 to 24 and yields the following allodynia categories: none (0 to 2 points); mild (3 to 5 points); moderate (6 to 8 points); and severe (9 points or more) (Lipton et al. 2008).

7. Sample Size and Statistical Methods

7.1. Determination of Sample Size

The study desires to enroll approximately 4100 patients (or more from additional geographies) with migraine to Stage 2 with country-specific targets of 1600 patients (with a 1:1 split, 800 patients each for galcanezumab and other migraine preventive treatments) from the US. Additionally, the following country-specific enrollment targets are planned (approximately split 1:1 between galcanezumab patients and other migraine preventive treatment patients): 1050 from Japan, 625 patients from Germany, 225 patients from Italy, and 200 patients each from Spain and United Kingdom (UK), and 200 patients from United Arab Emirates (UAE).

Patients enrolled in routine clinical care will include patients using galcanezumab, oral standard of care, other CGRP antagonists, or botulinum toxin A or B. To be able to detect a between-group difference of 54% for galcanezumab versus 45% for the oral migraine preventive standard of care in the proportion of responders achieving a 50% or 30% reduction in migraine headache days at Month 3 for episodic and chronic migraine, respectively, a minimal Stage 2 sample size of 1000 (equal sample size: 500 patients for galcanezumab versus 500 patients for oral standard of care) is required for 80% power. Further, after accounting for a 20% reduction in effective sample size due to either patient dropout or the application of a specific primary analysis method, such as a propensity score matching rate of 80%, 1250 patients (625 patients for each group) will be needed for 80% power. Thus, under the further assumption that at least 80% of the patients fall into the galcanezumab and oral treatment groups, the above sample size will provide at least 80% power for the primary analysis using only patients from the US and greater than 90% power using the overall sample.

For the analysis, multiple treatments comparisons may be conducted for galcanezumab versus migraine preventive treatments overall and possibly by drug classes (which may reduce the sample size and result in <80% power for those comparisons).

Also, analyses and summaries will be conducted within each country or by region. Given the smaller sample size from Germany, Italy, Spain, UK, UAE, or other regions, analyses within these countries will be underpowered (<80% power).

7.1.1. Assumptions

Response rates for achieving 50% (patients with episodic migraine) and 30% (patients with chronic migraine) reduction from baseline in monthly migraine headache days at Month 3 with galcanezumab are drawn from Studies I5Q-MC-CGAG, I5Q-MC-CGAH, and I5Q-MC-CGAI. The assumption is that 58.3% of episodic migraine and 49.7% of chronic migraine galcanezumab patients will achieve a 50% and 30% response rate, respectively. Estimates for the oral standard of care vary considerably and robust evidence lacks for patients with chronic migraine. For example, the proportion of 50% responders across 9 trials of episodic migraine with topiramate ranged from 26% to 63% (Linde et al. 2013). Thus it is assumed that 40% to 50% of patients with episodic migraine and 35% to 40% of patients with chronic migraine will achieve a 50%

and 30% response rate, respectively. It is assumed that at least 80% of the galcanezumab patients will be matched to patients in the comparator group.

7.2. Adjustments for Bias and Confounding

This is a noninterventional study to compare the effectiveness of galcanezumab to oral migraine preventive standard of care. Treatment selection may be influenced by patient characteristics. As a result, baseline characteristics of galcanezumab-treated patients may differ systematically from those of patients treated with oral migraine preventive standard of care. To make inference about the causal effect of a nonrandomized treatment on outcomes, propensity score will be used to account for underlying, observed differences between the galcanezumab and oral migraine preventive standard of care groups. The propensity score is the probability of treatment assignment conditional on measured baseline covariates. Several methods (see Table 1) will be used to estimate the propensity score with receiving galcanezumab as the dependent variable and all baseline characteristics, demographics, and prior treatments described above as the independent variables. Quadratic and interaction terms may be also included. The specific covariates for the propensity model and method for estimation will be finalized and documented in the SAP prior to conducting any baseline or outcome analyses. Differences in baseline characteristics between galcanezumab and oral migraine preventive standard of care groups will be assessed using standardized differences and variance ratios for the primary objective. A standardized difference greater than 0.25 is considered a meaningful imbalance that may require further investigation. Similarly, a variance ratio outside of the interval of 0.5 to 2.0 indicates further investigation is warranted.

We will examine overlap (region of common support) in the distribution of the estimated propensity score between galcanezumab and oral migraine preventive standard of care groups (by visual inspection and statistical methods) and derive the respective effective sample sizes. If the overlap in the propensity score distributions is small (based on the inspection), then further discussion of alternative methods or changes to the estimand (such as a narrower target population of inference) will be considered. Any changes would be made only after accessing baseline data and would be documented in a separate programming specifications SAP prior to accessing outcome data.

If patients have missing values for a covariate, then multiple imputation approaches will be used to impute these missing values for the propensity score estimation analysis. Details will be outlined in the SAP.

7.3. Missing Data

For the primary endpoint (proportion of patients achieving the desired reduction in monthly migraine headache days at Month 3: 50% for patients with episodic migraine and 30 % for patients with chronic migraine), the primary analysis will use a non-response single imputation (NRI) for imputing a missing value at Month 3. Patients that discontinue the study, are lost to follow-up, switch medication, or augment medication with a different preventive medication will be assumed to have not achieved the desired response at Month 3.

Multiple imputation approaches or other missing value imputation techniques will be used for missing data, so that covariates retain as many patients as possible in the analysis. Further details of missing value imputation will be outlined in the SAP.

Repeated measures analyses (see Section 7.5.1.4) and time-to-event models (see Section 7.5.1.6) are capable of dealing with missing data assuming missing at random pattern.

For the analyses of treatment patterns (see Section 7.5.1.5), missing data will be included as its own category.

Summary statistics will be calculated without imputation of missing values.

7.4. Significance Levels and Multiplicity

Adjustment for multiple testing for the primary endpoint is not necessary as a single comparison for the primary analysis has been prespecified. Adjustment for testing multiple secondary endpoints will be documented in the SAP to test key secondary endpoints, should the study team decide to implement this option; adjustment for subgroup comparisons will not be used.

All tests will be 2-sided and conducted at the 5% level of significance. All confidence intervals will be at 95% coverage.

7.5. Other Analyses

7.5.1. Outcomes Analyses

7.5.1.1. Analyses Population

The analyses population includes all migraine patients who have given informed consent and fulfill the inclusion/exclusion criteria (Section 6.3.1) and criteria specific to Stage 2 (Section 6.3.2).

Based on this, the following analyses datasets are defined:

- Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which includes all patients who will be categorized based on their initial treatments, regardless of treatment changes in the follow-up period.
- When change from baseline is assessed (secondary longitudinal analysis), the patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement. Treatment will be defined as time varying.

The visit schedule and allowable visit windows are provided in Attachment 1. Details for how to assign data to a visit for visits that occur outside the visit window will be outlined in the SAP.

For causal inference when basic propensity score analysis or marginal structural models (MSM) are used, 3 assumptions must be satisfied: 1) there are no unmeasured confounders; 2) there is a positive probability of each treatment for each set of covariates; 3) weighted models and outcome models are correctly specified. The only difference between basic propensity score and MSM analyses is that these assumptions apply not just at baseline, but over time, as MSM is a

longitudinal analysis. Violation of these underlying assumptions may lead to biased results. Caution is needed when interpreting the causal effects.

7.5.1.2. Primary Objective Analysis

The primary objective is to estimate the proportion of patients in the longitudinal follow-up who achieve a clinically meaningful reduction (50% reduction for episodic migraine and 30% for chronic migraine) from baseline in monthly migraine headache days at Month 3 between 2 groups receiving galcanezumab versus receiving oral migraine preventive standard of care.

The primary analysis aims to estimate the causal effect of galcanezumab versus oral migraine preventive standard of care when controlling for selection bias and measured confounders. For primary outcome analysis, the ITT population (see Section 7.5.1.1) will be used. Missing values of follow-up time points will be NRI imputed (see Section 7.3).

The primary analysis will be an application of inverse probability of treatment weights (IPW) in a logistic regression, such as wLr2 in Table 2, using the propensity score model deemed most appropriate (see Table 1 for guidance). However, if the anticipated power, based on the effective sample size prior to looking at the treatment outcome data (i.e., the square of the summed weights divided by the sum of the squared weights [Faries et al. 2020]), is less than 70%, then a modified primary analysis method may be specified in an updated SAP. Examples of alternative methods are trimming extreme weights, matching with replacement, or reducing the covariate set (see Table 1 and Table 2). This evaluation will be completed prior to Interim Analysis 2 and the selected method will be considered the a priori selected primary analysis method. It is recommended that the method selected consider including in the model all quadratic terms of each covariate and 2-way interactions (Zagar et al. 2017a). Country will be included as a fixed effect. Other examples of propensity score estimators and methods to fit the outcome model appear in Table 1 and Table 2.

Using matched or weighted data, depending on which primary method is selected, the observed proportion along with the 95% confidence interval of patients who achieve a clinically meaningful reduction at Month 3 will be presented both overall and by treatment groups. Clinically meaningful reduction in the number of migraine headache days within each country will also be reported. The difference in the proportion of patients achieving clinically meaningful reduction between treatment groups will be tested using the appropriate test for the selected primary method, as detailed in the SAP.

As an illustration, if the effective sample size from IPW is estimated to yield less than 70% power, we can re-establish a slightly reduced patient population for which we can attempt comparative analyses (Walker et al. 2013; equipoise argument) and evaluate the power for that group. We may also try other options: 1) Crump et al. (2009) or other more aggressive trimming of the population up front; 2) matching with replacement; 3) evaluate the imbalance by strata in a stratification approach; 4) evaluate the assumptions in a regression approach, or any other alternative methods that may provide greater power, such as those in Table 1 and Table 2. If we are unable to obtain a sufficient sample size to provide at least 70% power under the given

assumptions, then the primary will be descriptive within cohort summaries and comparative analyses considered exploratory. The details will be illustrated in the SAP.

The sensitivity analysis will be conducted using a model averaged average treatment effect (ATE) estimator comprised of the methods presented by Zagar et al. (2017b). The following analytical methods are proposed and may be modified where appropriate, for example, to exclude the primary analysis method. Weights are estimated for each individual method included in the model averaging procedure using mean square predicted error from cross validation. The final model averaging estimate is the weighted average of the treatment effects across all analytical methods included in the process. A list of methods for treatment selection and outcome modeling is given in Table 1 and Table 2 (adapted from Zagar et al. 2017a) respectively, with references to specific software and the relevant literature. Additionally, a sensitivity analysis of the results to potential biases from unmeasured confounding may be performed, as appropriate.

Table 1. Methods for Modeling Treatment Selection

Method	Label	Description
Logistic regression with main effects only	Lg1	Logistic regression for probability of receiving galcanezumab given all covariates in the candidate set.
Logistic regression with main and 2-way interaction effects	Lg2	Same as Lg1 but adding 2-way interaction effects (X_iX_j and squared covariates (X_j^2)
Penalized logistic regression, including 2-way interactions, Lasso	Lasso	Penalized linear regression (Lasso) (Hastie et al. 2009), including 2-way interactions and squared covariates.
Penalized logistic regression, including 2-way interactions, elastic net	GlmNet2	Penalized linear regression (Friedman et al. 2010) with elastic net penalty (α=0.5), including 2-way interactions and squared covariates; complexity criterion is selected using 10-fold cross-validation (fitted with R glmnet package or SAS HPGENSELECT).
Gradient boosting with tree base learner	GbmTree	Gradient boosting by Friedman (2001); implemented with programs such as the R GBM package (Ridgeway 1999) with a tree as the base learner, such as: n.trees = 1500, shrinkage = 0.005, interaction.depth = 4, bag.fraction = 0.5, train.fraction = 1.0, n. minobsinnode = 10. The number of trees in the model is selected by minimizing the IPW ASAM criterion. If the selected number of trees is on the boundary (e.g., close to 1500 trees) then n.trees is increased accordingly.
Entropy balancing by main effects only	Ebw	Implements entropy balancing (Hainmueller 2012) using only covariate main effects for estimating ATE. Optimal weights are determined separately for treatment and control groups so as to match the distribution of covariates in the full dataset (implemented with programs such as the R EBAL package)
Entropy balancing with main effects and 2-way interactions	Ebw2	Same as Ebw but implementing entropy balancing for both main and interaction effects (X_iX_j).

Table 2. Methods for Modeling Outcome Function

Outcome Model	Label	Details (software tuning parameters, variance)
Logistic regression with main effects (unweighted/IPW)	Lr1/wLr1	Logistic regression for Y, with treatment (T) and covariates X's as independent variables: unweighted or inverse probability weighted.
Logistic regression with main and interaction effects (unweighted/IPW)	Lr2/wLr2	Logistic regression for Y, with treatment (T) and covariates (X's) and 2-way interaction (X_iX_j, and TX_i) as independent variables: unweighted or inverse probability weighted.
Logistic regression with main effects including propensity scores	PsDrLr1	Direct covariate adjustment by a logistic regression for Y, with treatment (T), covariates (X's), and estimated propensity score as independent variables.
Logistic regression with main and interaction effects (covariates including propensity scores)	PsDrLr2	Direct covariate adjustment by a logistic regression for Y, with treatment (T), covariates (X's), estimated propensity score, and as 2-way interactions among T, X's, and the propensity score independent variables.
Penalized logistic regression with main and interaction effects (unweighted/IPW).	GlmNet2/ wGlmNet2	Penalized logistic regression for Y, as outcome variable with treatment (T), covariates (X's), 2-way interaction (X_iX_j, and TX_i) as independent variables. The model is fitted with R package glmnet or SAS HPGENSELECT. The elastic net penalty (the mixing parameter α=0.5) is used with optimal selection via10-fold cross-validation
Gradient boosting (unweighted/IPW).	GbmTree	Gradient boosting by Friedman (2001); implemented with programs such as the R GBM package (Ridgeway 1999) with a tree as the base, such as: n.trees = 1500, shrinkage = 0.1, interaction.depth = 4, bag.fraction = 0.5, train.fraction = 1.0, n.minobsinnode = 10. The number of trees in the model is selected by minimizing 10-fold cross-validation error. If the selected number of trees is on the boundary (e.g., close to1500 trees) then n.trees is increased accordingly.
Stratification by propensity score (K = 5 strata)	PsStrataK	Stratification by percentiles of estimated propensity scores into 5 strata.
Stratification by propensity score (optimal strata)		The number and boundaries of propensity score strata will be formed to optimize balance per the Imbens-Rubin (2015) approach.
Nearest-neighbor matching on covariates and propensity score	NNMatch	Nearest Neighbor matching with replacement using Mahalanobis distance based on all covariates(X's) and the logit (PS), with caliper = 0.2 SD, where SD is the standard deviation of the logit(PS).
Greedy matching on covariates and propensity score	NNGreedy	Nearest Neighbor matching without replacement.
Optimal full matching on covariates and propensity score	OptFullMatch	Optimal full matching using R package optmatch on the main effects of all covariates (X's) and logit(PS), caliper = 0.2 SD, where SD is standard deviation of logit(PS); no replacement, no restriction on the ratio treated:controls and no restriction on the ratio controls:treated.

7.5.1.3. Secondary Analysis – Cross-Sectional Assessment (Stage 1)

Secondary objectives for the cross-sectional assessment include a descriptive evaluation of baseline characteristics. For this analysis, the ITT population (see Section 7.5.1.1) will be used. Summary statistics will be calculated without imputation of missing values. Variables will be summarized using proportions for categorical variables and means with standard deviations or medians with quartiles for continuous variables. These will be done overall and by treatment groups, as well as by region and by country.

7.5.1.4. Analyses of Longitudinal Data

Descriptive summary statistics will be presented at different time points for different treatments and treatment groups (i.e., galcanezumab, other migraine preventive treatments) and drug classes or individually based on the sample sizes available overall and by countries using treatment as time varying. Analyses will be done without imputation of missing values.

The secondary objectives for the longitudinal follow-up are to compare the effectiveness of galcanezumab to other migraine preventive treatments on outcomes. The patient will be included in the analysis only if he/she has a baseline and a postbaseline measurement (see Section 7.5.1.1). The secondary analyses will be performed using MSM, which are multi-step estimation procedure designed to control for the effect of confounding variables that change over time, and are affected by previous treatment.

The first step is to estimate 2 weights for each observation (patient visit), one adjusting for treatment selection and one adjusting for study discontinuation (censoring). Computation of these estimated weights can incorporate time-independent and time-dependent factors. The stabilized weight is estimated as

$$SW = \prod_{k=0}^{t} \frac{f[A(k)|\overline{A}(k-1), V]}{f[A(k)|\overline{A}(k-1), \overline{L}(k)]}$$

where A(k) represents the treatment at time k and $\overline{A}(k-1)$ represents the treatment history prior to time k, V represents a vector of time-independent variables (baseline covariates), and $\overline{L}(k)$ represents a vector of time-varying covariates through time k – which includes baseline variables V (Hernán et al. 2000). The numerator of the weight is the probability a patient is on the observed treatment at time k, given the prior treatment history and baseline covariates. The denominator is basically the same factor, except it incorporates time-varying covariates as predictors.

To incorporate adjustment for early patient dropout, the same stabilized weight approach is used, except the outcome is not the treatment selection but a flag variable denoting whether the patient remained in the study. The treatment selection weight and the censoring weight are multiplied and yield the final weight for each patient's observation.

The second step of the MSM analysis is to conduct a weighted repeated measures model analysis using generalized estimating equations. In this second stage, time-dependent confounders are not included in the repeated measures model, as their effects have been incorporated into the

weights. Treatment is included as a time-dependent factor, and time-independent covariates may also be included as appropriate. This is done by using SAS PROC GENMOD and an exchangeable correlation matrix. For continuous outcomes (e.g., mean change from baseline in number of monthly migraine headache days), the analysis will include the time-varying treatment effect, investigative site, visit, and treatment-by-visit interaction, as well as baseline measure of the outcome (e.g., baseline number of monthly migraine headache days). For binary outcomes (e.g., reduction from baseline ≥50% in the number of monthly migraine headache days), the analysis will include the time-varying treatment effect, investigative site, visit, and treatment-by-visit interaction, as well as the continuous covariate of baseline value of the measure (e.g., baseline number of migraine headache days) from which the binary variable is derived.

If rates of switching between treatments are low, then instead of MSM, mixed model repeated measures (MMRM) analyses considering treatment as fixed (ITT) and censoring at the point of treatment switching may be implemented.

These analyses are capable of dealing with missing data. Therefore, no imputation will be applied (see Section 7.3).

7.5.1.5. Analyses of Treatment Patterns

For analyzing treatment patterns (e.g., persistence, number of switches), descriptive statistics will be used. This will include shift tables for patients switching from initial to another treatment.

Marginal structural models (see Section 7.5.1.4) will be performed for treatment patterns to compare changes in acute medication use for galcanezumab to other migraine preventive treatments with respect to mean change from baseline in the number of monthly days with acute headache medication use.

Missing data may be included as own category into the analyses (see Section 7.3).

7.5.1.6. Analyses of Time-to-Event Data

The objective of the analyses is to compare treatment discontinuation rates, all-cause time-to-treatment discontinuation, and time-to-treatment discontinuation for negative reasons (lack of effectiveness, intolerance to medication, lack of medication availability) between galcanezumab and other migraine preventive treatments initiated at baseline.

Survival analysis will be performed for treatment discontinuation. Patients prematurely discontinuing the study are censored from their last available values onward (i.e., when lost to follow-up, when the patient entered another research study, or after death). Overall and by treatment groups, the unadjusted cumulative incidence of treatment discontinuation will be estimated based on Kaplan-Meier estimates. Differences in discontinuation of treatment between treatment groups will be tested using log-rank tests.

To assess the treatment effect on discontinuation, the log-rank test will be applied, or Cox proportional hazard models will be fitted using IPW, or including the propensity score as a covariate in the model. If this is not appropriate, we will try to fit the models to the ITT dataset

using IPW or including propensity score as covariates into the models. These time-to-event analyses are capable of adjusting for missing data (see Section 7.3).

7.5.1.7. Analyses of Cost Data and Healthcare Resource Use (HCRU)

Total costs, cost components (total cost burden, direct expenditures, indirect costs), HCRU and cumulative costs at each visit, and the number of visits since baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum). These descriptive statistics will be computed by treatment group (i.e., galcanezumab, other migraine preventive treatments), by drug class (or individually, if sample sizes allow) and by country. Analyses will be conducted using the ITT population without imputation of missing values.

For FDAMA objectives related to health economic comparisons between galcanezumab and the oral migraine preventive standard of care on reduction of HCRU and total cost burden, the patient will be included in the analyses only if he/she has a baseline and a postbaseline measurement (see Section 7.5.1.1). This analysis will be performed using MSM (as described above).

For comparisons between galcanezumab and oral migraine preventive standard of care on cumulative costs and HCRU since baseline, a weighted analysis using the ATE weights generated from the propensity score model will be used. Bootstrap will be used to estimate the standard error of the estimated treatment effect. If the sample sizes within each country are large enough, the bootstrapping will be conducted at the country level. The details of how to estimate expenditures and HCRU will be documented in the study SAP.

All analyses will be documented in the SAP.

7.5.1.8. Key Secondary Endpoints

A subset of the secondary endpoints described above may be identified as key secondary endpoints and will be tested using a gated scheme and an appropriate multiple comparisons method. More details will be provided in the SAP.

7.5.2. Subgroup Analyses

Exploratory analyses using methods such as gradient boosting or value function optimization (Qi et al. 2019) may be performed to help identify subgroups with respect to differential response in either treatment effectiveness or switching/augmentation. There will be analysis of at least the primary endpoint and for treatment patterns (descriptive and inferential) at the country and select regional level. Additionally, predefined subgroups, such as defined by type of migraine, will be evaluated. Some subset of exploratory and subgroup analyses, properly identified in the SAP, will be performed in-house by Eli Lilly personnel.

7.5.3. Interim Analyses

The interim analyses will be conducted to understand outcomes and treatment patterns after specific lengths of longitudinal follow-up have been completed. An additional intent is to be able to provide data to Health Technology Assessment organizations/health authorities upon their request. Five interim analyses are planned for this study. The first interim analysis will be

conducted to describe baseline data for publication purposes after at least 3 months of study enrollment has been completed. The remaining interim analyses will occur after at least 1250 patients (625 patients each for galcanezumab and oral standard of care) in Stage 2 have completed 3, 6, 12, and 18 months of the study, respectively. The interim analyses at Month 3±1 in Stage 2 will conduct descriptive analyses of baseline data, propensity score estimation, sample size confirmation, and comparative analysis on the primary objective overall and by country level. The interim analyses at Months 6, 12, and 18 will compare the effectiveness of galcanezumab to oral migraine preventive standard of care on reductions in monthly migraine headache days:

- for episodic migraine, the proportion of patients with reduction from baseline ≥50%, ≥75%, and 100% in monthly migraine headache days
- for chronic migraine, the proportion of patients with reduction from baseline ≥30%, ≥50%, ≥75%, and 100% in monthly migraine headache days, and
- mean change from baseline in number of monthly migraine headache days by fitting an MMRM.

Additional interim analyses may be conducted, if necessary,

- for individual countries if specific data are requested by local Health Technology Assessment organizations/health authorities, or
- to provide early dissemination results to inform key external stakeholder decision-making.

Details will be documented in the SAP.

8. Safety Evaluations

8.1. Primary Data Collection Study

The only protocol-defined adverse event (AE) to be collected in this study is treatment discontinuation due to lack of effectiveness.

The study personnel will collect treatment discontinuation due to lack of effectiveness via electronic data entry, occurring in temporal association with Lilly product(s) and comparator product(s) that are under evaluation as defined in this protocol.

All other AEs will not be actively collected due to lack of relevance to the study objectives.

Treatment discontinuation due to lack of effectiveness will be summarized in the interim study report, if applicable, and in the final study report.

Study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (e.g., regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or serious adverse events (SAEs) in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

8.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any serious event of treatment discontinuation due to lack of effectiveness arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A serious event of treatment discontinuation due to lack of effectiveness is one that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Or is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

When a condition related to the galcanezumab drug delivery device 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.

8.1.2. Nonserious Adverse Events

The study personnel will record, via electronic data entry, any **nonserious** treatment discontinuation due to lack of effectiveness event arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness. Lilly or its designee will execute the extraction for EU sites to comply with the regulatory reporting requirements.

8.2. Product Complaints

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

Complaints related to unblinded comparator drugs or concomitant drug/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the approved labeling or to the authorities as defined by local law.

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

9. Subject Consent to Release Information, Ethical Review, and Regulatory Considerations

9.1. Subject Consent to Release Information

This is an observational research program and does not impose any form of intervention on the investigator. Hence, the assessment and treatment of the patient is based solely on the investigator's routine or usual practice in the provision of care to patients with migraine.

As this is an observational study and does not impose any form of intervention, the patient will provide authorization for the uses and disclosures of their personal health information as described in the study Consent to Release Information. This consent covers the collection and release of data regarding treatment and its outcomes for the entire period of the study. The confidential nature of the patient information will be maintained.

9.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought 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 the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

10. Record Keeping, Data Reporting, Data Quality Assurance, and Publications

Patient data are recorded on data forms. Investigators are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly. The investigator follows local laws and regulations or institutional practices for document retention.

An eDC system will be used in this study. The site maintains a separate source (electronic or paper) for the data entered by the site into the sponsor-provided eDC system.

Appropriate site personnel will be trained on the eDC technology.

Electronic devices will be used in this study for all eCOAs, that is, any patient-completed questionnaire as outlined in Section 6.5. Electronic clinical outcome assessment data should be directly reported and captured by the patient in an electronic device (see Attachment 1). When data are entered directly into the electronic device, the electronic device record is the source data.

The eDC/eCOA device data collected by the third-party vendor will be encoded by the third-party vendor and stored electronically in the third-party vendor's database system.

Validated data will subsequently be transferred to the sponsor's data warehouse, using standard Lilly file transfer processes.

All information about this observational study and individual patient medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

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Attachment 1. Observational Study Protocol Data Collection Schedule

Data Collection Schedule, Observational Study Protocol I5Q-MC-B004:

Collect data on the following as indicated:

	Stage 1	Stage 2					
Month		**Month 0**	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Interval Allowance (weeks)			**±4**	**±4**	**±4**	**±4**	**±4**
Visit Type	**Flexible[a]**	**Flexible[a,b]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**
Observation Number:		T1	T2	T3	T4	T5	T6
Patient and Physician Characteristics							
Physician characteristics	X						
Informed consent	X						
Inclusion/exclusion	X						
Demographics	X						
Height and weight	X						X
Medical history and comorbidities	X						
Migraine history	X						
Migraine treatment history	X						
Current disease state	X		X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Summary (reason for termination from study participation)							X[c]
Treatment Pattern Measures[d]							
Preventive treatments for migraine	X		X	X	X	X	X
Acute treatments for migraine	X		X	X	X	X	X
Non-pharmacologic treatments	X		X	X	X	X	X
Scales, Questionnaires, and Outcome Measures[e]							
MIDAS	X		X	X	X	X	X
MSQ v2.1		X	X	X	X	X	X
HIT-6		X	X	X	X	X	X
HCRU/Employment Status[f]		X	X	X	X	X	X
WPAI		X	X	X	X	X	X

Data Collection Schedule, Observational Study Protocol I5Q-MC-B004

	Stage 1	Stage 2					
		Month 0	Month 3	Month 6	Month 12	Month 18	Month 24
PGI-S	X		X	X	X	X	X
PSMQ-M			X		X		X
MIBS-4		X	X		X		X
mTOQ-6[g]	X		X		X		X
Exploratory Variables/Measurements							
Event-driven electronic patient headache diary entries[h]		X	X	X	X	X	X
PHQ-8		X	X		X		X
GAD-7		X	X		X		X
MARS-5			X	X	X	X	X
ASC-12		X	X	X	X	X	X

Abbreviations: ASC-12 = Allodynia Symptom Checklist; GAD-7 = 7-item Generalized Anxiety Disorder Scale; HCRU = Health Care Resource Utilization questionnaire; HIT-6 = Headache Impact Test-6; MARS-5 = Medication Adherence Reporting Scale; MIBS-4 = 4-item Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment; MSQ (v2.1) = Migraine-Specific Quality of Life Questionnaire version 2.1; mTOQ-6 = Migraine Treatment Optimization Questionnaire 6-item version; PGI-S = Patient Global Impression of Severity; PHQ-8 = Patient Health Questionnaire-8; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; T= time point; WPAI = Work Productivity and Activity Impairment Questionnaire.

[a] Visit can be office-, phone-, or web-based.

[b] Assessments/measures collected at Month 0 of Stage 2 will be completed at the Stage 1 visit following confirmation of Stage 2 eligibility.

[c] Month 24 or any postbaseline visit.

[d] Collected from medical records.

[e] Electronic clinical outcomes assessment (eCOA) measures completed by patient entry.

[f] Collected at baseline and monthly during Stage 2 from Months 1 through 24.

[g] Only for patients with acute medication use.

[h] These are event-driven entries and are not associated with scheduled study visits. Collection starts on or after Day 1 and spans the duration of Stage 2.

Attachment 2. Observational Study Protocol (b) I5Q-MC-B004 Summary preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH)

Overview

Observational Study Protocol I5Q-MC-B004: preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol. The overall changes and rationale for the changes made to this protocol are as follows:

- The sample size has been updated from 3450 to 4100 throughout the document due to the addition of 1 region- Japan. France and Taiwan have been excluded due to small sample size.
- One of the variables - Symptoms of Anxiety, depression and allodynia removed in Section 2.
- Criteria for determining Migraine headache days changed in Section 5.1
- Throughout the document, discontinuation related to lack of effectiveness of treatment has been specified as the primary adverse event between galcanezumab and other migraine preventive treatments initiated at baseline.
- Assess symptoms associated with migraine and attack characteristics instead of frequency collected by patient headache diary in Section 5.2.2
- Assessments under migraine specific patient reported disease burden distinctly separated, and further detailed for MIBS-4 in Section 5.2.2
- Assessments under General Health and other outcomes in Section 5.2.2 moved to Exploratory Section 5.3
- In Section 5.3, Migraine disease characteristics to be described by collecting data from headache diaries.
- In Section 6.1, new text added to clarify requirement of re-baseline and completing the baseline measures relative to first dose of preventive treatment
- Added details in Section 6.2, the data from patient's medical records, within eDC system, will be transferred as Electronic case report forms by the investigator or designated site personnel, as well as record details related to treatment patterns, along with disease status throughout the study. In addition, eCOA measures will be at Stage 1 (cross-sectional) visit and Stage 2 - Month 0, Month 3, Month 6, Month 12, Month 18 and Month 24 (longitudinal) visits.
- A total of 5 questionaries PHD, PHQ-8, GAD-7, MARS-5 and ASC-12 under Variables/Measures have been moved to a newly added subsection 6.5.1
- Country specific enrollment numbers updated in Section 7.1

- In Section 7.2, Standardized difference to assess differences in baseline characteristics increased from 0.1 to 0.25 in order to consider as a meaningful imbalance.
- In Section 7.5.1.6, updated the modelling method to assess the treatment effect on discontinuation.
- In Section 7.5.1.7, updated the modelling method for cost and HCRU.
- Minor editorial changes have been done throughout the protocol.

Attachment 3. Observational Study Protocol (a) I5Q-MC-B004 Summary preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH)

Overview

Observational Study Protocol I5Q-MC-B004: preventive TReatment of mIgraine: oUtcoMes for Patients in real-world Healthcare systems (TRIUMPH) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol. The overall changes and rationale for the changes made to this protocol are as follows:

- The sample size has been updated from 2850 to 3450 throughout the document due to the addition of several regions.
- Details regarding the Study report have been added to the Milestones list in Section 2.
- Details regarding patients who do not initiate the index preventive treatment within 14 days of the baseline visit have been added to Section 6.1.
- Exclusion criterion 13 has been added in Section 6.3.1 to exclude patients who do not initiate the index preventive treatment within 56 days of the baseline visit or treatment assignment, per additions made in Section 6.1.
- In Section 7.2, the statement, "Differences in baseline characteristics between galcanezumab and oral migraine preventive standard of care groups will be assessed before and after propensity score greedy match using standardized differences and variance ratios for the primary objective" was amended to remove "before and after propensity score greedy match," as this is no longer the primary method being used.
- Changes have been made to Section 7.4 to reflect that adjustment for testing multiple secondary endpoints will be documented in the SAP to test key secondary endpoints, should the study team decide to implement this option.
- Details regarding the primary analysis have been changed to reflect that the primary analysis will be an application of inverse probability of treatment weights (IPW) in a logistic regression using the propensity score model deemed most appropriate. Additional details regarding this has been added throughout Section 7.5.1.2.
- Section 7.5.1.8 Key Secondary Endpoints has been added to describe that a subset of the secondary endpoints may be identified as key secondary endpoints.
- A statement regarding a subset of exploratory and subgroup analyses that will be performed in-house by Eli Lilly personnel has been added to Section 7.5.2.
- Minor editorial changes have been done throughout the protocol.

Revised Observational Study Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.
Only text with deletions or additions have been included.	

2. Abstract

- Variables:
    - demographics
    - concomitant medications
    - medical history and comorbidities
    - migraine history, migraine treatment history, and current disease state
    - preventive and acute treatment use and rationale for changes
    - migraine headache days and headache days, headache hours, severity, and symptoms
    - health-related quality of life
    - migraine-related burden and disability
    - healthcare resource utilization
    - work productivity and activity impairment
    - acute treatment outcomes
    - ~~symptoms of anxiety, depression, and allodynia~~
    - medication adherence, persistence, and satisfaction
- Study size: Stage 1 will include a sufficient number of patients to achieve approximately ~~3450~~ 4100 total patients entering Stage 2. The study will enroll patients from multiple sites and countries, with enrollment targets stratified by country.

5.1 Primary Objective

The primary objective of this multi-country noninterventional study is to compare the effectiveness of galcanezumab to oral migraine preventive standard of care overall in adult patients with migraine who are switching or initiating preventive treatment in clinical practice settings. Specifically, this will estimate the proportion of patients in the longitudinal follow-up who achieve a clinically meaningful reduction from baseline in monthly migraine headache days at Month 3. Migraine headache days will be determined from patient responses in the electronic case report form (eCRF) at the 3-month visit ~~based on criteria evaluated from patient headache diary entries~~.

5.2.2. Longitudinal Follow-up (Stage 2)

- Compare the long-term, real-world effectiveness of galcanezumab to other migraine preventive treatments on reductions in monthly migraine headache days as collected from the CRF,

- Compare treatment discontinuation rates, all-cause time-to-treatment-discontinuation, and time-to-treatment-discontinuation for negative reasons (lack of effectiveness, /intolerance to medication, lack of medication availability ~~lack of tolerability/ noncompliance~~) between galcanezumab and other migraine preventive treatments initiated at baseline
- Describe treatment patterns specific to the acute treatment of migraine attacks, including switching or initiating new acute treatment, as well as reasons for treatment discontinuation.
- ~~Assess migraine-specific patient-reported disease burden, including:~~
- ~~changes in~~ Assess symptoms associated with migraine and ~~including~~ attack characteristics ~~frequency collected by patient headache diary~~
- time between headache attacks and interictal burden using the Migraine Interictal Burden Scale (MIBS-4)
- ~~Assess general health, including:~~
    - ~~depression symptomatology using the Patient Health Questionnaire-8 (PHQ-8)~~
    - ~~anxiety symptomatology using the 7-item Generalized Anxiety Disorder Scale (GAD-7)~~
    - ~~presence and severity of allodynia using the Allodynia Symptom Checklist (ASC-12)~~
- Assess other outcomes, including:
    - patient satisfaction with medication using the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M)
    - ~~migraine preventive treatment adherence using the Medication Adherence Reporting Scale (MARS-5)~~

5.3. Exploratory

- Describe migraine disease characteristics, including clinical features and symptoms, collected by headache diaries.

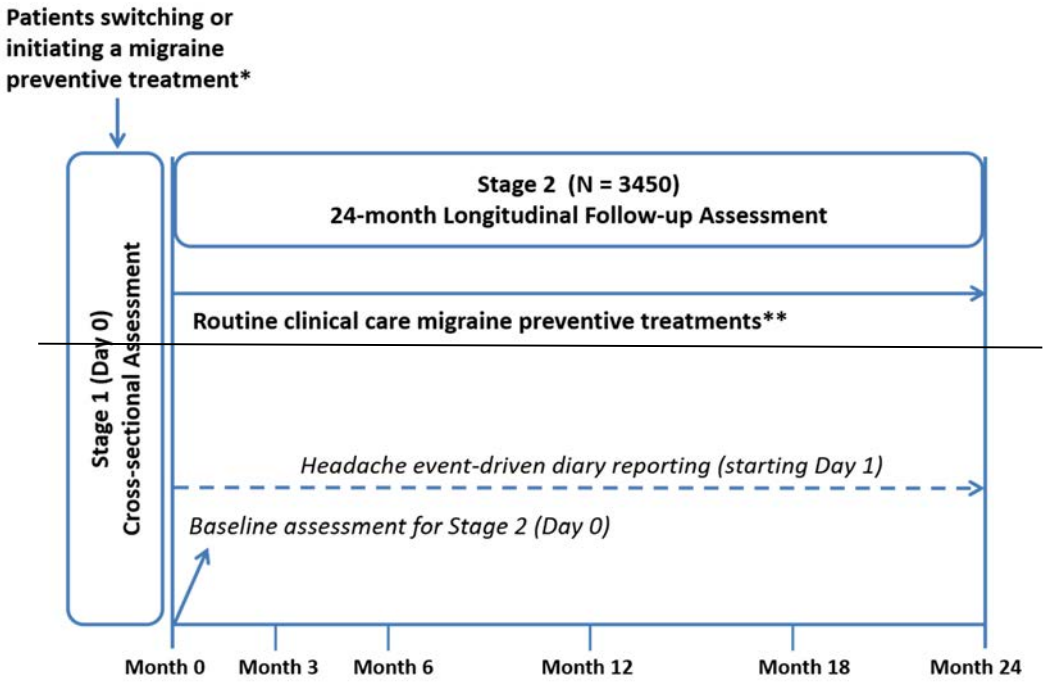
The protocol was amended to shorten the duration of PROs collected in the study, so the following questionnaires were collected only for the patients enrolled prior to the implementation of this amendment:

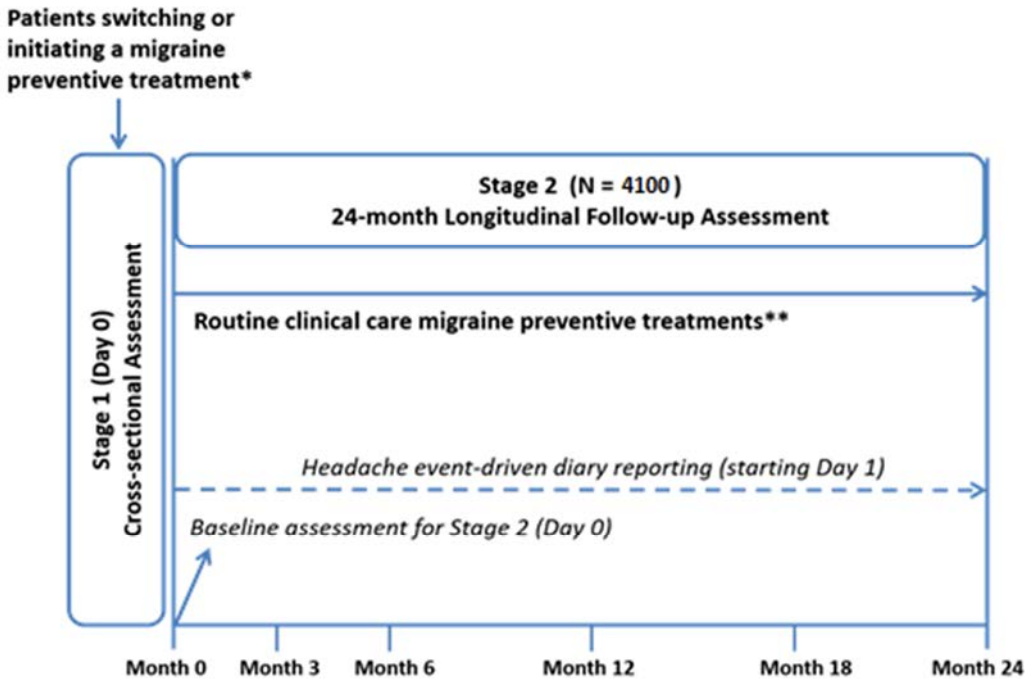
- Assess general health, including:
    - depression symptomatology using the Patient Health Questionnaire-8 (PHQ-8)
    - anxiety symptomatology using the 7-item Generalized Anxiety Disorder Scale (GAD-7)

- presence and severity of allodynia using the Allodynia Symptom Checklist (ASC-12).

- Assess ~~other outcomes, including:~~ migraine preventive treatment adherence using the Medication Adherence Reporting Scale (MARS-5).

6.1. Summary of Research Design





* All patients must meet the study selection criteria listed in Section 6.3.1 to participate in the study.
** Patients who are receiving one of the migraine preventive treatments/classes listed in Section 6.3.2 in routine clinical care at Month 0 will be eligible to participate in Stage 2.

Figure 1. Study design.

The purpose of Stage 1 is two-fold. It will be used to capture important real-world information in qualified patients. Additionally, Stage 1 will be used to generate a pool of patients, from which patients eligible for Stage 2 will be identified. A sufficient number of patients will be enrolled into Stage 1 to achieve approximately ~~3450~~ 4100 total patients entering Stage 2. In order to evaluate the study objectives in additional geographies, the number of patients in Stages 1 and 2 may be increased and their proportion is flexible, based on operational needs.

At Month 0 (Day 0), Stage 1 cross-sectional assessments will be collected, as well as baseline measures for those patients entering Stage 2. Migraine characteristics, including frequency of headache days and migraine headache days, will be collected by the investigator on Day 0 and will be based on the prior 30 days. If a patient does not initiate the index preventive treatment within 14 days of the baseline visit, they will be offered the opportunity to provide updated responses to the relevant variables for baseline migraine characteristics at the time that they initiate the first preventive treatment administration. If the patient does not provide updated responses to the relevant variables for baseline migraine characteristics, they will be excluded

from the study. A maximum of 56 days will be allowed between treatment assignment and first dose; patients whose first dose occurs 57 or more days after treatment assignment will be excluded from the study. Baseline measures including PROs should be completed prior to initiating the first preventive treatment. However, patients who complete baseline measures including PROs in the 3 days after initiating the first preventive treatment will still be allowed to remain in the study.

6.2 Data Collection

The investigator or designated site personnel will transfer data from the patient's medical record into electronic case report forms (eCRF) within the eDC system directly at the site for collection of patient characteristics at baseline, as well as recording details related to treatment patterns and disease status throughout the study.

In addition, an electronic device will be used in this study to collect electronic clinical outcomes assessment (eCOA) measures at the Stage 1 (cross-sectional) visit and Stage 2 Month 0, Month 3, Month 6, Month 12, Month 18 and Month 24 (longitudinal) visits. For eCOA data where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

6.3.2. Patient Groups

The following migraine preventive treatments will be evaluated in Stage 2. Patients will be eligible to enter Stage 2 if they are initiating one of the following treatments in routine clinical care on Day 0.

6.5. Variables/Measures

Details of the ~~patient headache diary and~~ questionnaires for the secondary objectives ~~to be used~~ are provided below. The timing of each assessment is provided in Attachment 1. It is anticipated that the total time to complete ~~all~~ these questionnaires at each visit would be approximately 20 minutes.

~~**Patient Headache Diary:** Headache event-driven diary reporting will begin on or after Day 1. Patients will be asked to record headache information via headache diary entries using their personal electronic device or web portal. Study investigators should encourage patients to complete the diary each time they experience a headache, within 48 hours of onset. Patients will receive a reminder to go into the diary to either verify all headache information has been entered or, if necessary, to update the diary.~~

~~The diary will be used by the patient to report:~~

- ~~headaches, including duration and severity~~
- ~~migraine-associated symptoms, and~~
- ~~use of any acute medication, by medication class.~~

Patient Health Questionnaire-8: The PHQ-8 is an 8-item patient-completed instrument used to detect depression and measure the severity of depressive symptoms (Kroenke and Spitzer 2002; Kroenke et al. 2009). The 8 items pertain to: anhedonia; depressed mood; trouble sleeping; feeling tired; change in appetite; guilt, self-blame, or worthlessness; trouble concentrating; and feeling slowed down or restless. Each item is rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), based on symptoms over the past 2 weeks. The overall score ranges from 0 to 24, with the levels of depression severity defined as follows: 0-4 no significant depressive symptoms; 5-9 mild; 10-14 moderate; 15-19 moderately severe; and 20-24 severe. The full instrument (PHQ-9, which includes a ninth item specific to suicide) is considered reliable and valid for use in research and clinical settings (Kroenke et al. 2001), including in patients with migraine (Seo and Park 2015a).

7-Item Generalized Anxiety Disorder Scale: The GAD-7 is a patient-completed questionnaire that was designed to screen for GAD and for measuring the severity of anxiety symptoms (Spitzer et al. 2006). The tool was developed based on symptom criteria for GAD in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (still applicable for the fifth edition), as well as review of existing anxiety scales, with items addressing the following: feelings of nervousness; uncontrollable worrying; excessive worrying; trouble relaxing; restlessness; irritability; and fearfulness. The patient identifies how much they have been bothered by these symptoms over the past 2 weeks. Each of the 7 items is rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), with total score ranging from 0 to 21. The levels of anxiety severity are defined as follows: 0-4 minimal; 5-9 mild; 10-14 moderate; and 15-21 severe. The instrument is considered reliable and valid for use in research and clinical settings (Spitzer et al. 2006), including in patients with migraine (Seo and Park 2015b).

Medication Adherence Reporting Scale: The MARS-5 is a patient-reported measure that consists of 5 common patterns of nonadherent behavior that respondents score on a 5-point Likert scale, with: 1 = always; 2 = often; 3 = sometimes; 4 = rarely; and 5 = never. Scores are summed and totals range from 5 to 25, with higher scores indicating higher self-reported adherence (Mahler et al. 2010).

Allodynia Symptom Checklist (ASC-12): The ASC-12 is a 12-item validated, quantitative, and patient-completed instrument to measure the presence and severity of cutaneous allodynia in association with headache attacks. The tool was developed to provide graded responses rather than dichotomous (present/absent) responses. The ASC-12 asks how often the patient experiences increased pain or an unpleasant sensation on the skin during the most severe type of headache when engaging in each of 12 items, such as combing hair, wearing eyeglasses, and exposure to heat or cold. Each of the 12 items has the following response options: does not apply to me (0 points); never (0 points); rarely (0 points); less than half the time (1 point); and half the time or more (2 points). The total score ranges from 0 to 24 and yields the following allodynia categories: none (0 to 2 points); mild (3 to 5 points); moderate (6 to 8 points); and severe (9 points or more) (Lipton et al. 2008).

6.5.1. Exploratory Variables/Measurements

Patient Headache Diary: Headache event-driven diary reporting will begin on or after Day 1. Patients will be asked to record headache information via headache diary entries using their personal electronic device or web portal. Study investigators should encourage patients to complete the diary each time they experience a headache, within 48 hours of onset. Patients will receive a reminder to go into the diary to either verify all headache information has been entered or, if necessary, to update the diary.

The diary will be used by the patient to report:

- headaches, including duration and severity
- migraine-associated symptoms, and
- use of any acute medication, by medication class.

The protocol was amended to shorten the duration of PROs collected in the study, so the following questionnaires were collected only for the patients enrolled prior to the implementation of this amendment:

Patient Health Questionnaire-8: The PHQ-8 is an 8-item patient-completed instrument used to detect depression and measure the severity of depressive symptoms (Kroenke and Spitzer 2002; Kroenke et al. 2009). The 8 items pertain to: anhedonia; depressed mood; trouble sleeping; feeling tired; change in appetite; guilt, self-blame, or worthlessness; trouble concentrating; and feeling slowed down or restless. Each item is rated on a 4-point scale (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day), based on symptoms over the past 2 weeks. The overall score ranges from 0 to 24, with the levels of depression severity defined as follows: 0-4 no significant depressive symptoms; 5-9 mild; 10-14 moderate; 15-19 moderately severe; and 20-24 severe. The full instrument (PHQ-9, which includes a ninth item specific to suicide) is considered reliable and valid for use in research and clinical settings (Kroenke et al. 2001), including in patients with migraine (Seo and Park 2015a).

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7.1. Determination of Sample Size

The study desires to enroll approximately ~~3450~~ 4100 patients (or more from additional geographies) with migraine to Stage 2 with country-specific targets of 1600 patients (with a 1:1 split, 800 patients each for galcanezumab and other migraine preventive treatments) from the US. Additionally, the following country-specific enrollment targets are planned (approximately split 1:1 between galcanezumab patients and other migraine preventive treatment patients): 1050 from Japan, 625 patients from Germany, 225 patients from Italy, and 200 patients each from Spain and United Kingdom (UK)~~, France, Taiwan~~, and 200 patients from United Arab Emirates (UAE).

Also, analyses and summaries will be conducted within each country or by region. Given the smaller sample size from Germany, ~~France,~~ Italy, Spain, UK, ~~Taiwan,~~ UAE, or other regions, analyses within these countries will be underpowered (<80% power).

7.2. Adjustments for Bias and Confounding

This is a noninterventional study to compare the effectiveness of galcanezumab to oral migraine preventive standard of care. Treatment selection may be influenced by patient characteristics. As a result, baseline characteristics of galcanezumab-treated patients may differ systematically from those of patients treated with oral migraine preventive standard of care. To make inference about the causal effect of a nonrandomized treatment on outcomes, propensity score will be used to account for underlying, observed differences between the galcanezumab and oral migraine preventive standard of care groups. The propensity score is the probability of treatment assignment conditional on measured baseline covariates. Several methods (see Table 1) will be used to estimate the propensity score with receiving galcanezumab as the dependent variable and

all baseline characteristics, demographics, and prior treatments described above as the independent variables. Quadratic and interaction terms may be also included. The specific covariates for the propensity model and method for estimation will be finalized and documented in the SAP prior to conducting any baseline or outcome analyses. Differences in baseline characteristics between galcanezumab and oral migraine preventive standard of care groups will be assessed using standardized differences and variance ratios for the primary objective. A standardized difference greater than 0.25~~1~~ is considered a meaningful imbalance that may require further investigation. Similarly, a variance ratio outside of the interval of 0.5 to 2.0 indicates further investigation is warranted.

7.5.1.6. Analyses of Time-to-Event Data

The objective of the analyses is to compare treatment discontinuation rates, all-cause time-to-treatment discontinuation, and time-to-treatment discontinuation for negative reasons (lack of effectiveness, intolerance to medication, lack of medication availability~~/lack of tolerability/noncompliance~~) between galcanezumab and other migraine preventive treatments initiated at baseline.

To assess the treatment effect on discontinuation, the log-rank test will be applied, or Cox proportional hazard models will be fitted using IPW, ~~to~~ or including the propensity score as ~~matched data (derived for the primary analysis).~~a covariate in the model.

Survival analysis will be performed for treatment discontinuation. Patients prematurely discontinuing the study are censored from their last available values onward (i.e., when lost to follow-up, when the patient entered another research study, or after death). Overall and by treatment groups, the unadjusted cumulative incidence of treatment discontinuation will be estimated based on Kaplan-Meier estimates. Differences in discontinuation of treatment between treatment groups will be tested using log-rank tests.

7.5.1.7. Analyses of Cost Data and Healthcare Resource Use (HCRU)

For comparisons between galcanezumab and oral migraine preventive standard of care on cumulative costs and HCRU since baseline, a weighted analysis using the ATE weights generated from the propensity score ~~matched data~~model will be used.

7.5.3. Interim Analyses

The interim analyses will be conducted to understand outcomes and treatment patterns after specific lengths of longitudinal follow-up have been completed. An additional intent is to be able to provide data to Health Technology Assessment organizations/health authorities upon their request. Five interim analyses are planned for this study. The first interim analysis will be conducted to describe baseline data for publication purposes after at least 3 months of study enrollment has been completed. The remaining interim analyses will occur after at least 1250 patients (625 patients each for galcanezumab and oral standard of care) in Stage 2 have completed 3, 6, 12, and 18 months of the study, respectively. The interim analyses at Month 3±1

in Stage 2 will conduct descriptive analyses of baseline data, propensity score ~~matching~~ estimation, sample size confirmation, and comparative analysis on the primary objective overall and by country level.

8.1. Primary Data Collection Study

The only protocol-defined adverse event (AE) to be collected in this study is treatment discontinuation due to lack of effectiveness.

The study personnel will collect treatment discontinuation due to lack of effectiveness via electronic data entry ~~lack of effectiveness, including all associated fatal outcomes,~~ occurring in temporal association with Lilly product(s) and comparator product(s) ~~(as applicable)~~ that are under evaluation as defined in this protocol.

All other AEs will not be actively collected due to lack of relevance to the study objectives.

Treatment discontinuation due to ~~L~~lack of effectiveness will be summarized in the interim study report, if applicable, and in the final study report.

Study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (e.g., regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or serious adverse events (SAEs) in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

8.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any serious event of treatment discontinuation due to lack of effectiveness arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A serious event of treatment discontinuation due to lack of effectiveness is one that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Or is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

8.1.2. Nonserious Adverse Events

The study personnel will record, via electronic data entry, any **nonserious** treatment discontinuation due to lack of effectiveness event arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness. Lilly or its designee will execute the extraction for EU sites to comply with the regulatory reporting requirements.

Attachment 1: Data Collection Schedule, Observational Study Protocol I5Q-MC-B004

	Stage 1	Stage 2					
Month		**Month 0**	**Month 3**	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Interval Allowance (weeks)			**±4**	**±4**	**±4**	**±4**	**±4**
Visit Type	**Flexible[a]**	**Flexible[a,b]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**	**Flexible[a]**
Observation Number:		T1	T2	T3	T4	T5	T6
Patient and Physician Characteristics							
Physician characteristics	X						
Informed consent	X						
Inclusion/exclusion	X						
Demographics	X						
Height and weight	X						X
Medical history and comorbidities	X						
Migraine history	X						
Migraine treatment history	X						
Current disease state	X		X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Summary (reason for termination from study participation)							X[c]
Treatment Pattern Measures[d]							
Preventive treatments for migraine	X		X	X	X	X	X
Acute treatments for migraine	X		X	X	X	X	X
Non-pharmacologic treatments	X		X	X	X	X	X
Scales, Questionnaires, and Outcome Measures[e]							
MIDAS	X		X	X	X	X	X
MSQ v2.1		X	X	X	X	X	X
HIT-6		X	X	X	X	X	X
HCRU/Employment ~~Status[e]~~Status[f]		X	X	X	X	X	X
WPAI		X	X	X	X	X	X
PGI-S	X		X	X	X	X	X
PSMQ-M			X		X		X
MIBS-4		X	X		X		X
mTOQ-~~6[h]~~ 6[g]	X		X		X		X
~~Event-driven electronic patient headache diary entries[f]~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
HCRU/Employment Status[e] [f]		X	X	X	X	X	X

~~PHQ-8~~		~~X~~	~~X~~		~~X~~		~~X~~
~~GAD-7~~		~~X~~	~~X~~		~~X~~		~~X~~
mTOQ-6~~h~~ g	X		X		X		X
~~MARS-5~~			~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
~~ASC-12~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Exploratory Variables/Measurements							
Event-driven electronic patient headache diary entries~~f~~ h		X	X	X	X	X	X
PHQ-8		X	X		X		X
GAD-7		X	X		X		X
MARS-5			X	X	X	X	X
ASC-12		X	X	X	X	X	X

Abbreviations: ASC-12 = Allodynia Symptom Checklist; GAD-7 = 7-item Generalized Anxiety Disorder Scale; HCRU = Health Care Resource Utilization questionnaire; HIT-6 = Headache Impact Test-6; MARS-5 = Medication Adherence Reporting Scale; MIBS-4 = 4-item Migraine Interictal Burden Scale; MIDAS = Migraine Disability Assessment; MSQ (v2.1) = Migraine-Specific Quality of Life Questionnaire version 2.1; mTOQ-6 = Migraine Treatment Optimization Questionnaire 6-item version; PGI-S = Patient Global Impression of Severity; PHQ-8 = Patient Health Questionnaire-8; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; T= time point; WPAI = Work Productivity and Activity Impairment Questionnaire.

a Visit can be office-, phone-, or web-based.

b Assessments/measures collected at Month 0 of Stage 2 will be completed at the Stage 1 visit following confirmation of Stage 2 eligibility.

c Month 24 or any postbaseline visit.

d Collected from medical records.

e Electronic clinical outcomes assessment (eCOA) measures completed by patient entry. ~~f These are event-driven entries and are not associated with scheduled study visits. Collection starts on or after Day 1 and spans the duration of Stage 2.~~

~~g~~ f Collected at baseline and monthly during Stage 2 from Months 1 through 24.

~~h~~ g Only for patients with acute medication use.

~~f~~ h These are event-driven entries and are not associated with scheduled study visits. Collection starts on or after Day 1 and spans the duration of Stage 2.