1. Protocol Amendment(c) 2017-6229 US Population-Based Longitudinal Survey in Migraine: OberVational survey of the Epidemiology, tReatment and Care Of MigrainE (OVERCOME)

Confidential Information

[galcanezumab (LY2951742), lasmiditan (LY573144)]

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Observational Study Protocol Electronically Signed and Approved by Lilly 16 AUG 2018
Amendment (a) Approved 21 MAY 2020
Amendment (b) Approved 26 JUN 2020
Amendment (c) Approval Date Provided Below

2. Abstract

- Title: 2017-6229 US Population-Based Longitudinal Survey in Migraine: ObserVational survey of the Epidemiology, tReatment and Care Of MigrainE (OVERCOME)
- Rationale and background: While there are a number of prior population-based surveys of migraine, they are limited by their focus on specific subsets of the migraine population (e.g., chronic migraine) or may be out-of-date. With new acute and preventive migraine medications coming to the market, it is important to understand how their introduction influences health care delivery, as well as how they are being prescribed and used, and their impact to people with migraine
- Research question and objectives: Understand the epidemiology and burden of migraine prior to, concurrent with, and following the introduction of novel medications for the acute and preventive treatment of migraine, identify factors influencing the initiation/ switching/ discontinuation of preventive and acute therapies in migraine, understand how the introduction of novel medications (e.g., calciton gene-related peptide (CGRP) monoclonal antibody (mAb) antagonists, oral CGRP antagonists, ditans) for migraine influences health care delivery and migraine care, and understand perceptions/attitudes about people with migraine.
- Study design: Multi-cohort, multi-wave prospective web-based survey
- Variables: Broad range of variables including: Demographics, lifestyle, comorbidities/health status, acute and/or preventive medication use, clinical features of migraine, quality of life/burden/impact, healthcare resource utilization, barriers to care seeking/medication use, stigma
- Data sources/Data Collection: Web-based survey (subset linked to claims)
- Study size: Three migraine cohorts, N=~20,000 each, 2 year longitudinal follow-up (5 web-based survey completions at 6-month intervals); a non-migraine (control) cohort at first and last cohort, N=~10,000, cross-sectional survey
- Data analysis: Observational study examining (1) Within migraine cohort analyses, (2) Between migraine cohort analyses (includes primary objective), (3) Longitudinal (within-patient) migraine cohort analyses (4) non-migraine (control) cohort and (5) migraine cohort (aggregate) analyses
- Milestones: Protocol approval by Lilly and ERB, Survey launch, Follow-up Surveys, Survey Complete, Database Lock, Scientific Disclosures

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4. Background and Rationale

Migraine is a debilitating neurological condition that affects approximately 15% of individuals in the United States (US) annually.[1,2] Migraine is categorized by the frequency of headache days—the number of days per month a patient experiences migraine. Approximately 91-93% of people diagnosed with migraine have episodic migraine (<15 monthly headache days), and the remaining 7-9% have chronic migraine (15 or more MHD per month for three or more consecutive months).[3]

Migraine is more prevalent among females than males (17% and 6% of females and males, respectively[4] and is more common among those with lower socioeconomic status (SES) and education, and with no notable difference among various racial or ethnic groups[5,6]. Migraine is most prevalent in people between 25 and 55 years of age, with females between the ages of 18 to 44 years experiencing the highest prevalence at 26.1%.[5]

The World Health Organization ranks migraine as one of the most debilitating illnesses.[7]

During migraine attacks, patients face intolerable pain and physical impairment, which is frequently accompanied by nausea, vomiting, and significant disruption of daily activities. Interictal burden can also be disruptive to normal function. Migraine patients face a variety of challenges, including significant missed school days in children and work days in adults,[8,9] medication overuse,[10] lower health-related quality of life (HRQoL),[11] and increased healthcare utilization (HCRU) and costs.[12,13] The costs of migraine in the US have been estimated at $56 billion (total) and $9 billion (incremental) annually.[14]

Migraine patients may be managed by general practitioners and neurologists, a small percentage of whom consider themselves 'headache specialists'.[15] Therapeutic management of migraine in current evidence-based guidelines[16,17] recommend individualized pharmacological management of acute attacks. These involve migraine specific medication classes such as triptans and ergotamines, and non-specific classes including non-steroidal anti-inflammatory medications, analgesics, and combination analgesic/NSAIDs. Within these classes are medications that are approved for the acute treatment of migraine in the US and others that are commonly used; these make up standard of care (SOC) for the acute treatment of migraine. Preventive therapy is generally recommended for patients who have at least 4 monthly headache days and/or significant impairment due to their migraine attacks. The AHS/AAN Guidelines for migraine prevention[17] as well as a recent AHS consensus statement regarding integrating new medications for migraine[18] include several medications that represent classes of medication (anti-seizure, anti-depressant, cardiovascular, neurotoxin) with high levels (Level A or B) of evidence supporting their safety and efficacy[17–19] Within those classes are medications that are FDA-approved for the preventive treatment of migraine in the US and others that are commonly used; these make up SOC for the preventive treatment of migraine.

There are several areas of unmet need in the therapeutic management of migraine. First, preventive-eligible patients remain under-treated; approximately 38% of the migraine population meet the requirement for preventive therapy, yet only approximately 3% to 13% actually receive

this form of care.[17,20] Second, inappropriate treatment of migraine also occurs. Triptans have established effectiveness, while opioids do not. Despite this, 1 out of 3 patients seeking care in emergency department settings receive an opioid for headache, while fewer than 1 out of 100 receive a triptan.[1] Despite the low relative frequency of use, overuse of triptans may also be problematic, as this acute treatment has been shown to be related to a faster progression to medication overuse headache (MOH), daily headaches and increasing migraine frequency, even at low doses.[21]

Several population-based surveys in migraine have been conducted in the past 20 years. The American Migraine Prevalence and Prevention (AMPP)[20] study was initially conducted in 2004 with iterations conducted over several years. The AMPP is the landmark study describing the population epidemiology, treatment patterns, and disease burden of migraine. AMPP screened 162,756 respondents using The International Classification of Headache Disorders (ICHD)-2nd Edition diagnostic criteria, enrolling a final sample of 19,189 people with migraine. Another notable survey, the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study,[22] was a web-based quota sample of 58,418 respondents screened using modified ICHD-3 beta diagnostic criteria, with a final sample of 16,789 people with migraine. Lilly will build upon these seminal studies with the current initiative, aiming to generate up-to-date data on the entire spectrum of migraine patients.

New classes of migraine-specific medications – monoclonal antibodies (mAbs) that target calcitonin gene-related peptide (CGRP; referred to as CGRP mAbs or anti-CGRP herein), small molecule CGRP receptor antagonists, and serotonin 5-HT1F agonists)– began gaining approval in the US beginning in 2018.[23–29] The uptake of CGRP mAbs, ditans, and oral CGRP antagonists and how they influence health care delivery and migraine care is of great interest to a broad range of stakeholders, including patients, providers (headache specialists and non-headache specialists alike), payers, and policy makers. Given the epidemiology of migraine, its impact on patients and the US healthcare system, high unmet needs, and the anticipated approval of a new medications to treat migraine, it is important to gather new data to further understand the economic implications, treatment patterns, and the burden from the perspective of people with and without migraine. Additionaly, it is valuable to observe the change in treatment landscape as new products enter into the market.

5. Purpose and Objectives

The purpose of this research is to understand the epidemiology and burden of migraine prior to, concurrent with, and following the introduction of novel medications for the acute and preventive treatment of migraine, identify factors influencing the initiation/ switching/ discontinuation of preventive and acute therapies in migraine, understand how the introduction of novel medications for migraine influences health care delivery and migraine care, and understand perceptions/attitudes about people with migraine. While retrospective claims studies, optimally substantiated by linkage to electronic medical records (EMR) data, can provide insights into treatment patterns, these approaches offer little opportunity to gain understanding of a large proportion of people with migraine suboptimally treated or unexposed to the healthcare system. Furthermore, disconnect between clinician and patient perception of disease management elicits the need for a person-based survey design to obtain a complete picture of migraine management.

5.1. Primary Objective

The primary objective of this research is to monitor and understand changes in health care delivery, acute/preventive migraine medication use, and impact to people with migraine with the introduction of new classes of migraine medications, including the new class of CGRP mAbs and new acute migraine medications (ditans, oral CGRP antagonists).

Specifically, this study, which is descriptive in nature, will address the following changes in health care delivery, migraine care, and outcomes from a baseline state (pre-/peri-approval of novel acute and preventive migraine medication classes) to a future state (post-approval of novel acute and preventive migraine medication classes). Three cohorts will be surveyed at different time points and longitudinal follow up surveys within each cohort will be conducted in order to understand the current and post-market (acute and preventive) state of care and migraine-related health. Our analyses will focus on the following:

1. Use of acute medications (relative frequency, combination therapy, reasons for initiating, switching, discontinuation/non-initiation, prescribing care location) and factors influencing their use
2. Use of preventive medications (relative frequency, combination therapy, adherence, reasons for initiating, switching, discontinuation/non-initiation, prescribing care location) and factors influencing their use
3. HCRU (visit frequency, diagnostic testing, emergency room (ER) dynamics, care location consulted) and factors influencing HCRU
    a. Health care costs will be examined if service provision can be appropriately estimated OR if sufficient linkage to health care claims data can be established
4. Impact of acute and/or preventive medications to the person with migraine (e.g., allodynia, frequency/severity of migraine attack symptoms, QOL, disability, functionality, barriers to care seeking, stigma, interictal burden) and factors influencing impact

5. How people without migraine perceive people with migraine, as well as issues related to their perceptions or attitudes of the disease and any stigma associated with it

Analyses will be conducted cross-sectionally, longitudinally, and in some cases (e.g., objectives 3 and 4) in reference to a non-migraine (control) group. Analysis #5 would be restricted to the non-migraine (control) group.

In addition, and if sample size allows, additional comparisons will be made for monthly headache day categories including those with episodic migraine (combined or separate for those with 0-3, 4-7, 8-14 monthly headache days) and chronic migraine (15+ monthly headache days).

5.2. Secondary Objectives

Compare cohorts of people with migraine on novel treatments compared with SOC treatments for migraine. Specifically, if uptake of novel treatments allows for sufficient sample size, we will perform class-level comparisons of how novel treatments for migraine influence clinical, humanistic, and economic outcomes compared with SOC treatments for migraine. Specifically, we will assess the association between clinical, humanistic, and economic outcomes with various medication groups of interest as sample sizes allow. Examples include, but are not limited to,

1. We will compare outcomes for people with migraine treated with CGRP mAb medications versus people using other approved treatments for migraine prevention (including divalproex sodium, propranolol, timolol, and topiramate) and other recommended (SOC based on AHS/AAN guidance) medications for migraine prevention.
2. Similarly, we will compare outcomes among people with migraine using novel acute medications (ditans, oral CGRP anatagonists [aka “gepants’]) vs. prescription (triptans, ergotamines) and OTC (including analgesics, combination analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids) medications used for the acute management of migraine

In addition, and if sample size allows, additional comparisons will be made for monthly headache day categories including those with episodic migraine (combined or separate for those with 0-3, 4-7, 8-14 monthly headache days) and chronic migraine (15+ monthly headache days).

5.3. Exploratory Objectives

None.

6. Research Design

6.1. Summary of Research Design

The study design is a multi-cohort, multi-wave longitudinal web-based survey. There are several elements to our approach:

1. To set a 'baseline' by characterizing the population of people with migraine prior to the introduction of novel acute and preventive treatments for migraine
    a. Approach: Cross-sectional study – the first wave of each of the three cohorts (2018, 2019 and 2020) will serve to characterize the population of people with migraine at each point in time
2. To create a reference group of people without migraine (controls) from the general population in order to have a reference group to compare with migraine group (e.g., HCRU, comorbidities) and understand attitudes of people without migraine towards those with migraine
    a. Approach: Cross-sectional study – during first wave of the first (cohort 1 (C1): 2018) and third (cohort 3 (C3): 2020) cohorts
3. To collect longitudinal data (within each cohort for up to approximately 2 years) for people with migraine
    a. Approach: Longitudinal study with 5 web-based survey completions at 6-month intervals (cohort 1 (C1): 2018-2020; cohort 2 (C2): 2019-2021; cohort 3 (C3): 2020-2022)

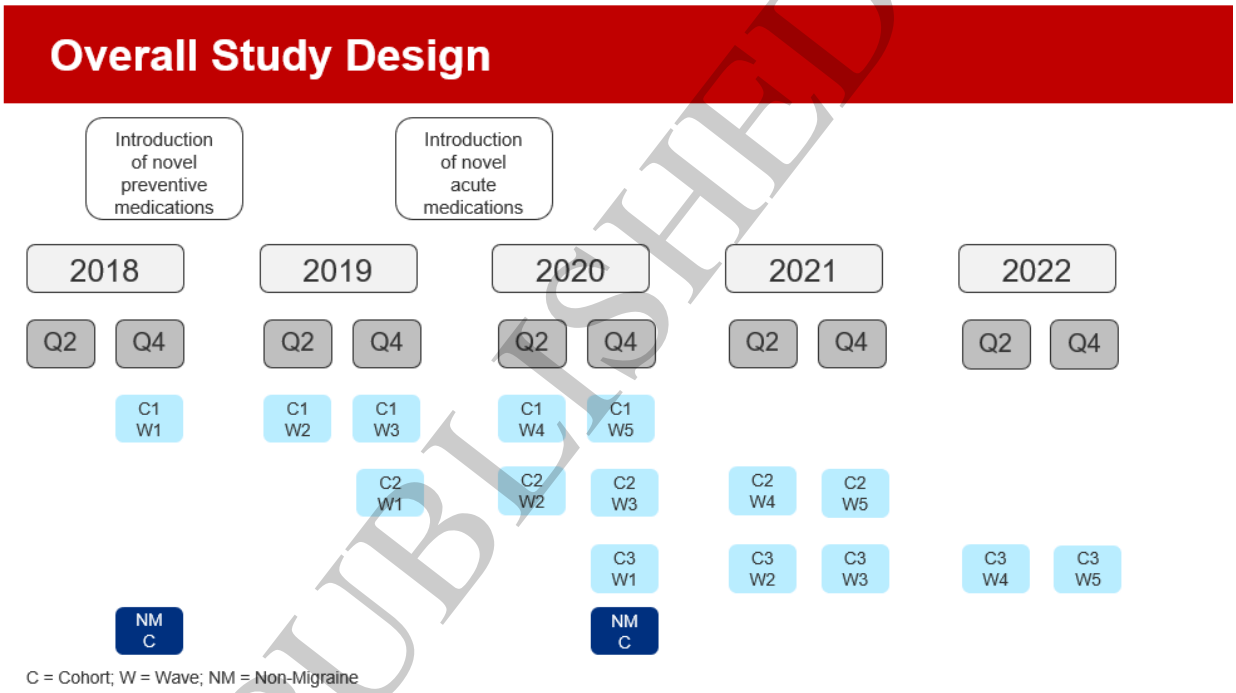
Eli Lilly and Company wishes to conduct three web-based panel survey studies of adults to accomplish our study objectives. To the extent possible, the study sample will represent the US adult population in terms of key demographic characteristics (age, gender, race, ethnicity, geography). Respondents with migraine will be identified from this demographically representative sample and, *if needed*, the sample will be stratified into groups based on the number of monthly headache days (0-3 vs 4+) in order to ensure adequate representation of people who may be eligible for preventive medications (4+ monthly headache days). This will be accomplished by oversampling respondents with 4 or more monthly headache days from an anticipated N~4,000 (based on the known distribution of monthly headache days in people with migraine) to N~6000. Among the remaining 14,000 target participants, most will be identified according to their ICHD-3 criteria then according to frequency (0-3 monthly headache days). Respondents without migraine will be collected using targeted sampling to represent the US adult population in terms of key demographic characteristics (age, gender, race, ethnicity, geography).

Key considerations regarding sample size: Make the study sample of sufficient size to potentially estimate the relative frequency of migraine in key demographic groups, with (i) key estimates (relative frequency of migraine and novel preventive medications) to be estimated with appropriate precision and (ii) to ensure the feasibility of accomplishing secondary objective #2 (impact of CGRPs as a class). The latter consideration is enhanced by the stratification approach to be used *if needed*, with over-selection of the cohort according to monthly headache days such

that an increased number of patients with 4+ monthly headache days, and therefore more likely to receive anti-CGRP therapy, will be included if needed. An additional driver of sample size is to survey each cohort of subjects repeatedly at 6-month intervals over a 24-month period (5 web-based survey completions for each cohort).

Figure 1 illustrates the overall study design. The observation periods are denoted with C for Cohort, W for Wave. Each migraine cohort will involve five observation periods (waves). Each non-migraine control group cohort will involve one cross-sectional survey.

Figure 1. Overall study design.



The 2 non-migraine (control) cohorts will facilitate comparisons of interest (e.g., demographics, comorbidities, HCRU) and understanding their perceptions of people with migraine. This survey is anticipated to be 10 minutes in length and contain questions about demographics, lifestyle, comorbidities/health status, HCRU, QOL/burden/impact, and attitudes/perceptions about persons with migraine (“stigma”).

The formal name of the study is ObserVational survey of the Epidemiology, tReatment and Care Of MigrainE, or the OVERCOME study.

6.2. Data Source

Data for the study will be obtained using responses from a customized web-based survey of invited consumers who meet inclusion and exclusion criteria and who agree to participate. Consumers will initially be recruited from Lightspeed Research (LSR) which is wholly owned by Kantar, with supplemental panels obtained from LSR partners Global Market Insite,

MarketCube, Dynata (Research Now), Disqo (Active Measure), Empanel, EMI and Mfour, if needed. These are large commercial consumer panels that profile their panelists on self-reported characteristics such as age, gender, location, income, ethnicity, household size, marital status, presence of young children, and education. The panels are reflective of the U.S. population. Although panels are not balanced to the U.S. census, they are sizeable enough to generate ending samples that are representative of the U.S. population. This ensures that our sample source is a reliable representation of the U.S. online population.

The online panels are opt-in panels where consumers who join make a conscious decision to participate regularly in surveys. Several methodologies, such as email, e-newsletter campaigns, banner placement, partnerships, direct mail, etc. are used by the panel companies to recruit panelists. Potential panelists are asked to complete an in-depth registration profile which includes numerous logic checks to ensure data quality. Steps taken to ensure data quality include, but are not limited to:

- Use of proxy detection which detects a proxy server used to mask the registrant's true IP address and past fraudulent activity;
- IP GeoFencing which detects the registrant's location via his/her IP address and determines his/ her eligibility for registration based on location-specific rules;
- CAPTCHA technology which prevents automated programs from joining our site through challenge-response tests; and
- Email address verification which queries our database to ensure the email address is unique (all registrants must verify their email addresses through a double opt-in registration process)

In addition, registrants' postal address and zip/postal code are verified against a current local address directory. Each computer is also tagged with a unique ID to ensure only one respondent per computer can participate in a survey. This ID would block survey respondents who attempt to complete the same survey from multiple panels and those who attempt to take a survey multiple times using different identities. Extensive analysis is conducted to understand and measure panelist activity. These analyses include the following: recruitment source, panel composition, longevity on panel, response, participation and dropout rate, and response quality.

The panel member details are maintained in confidence and are used for research purposes only. No information that could personally identify the respondent can be released, nor can personal information be sought from the panelists or about the panelists without their consent.

Based on panelist self-reported background information, *a representative sample* reflecting socio-demographic characteristics of the adult population based on U.S. Census data will be selected from these panels reflecting the marginal distribution of age, gender, and ethnicity / race. Next, a sampling frame consisting of all legal age panelists from each state will be created. Panelists with required demographic profiles will be randomly selected for inclusion in the invited sample until demographic profile quotas are met in each study cohort.

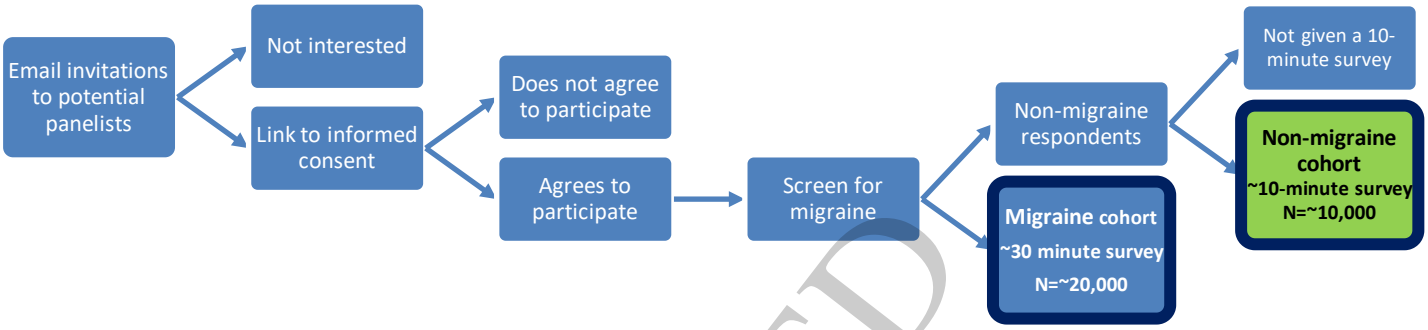
Online panel sampling tools will be used to generate traffic to the survey, based on the targeted demographics and considering expected response rates for the different demographic strata.

During the fieldwork, sample performance will be monitored daily; analysis of response rates and qualifying rates will be done for each demographic quota within cohorts. The panels will utilize manual monitoring and dynamic automated tools to ensure that the sampling process results in the desired demographic quotas. As quota targets are achieved, the random sample selection process will be refined to target only panelists matching those demographic characteristics whose quotas have not yet been reached.

Like the socio-demographic variables, panel source will also be balanced across cohorts through sample assignments, daily monitoring, and sample management, as well as extended duration of fielding. Prior to launching the study in full, Kantar will execute a soft launch. The goal of the soft launch process is to confirm that all facets of the data collection process function according to protocol; items of specific interest include the initial incidence rate, the length of interview, and the accuracy of the web-based instrument (i.e., survey), all of which work to ensure the primary objectives of the research are met. Soft launch data will be used as part of the final data set, unless quality control checks suggest an error or unintended issue that may have compromised the data. In that event, the data will be saved but not included in the final data set. A staggered approach will be taken, e.g., Kantar will check data for the first ~200 completes, then check additional data for up to ~500 completes as needed.

Once the accuracy of the web-based instrument is verified through soft launch, the study will be fully launched with invitations being sent to a broader number of potential respondents. The flow or derivation of the samples is illustrated in Figure 2. All potential respondents will receive their invitations from their respective panels to participate in the survey. The email will include the following: (1) general invitation; and (2) a link to the panelist welcome page. Approximately 2 to 4 days after the initial invitation, non-responders will be sent an e-mail reminder regarding the availability of the survey. New invitations will be sent until the target sample size is reached. Panelists previously invited will still be able to participate if their desired quota is not reached. Respondents will be able to complete the online survey via computer, tablet, or smartphone. See Appendix for all panel correspondence materials (*in development*).

Figure 2 Survey panel process



If invited panelists are interested in participation, they click on the link at the bottom of the invitation or copy and paste the link into their browser. The link takes respondents to the panelist welcome page where they are asked to agree to the conditions of the informed consent (Appendix 3). Participants with a positive informed consent are presented with another link to the screener. Specifically, if potential respondents agree to participate in the study after reading the statement of informed consent, they will select "I agree to participate" and will then be taken to the screener. Those who select "I do not agree to participate" will be thanked before exiting. The informed consent includes information about the goals of the study, the approximate length of the survey (~30 minutes for migraine cohort; ~10 minutes for non-migraine cohort – based on preliminary testing) and their participation, and compensation for participation, being sensitive to both the general population and migraine surveys. Lastly, the statement of informed consent provides potential respondents with the contact information for panel managers to address any concerns they may have.

Panelists who agree to participate receive a nominal amount of points for completing a survey which are deposited into their account and are aggregated over time and can later be redeemed for online gift certificates. Each point is worth about 1/100th of a penny, which equates to a dollar value of several pennies per survey. Point values are based on length of interview.

All data collection, data management, and data cleaning will be conducted by Kantar. All screener data will be saved. Kantar and Eli Lilly and Company will be responsible for the statistical analysis.

Data will be stored at Kantar and transferred to Lilly using a secured, password-protected online data transfer system.

6.3. Data Collection

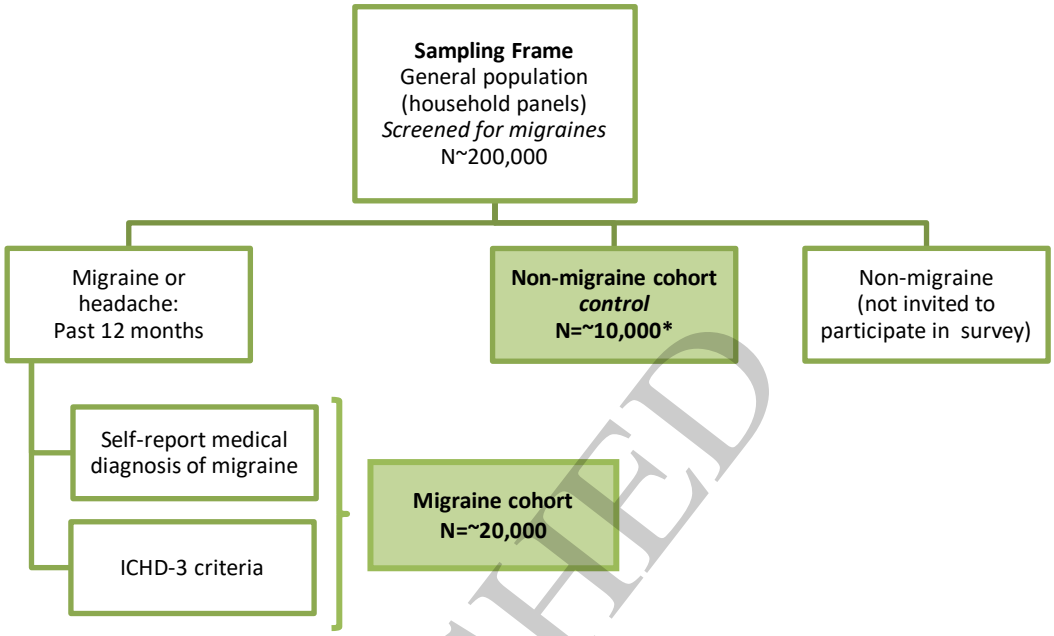
Kantar will work in partnership with HealthVerity to provide linked claims data for the participants of the survey. HealthVerity (www.healthverity.com) is a healthcare data broker for

multiple medical and pharmacy claims, as well as EMR datasets. HealthVerity will link the datasets using HIPAA-certified de-identification linking software. The linking software uses a proprietary probabilistic matching algorithm on the Protected Health Information (PHI) from claims and Personally Identifiable Information (PII) from the survey to find the matches and a bloom filter hash on each variable. HealthVerity has validated the linking engine with a 0.2% false positive rate and 2% false negative rate, well below the industry standards of 1% and 7-12%, respectively. Kantar will ensure that survey questions will not cause any HIPAA-related privacy issues when linked with claims data (i.e., that 're-identification' does not occur with data linkage). A HIPAA-certified statistician will review the questionnaire and flag any questions that need to be aggregated prior to linkage to claims data. Specifically, in order to reduce the likelihood of patient identification, questions with less common response options will be aggregated. For example, number of persons in a household greater than 5 will be collected as 5+ (and not as 6, 7, 8, etc) or ages over 85 years will be collected as an 85+ year old and not according to the specific age. In the event that data must be collected at a more granular level (e.g., if we need to collect information about specific insurance rather than whether a person has private or public insurance), Kantar would structure analyses in such a way that the person or persons working with linked claims data will never have access to the survey data as collected, only to the survey data once aggregated to meet HIPAA requirements.

6.4. Study Population

Figure 3 shows a high-level summary of respondent selection. Survey respondents will be identified from the US adult population from panels as outlined previously. Respondents (current headache/migraine and identified as having migraine EITHER via a validated screener and/or self-reported diagnosis of migraine from a healthcare provider) and if they qualify, will become part of the longitudinal cohort which will be surveyed at baseline and followed for two years. If a respondent does not screen positive for migraine, they will be invited to be part of the 'general population non-migraine (control) group' (for cohort 1 and cohort 3 only) and will be surveyed once. The 'green' boxes indicate the migraine and non-migraine study groups that will be studied. Cohort 1 migraine respondents will be a representative sample of the general population while cohorts 2 and 3 sample will be based on the migraine population demographic proportions observed in cohort 1. The general population non-migraine (control) group' (for cohort 1 and cohort 3 only) sample will closely mirror the latest US census by region, sex, age, and ethnicity/race.

Figure 3 **Planned respondent selection.**



*Non-migraine cohort will be collected during for cohort 1 and 3

6.4.1. Selection Criteria

Included in the study are participants who are:

1. Aged 18 years or older
2. Residence in the United States
3. Member of online survey panel
4. Access to the internet
5. Ability to read and write English
6. Provide electronic informed consent
7. According to survey population:
    a. [Migraine cohort] Persons reported having a headache or migraine (any type) in the last 12 months AND identified as having migraine based EITHER on the modified ICHD-3 screening criteria (with a frequency of less than half the time, half the time or more with their severe headaches, report 2 or more of 4 pain symptoms (the pain is worse on just one side, the pain is pounding, pulsating, or throbbing, the pain has moderate or severe intensity, the pain is made worse by routine activities such as walking or climbing stairs) and report either nausea or vomiting, or both photophobia and phonophobia) OR self-reported physician diagnosis of migraine

b. [Non-migraine (control) cohort] General population of people without migraine

Excluded from the study are participants who are:

1. Unwilling or unable to provide electronic informed consent
2. [For cohort 3] Having a self-reported medical diagnosis of cluster headache with no other self-reported medical diagnosis for migraine

Excluded from the Migraine cohort:

1. Anyone with all headaches in the past 12 months due to hangover or illness
2. [For cohort 3] Having a self-reported medical diagnosis of cluster headache with no other self-reported medical diagnosis for migraine

6.4.2. Subject Groups

This study will involve numerous between-subject and within-subject comparisons. All comparisons will be outlined *a priori* in specification documents.

As described previously, the subset of patients taking anti-CGRPs is one subgroup of interest.

In addition, specific group comparisons include, but are not limited to the following:

3. Class-level comparison of CGRP mAbs vs. the four SOC medications that are indicated and approved in the US for the prevention of migraine (divalproex sodium, propranolol, timolol, and topiramate) and other recommended (SOC based on AHS/AAN guidance) medications for migraine prevention.

   In addition, and if sample size allows, additional comparisons will be made in the subgroup of patients with chronic migraine (i.e., CGRP mAbs vs. botulinum toxin)

4. Class-level comparison of novel acute medications vs. SOC medications that are indicated and approved in the US for the treatment of acute migraine (triptans, ergotamines)
5. Class-level comparison of novel acute medications vs. OTC/other prescription medications (analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids) that are used for the treatment of acute migraine

In addition, and if sample size allows, additional comparisons will be made for monthly headache day categories including those with episodic migraine (combined or separate for those with 0-3, 4-7, 8-14 monthly headache days) and chronic migraine (15+ monthly headache days).

It should be noted that all comparisons highlighted in #1-3 are conditional on their introduction to market and sample size.

No subject withdrawal criteria is required rather there will be loss-to-follow-up of participants not participating in subsequent survey waves.

6.5. Time Periods

Figure 1 above illustrates the planned study time periods comprising respondent enrollment for baseline and follow-up surveys (see Table 3 below). Timelines are approximations.

6.6. Study Therapies

As this is an observational study, treatment pattern and treatment initiation or changes are solely at the discretion of the physician and the subject. 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. Participation in the study will in no way influence payment or reimbursement for any treatment received by subjects during the study

6.7. Variables/Measures

Table 1 presents the study variables and operational definitions for the migraine survey, and Table 2 presents the study variables and operational definitions for the non-migraine control survey.

Table 1. Study Variables: Migraine Survey

Domain	Variable
Confirmation of eligibility	Consent to release information
	AE reporting consent
	Confirmation of selection criteria (see Section 6.4.1)
	Confirmation of identity from Wave 1 via Age and Sex (follow-up waves only)
Demographics	Age
	Sex at birth
	Location
	Household composition
	Marital status
	Employment status
	Education
	Household income before taxes
	Primary income earner
	Ethnicity
	Race
Lifestyle	Body Mass Index (BMI)
	Current smoker/tobacco/other substance use
Comorbidities & health status	Comorbidities ever diagnosed by healthcare professional (HCP)
	Comorbidities in past 12 months
	Mental health (PHQ-4/8; GAD-7)
	Cardiovascular comorbidities
	Cardiovascular procedures
	Women's health
	Constipation
Acute medication	Acute medication ever/recently used
	Acute medication currently use
	Last use of acute medication
	Reason(s) for not taking acute medication to treat headaches
	When and why acute medication is used
	Experiences with HCP and insurance

Domain	Variable
	Order of medications used
	Efficacy of medication (including mTOQ)
Preventive medication	Preventive medication ever/recently used
	Preventive medication currently use
	Time on preventive medication
	Health condition ever used preventive medication for
	Last use of preventive medication
	Reason(s) for not taking preventive medication
	When and why preventive medication is used
	When most recent preventive medication was stopped
	How long took preventive medication before stopping
	Experiences with HCP
	Efficacy of medication
HCRU	HCP/ER visit
	HCP consultation by specialty
	HCP communication type
	Medication used before/during/after ER visit
	Migraine Diagnosis
	Age at first diagnosis (headache/migraine)
	Medical tests
	Pharmacy use
Clinical feature of migraine	Symptoms (including ASC-12, MSSS)
	Frequency of symptoms
	Age of first attack
	Migraine disability
	Experience and timeline of most recent attack
	When previous attack ended
	Management of most recent attack
	Impact of most recent attack
	Symptoms of most recent attack
QOL/burden/Impact	MSQL v2.1
	IMPAC scale
	How much pain and symptoms interfere with everyday life
	Driving attitudes and behavior
	MIDAS
	EQ-5D-5L & EQ-VAS
	Interictal burden/MIBS-4
	Work productivity and activity impairment WPAI
	Lifestyle/workstyle/employment circumstance changes due to unexpected environmental factors (e.g., coronavirus (COVID-19) pandemic)
Barriers to care seeking/medication use	Hesitation to seek care
	Reasons for hesitation to seek care
	Barriers to using medication
Stigma	Perception and behaviors regarding migraine
	Consequences of migraine burden

Table 2. Study Variables: Non-Migraine (Control) Group Survey

Domain	Variable
Confirmation of eligibility	Consent to release information
	Confirmation of selection criteria (see Section 6.4.1)
Demographics	Age
	Sex at birth
	Location
	Household composition
	Marital status
	Employment status
	Education
	Household income before taxes
	Primary income earner
	Ethnicity
	Race
Lifestyle	Body Mass Index (BMI)
	Current smoker/tobacco/other substance use
Comorbidities & health status	Comorbidities ever diagnosed by healthcare professional (HCP)
	Comorbidities in past 12 months
	Mental health (PHQ-4/8; GAD-7)
	Cardiovascular comorbidities
	Cardiovascular procedures
	Women's health
	Constipation
HCRU	HCP consultation
QOL/burden/Impact	EQ-5D-5L & EQ-VAS
Stigma	Perception and attitudes towards migraine or other diseases
	Consequences of migraine and other disease

7. Sample Size and Statistical Methods

7.1. Determination of Sample Size

The sample size was selected to provide 90% power for a) detecting an effect size of at least 0.11 for the 1 year difference within a longitudinal cohort; b) 90% power to detect individual factors associated with at least a 9.7% difference for the change in a pre-defined binomial attribute (eg change in opiod use) within a longitudinal cohort; c) 90% power to detect at least a 3.0% difference between Cohort 1-1 and Cohort 2-1 (or Cohort 2-1 and Cohort 3-1) in percentage of patients exhibiting a pre-defined binomial attribute. Additionally, the sample size will allow precision of at least 5.7% in the estimate for the percentage of migraine patients exhibiting a pre-defined binomial attribute.

7.1.1. Assumptions

The estimated sample size for each cohort and survey wave are presented in Table 3.

Table 3. Sample sizes for the study – migraine and non-migraine cohorts

Study	Estimated N	Estimated % of primary cohort
Migraine Cohort (C)1_Wave (W)1 – Baseline	20,000	100%
Non-migraine Cohort 1	10,000	na
Migraine C1W1 – claims	2,000-3,000	10-15%
Migraine C1W2 – 6 months post-baseline	5,600	28.0%
Migraine C1W3 – 12 months post-baseline	4,000	20.0%
Migraine C1W4 – 18 months post-baseline	2,000	10.0%
Migraine C1W5 – 24 months post-baseline	1,000	5.0%
Migraine C2W1 – Baseline	20,000	100%
Migraine C2W2 – 6 months post-baseline	7,000	35.0%
Migraine C2W3 – 12 months post-baseline	4,000	20.0%
Migraine C2W4 – 18 months post-baseline	2,000	10.0%
Migraine C2W5 – 24 months post-baseline	1,000	5.0%
Migraine Cohort (C)3_Wave (W)1 – Baseline	20,000	100%
Non-migraine Cohort 3	10,000	na
Migraine C3W2 – 6 months post-baseline	7,000	35.0%
Migraine C3W3 – 12 months post-baseline	4,000	20.0%
Migraine C3W4 – 18 months post-baseline	2,000	10.0%
Migraine C3W5 – 24 months post-baseline	1,000	5.0%

We based our estimation of sample size needed on the key study objectives: understand the epidemiology and burden of migraine prior to, concurrent with, and following the introduction of novel medications for the acute and preventive treatment of migraine, identify factors

influencing the initiation/ switching/ discontinuation of preventive and acute therapies in migraine, understand how the introduction of novel medications for migraine influences health care delivery and migraine care, and understand perceptions/attitudes about people with migraine. We made the following assumptions:

1. The one-year prevalence of migraine in the US population is approximately 12% [17]
2. Approximately 20% of migraine patients use preventive medications [11,17,20]
3. *If needed*, a stratified sample will be used to ensure sufficient responses among migraine sufferers who are eligible for CGRPs (i.e., respondents with 4+ monthly headache days). Target completes for 4+ are approximately 6,000 of the 20,000 total or 30%, a 7% increase from the expected 23%
4. New acute and preventive medications for migraine increased by 85% from Q2 2019 to 2020.[29] In their first full year of launch, the share of market for all approved anti-CGRP therapies was estimated to be approximately 5% (2019) and will be approximately 15% by 2023 (Analyst report, link)
5. Longitudinal participation rates at each 6-month interval of the original cohort (i.e., respondents for each wave are identified from baseline cohort regardless of prior wave participation) are expected to vary between approximately 5%-35%. We note that there is an expected loss-to-follow-up of active panel participants at each survey wave. Estimated percentage of respondents in each cohort that will complete a survey for all 5 visits is <5%; with the desire to have at least 1,000 patients available at that time (2 years).
6. Based on Kantar's National Health and Wellness Survey (NHWS) prevalence estimates for 2017 of persons who experience 4+ migraines in the past 30 days (i.e., those who would be eligible for preventative treatment), with a "base" sample of 20,000, we would expect to gain ~4,000 completed surveys in Migraine Cohorts 1 and 2 among persons who experience 4+ migraines per month. Increasing the proportion of preventive-eligible respondent completes to 6,000 increases the power of the study to detect changes in use of opioids from Migraine Cohort 1 to Cohort 2 by ~20% (internal communication, J Cambron-Mellott, May 2019). This will be done if needed.
7. Based on prior internal Lilly research, approximately 10% of the preventive-eligible population uses opioids specifically for treatment of migraine

7.1.2. Precision and Power

The sample size was selected to meet the primary objective and key secondary objectives. To simplify, the power/precision produced by the planned sample size is provided for 4 general types of analyses: (1) Within Cohort analyses [e.g. within Migraine Cohort 1_1 Baseline and within Migraine Cohort 2_1 Baseline], (2) Cohort 2 vs Cohort 1 analyses [(Migraine Cohort 2_1 Baseline - Migraine Cohort 1_1 Baseline; includes primary objective), and (3) Longitudinal (within-patient) Cohort analyses. Within each type of analyses, we assess power/precision in 3 general patient populations: full migraine population, preventive eligible patients, and anti-CGRP treated patients.

7.1.2.1. Within Migraine Cohort Analyses

Inclusion of 20,000 patients within each of the three baseline cohorts will allow for the following precision (the half-width of a 2-sided 95% confidence interval) for an estimated percentage in a particular cohort (1,2 or 3).

Population	Precision for Estimates
Full Migraine (N = 20,000)	0.75%
Preventive Eligible	1.3%
Anti-CGRP treated	5.7%

For example, the estimate of the percentage of migraine patients who are preventive eligible will have a 2-sided 95% confidence interval width of 1.5% (+/- 0.75%). Estimation of the percentage of preventive patients who are treated with a CGRP medication will have a 2-sided 95% confidence interval width of approximately 2.6% (+/- 1.3%). Note that for these calculations we are using a binary variable and assume an observed rate of 50%. Thus, the precision values shown provide the maximum confidence interval widths.

While the anti-CGRP class is mentioned above as one subgroup of interest, section 7.5.3 lists other subgroup comparisons of interest if sample sizes allow. While minimum subgroup sizes necessary for analysis will depend on the question and outcome, in general – a minimum total sample size of 225 will provide the ability to detect effect sizes of 0.5.

7.1.2.2. Migraine Cohort to Migraine Cohort Analyses

Comparisons between data in Migraine Cohort 2_1 and/or Migraine Cohort 3_1 vs Migraine Cohort 1_1 will allow us to address the primary objective of measuring changes in health care delivery, medication use, and impact to patients over time as new classes of treatments are introduced. Power for detecting differences in percentages (assuming a binary outcome) between Migraine Cohort 1_1 and Migraine Cohort 2_1 and/or Migraine Cohort 3_1 for each population is provided below.

Population	Migraine Cohort 2_1 vs Migraine Cohort 1_1 or Migraine Cohort 3_1 vs Migraine Cohort 2_1Differences that can be detected with 90% Power
Full Migraine	1.7%
Preventive Eligible	3.0%

For example, this sample size will provide 90% power for testing for detecting a 3% increase in the percentage of patients in use of anti-CGRP medications among Preventive eligible patients in Migraine Cohort 2_1 vs Migraine Cohort 1_1. Similarly, we will have 90% power to detect a decrease of 1.7% in the use of opioid medications in Migraine Cohort 2_1 vs Migraine Cohort 1_1 in the full migraine population. Again, these calculations provide a lower bound on the power as we assume an observed rate of approximately 50% in these calculations.

7.1.2.3. Longitudinal Cohort Analyses

Assuming a 5-35% participation rate at each time point, the power calculations for analyses with the longitudinal cohort are based on 5000 patients with 1-year data in the full Migraine population (1500 Preventive eligible; ~30%). This sample size will provide the following power for (1) comparing 1-year outcomes between cohorts of interest (assuming at least 25% of the sample in each cohort of interest); (2) statistically detecting associations between a factor and 1-year outcomes of interest.

Note that though the power is based on patients remaining at 1-year, all patients with any post baseline data will be used in the analysis as described in Section 7.5.1.3. Thus, the sample size calculations below may be conservative.

Population	Cohort Effect Sizes at 1 year detectable with 90% Power	Factor Associations detectable with 90% Power
Full Migraine	.11	5.3%
Preventive Eligible	.20	9.7%

For example, we will have 90% power to detect individual factors associated with at least a 5.3% difference in reduction in opioid use and 90% power for detecting effect size differences of 0.20 between preventive eligible patients taking anti-CGRPs and those not taking anti-CGRPs.

The following table shows the estimated lower bound for power at 12 months and 24 months to detect a specified change from the baseline percentage for binomial endpoints (for example, 5% corresponds to 50% changing to 55%).

Population	Change (x 100%)	Power	
		12-month change from baseline	24-month change from baseline
Full migraine	5%	99%	61%
	10%	≈100%	99%
	15%	≈100%	≈100%
Preventive eligible	5%	66%	22%
	10%	≈100%	66%
	15%	≈100%	95%

7.1.2.4. Healthcare Claims Data Linkage

For the claims data, we estimate the match rate at 10-15% (2,000-3,000 for each of the 20,000 cohorts), based on the following:

- During the matching process, we have seen approximately 80% (in this case, 16,000 people) to have strong enough PII to match against HealthVerity's patient master, the first step in the process
- HealthVerity's databases show they contain approximately 20% of the people in the US with at least 1 medical and pharmacy claim. This attrition brings the number of people to 3,200.

Leaving a buffer for lower estimates, less strong PII, etc., we brought the conservative number to 2,000 – 3,000 people for each wave of 20,000 participants.

7.2. Adjustments for Bias and Confounding

7.2.1. Approach to Ensure Generalizability

Respondents will be recruited based on their membership with an online market research panel and their recruitment could be considered a convenience sample. While multiple panels are used, similar to any other data source used (e.g. random-digit dialing), consumers who are not part of these data sources will not have the opportunity to participate. Further, due to sample selection during recruitment, segments of the general population may be over-represented such as those healthy enough to participate, hence the possibility of selection bias. Although these issues raise concerns about the external validity of the findings (e.g., our sample may not be fully generalizable to all people with migraine), the recruitment plan is designed to mirror the underlying populations. Even with efforts to ensure a representative sample using stratification based on the US for age, gender and race, ethnicity, the precise proportion of subgroups which will appear in the study sample cannot be completely controlled. In fact, regardless of how respondents are recruited, there will always exist the possibility that the people who decline the opportunity to participate in the research differ in a systematic way from the people who accept the opportunity. Weighting may be used to bring the study sample more in line with the distribution of the population and mitigate the effects of over-representation.

7.2.2. Approach to Adjust for Bias/Confounding

Indeed, given the oversampling of persons according to the frequency of monthly headache days, we anticipate re-weighting the final included population so that it is representative of the US migraine population. However, we note that weighting the data will be determined following the data fielding and performed if needed.

If perfomed, weights may be derived from the empirical distribution of monthly headache days for age and sex groups from other population-based studies of migraine (e.g., NHWS, AMPP). Thus, under-represented respondents (0-3 monthly headache days) will receive a weight >1 and over-represented respondent (4+ monthly headache days) will receive a weight <1.

As noted above (section 7.2.1), weighting will be used to adjust prevalence rates if needed, since, by design, the study design is biased to overrepresent persons with 4+ monthly headache days. Data from this study will depend on respondent self-reporting, subsequently reported variables may also be subjected to recall bias. Self-reported data collection is a standard approach and any potential problems with recall bias are anticipated to be constant across time points. The use of linked claims data reduces this bias for the specific outcomes such as HCRU and treatment history.

For selected analyses, comparisons of outcomes between groups based on medication treatments may be performed. In such cases, analyses adjusting for potential confounding variables will be performed. Variables included as confounders will be based on prior research and specific models included in statistical analysis plans. Several possible statistical approaches will be considered to adjust for potential bias or confounding, including sample stratification (e.g., by gender), adjusted analyses (e.g., multivariable regressions adjusting for covariates), or propensity score matching (i.e., with the general population cohort).

Statistical analysis will be conducted by staff at Kantar and Eli Lilly and Company.

7.3. Missing Data

All data will be collected using a programmed web-based survey. Based on the programming of the survey, out-of-range or implausible responses will not be possible. Prior to initiating the study, appropriate edit programming will be conducted to assure the final dataset requires minimal cleaning of invalid responses. The questionnaire will be designed so that instructions are as easy to understand and clear as possible to help avoid missing data. These programming procedures for the web-based survey data entry tool will include response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or data manipulations will be cross checked by Kantar team members who independently replicate the results and/or verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before any further analysis is completed.

Once final datasets have been created, missing data will be noted and reported as its own category. No imputation strategy will be employed.

7.4. Significance Levels and Multiplicity

Two-tailed p-values of less than 0.05 will be considered statistically significant, unless otherwise noted. There will be no adjustment for multiplicity.

7.5. Other Analyses

7.5.1. Outcomes Analyses

Below is a general outline of the analysis plan for this study. Analyses are grouped into five general categories: cross-sectional cohort analyses, differences between cohort analyses, longitudinal follow-up analyses, linked claims, and non-migraine population analysis. For key

analyses, separate specification documents will be developed that will provide the analytical methods in detail. For analyses (e.g., cross-sectional, longitudinal), all data will be used.

Descriptive statistics will be conducted to provide summaries for all variables in each cohort and specific subgroups of interest (e.g. preventive eligible, patients taking CGRP mAbs, etc.). Continuous variables will be summarized as means with standard deviations, or medians and ranges, as appropriate. Categorical variables will be summarized as frequencies and percentages.

7.5.1.1. Analysis of Cross-Sectional Cohorts

This section describes the analysis of Migraine Cohort 1_1 (and repeated for Migraine Cohort 2_1 and Migraine Cohort 3_1), the cross-sectional data from the full migraine population. Analyses are descriptive in nature, providing a baseline assessment of the epidemiology, healthcare use, impact of migraine to the patients, barriers to care, etc.

Estimation of key measures will be conducted using means/proportions along with 2-sided 95% confidence intervals (large sample normal approximation). For extremely skewed continuous data, bootstrapping may be utilized. If an oversampling of those with 4+ monthly headache days is needed, a weighed mean/proportion and variance will be used in the above analysis in order to draw inferences to the full migraine population. Expected weights will be 0.67 for 4+ monthly headache days (as this subpopulation will be over-sampled) and 1.14 for the remainder of the migraine population

Estimates within subgroups of interest will be performed based on pre-specified subgroups and questions. Various appropriate analytic approaches may be taken based on the scientific question and data. The specification document for an analysis will articulate the identified analytic approach. Examples include identifying factors associated with key variables where the factors may be identified using classification and regression tree (CART) or Chi-square Automatic Interaction Detector (CHAID) methodology, clustering, bivariate analyses, and/or regression-based methods.

7.5.1.2. Analysis of Changes between Cohorts

These analyses cover the primary study objective of assessing changes in medication use, health care delivery, migraine care, outcomes, and factors influencing each of these from a baseline state (Migraine Cohort 1_1: pre-/peri-approval of new migraine medication classes) to a future state (Migraine Cohort 2_1: post-approval of new migraine medication classes and Migraine Cohort 3_1: post-approval of new migraine medication classes). Outcomes will include use of acute and preventive medications, HCRU, and impact to patients with migraine. Changes in the proportion of patients using an opioid medication over time (e.g., Migraine Cohort 3_1 vs Migraine Cohort 2_1 vs Migraine Cohort 1_1) is a specific example of an outcome measure that may be assessed.

Descriptive statistics will summarize the differences between Migraine Cohort 3_1, Migraine Cohort 2_1 and Migraine Cohort 1_1. T-tests / Chi-square tests will be the primary comparison of differences in each measure between Migraine Cohort 3_1, Migraine Cohort 2_1 and Migraine Cohort 1_1. Differences will also be summarized by point estimates and 2-sided 95%

confidence intervals. Non-parametric tests may be conducted in addition as necessary. Analyses will be performed within key subgroups of interest – such as the preventive eligible subpopulation. Subgroup identification / machine learning algorithms may be used to identify factors/groups associated with changes between cohorts.

Comparability of Migraine Cohort 3_1 vs Migraine Cohort 2_1 vs Migraine Cohort 1_1 (e.g., demographics, health status, and other variables) will be assessed and adjustments (via regression methods or various matching methodologies) will be made as appropriate.

7.5.1.3. Longitudinal Analyses

A subset of patients will provide within patient longitudinal data every 6 months over a two year period. Likelihood-based repeated measures mixed models or generalized linear mixed models will be used to assess outcomes over time. The specific factors in the model will vary by question, but in general time will be included as a class variable to avoid assumptions on trends over time.

We will consider comparing changes in outcomes for preventive eligible patients who remain on non-anti-CGRP treatment vs those who switch to anti-CGRP treatment using a repeated measures model with Treatment Group (switch to anti-CGRP or not), time, and various adjustment factors as appropriate.

We will compare the subset of patients providing longitudinal data versus those who do not. We note that changes in comorbidities or co-existing conditions will not be examined.

7.5.1.4. Linked Claims and Survey Data

Linked claims data can be used to assess treatment patterns, health care resource utilization, costs, etc., with respect to patient reported outcomes (e.g., quality of life – EQ-5D, disability burden – MIDAS). Descriptive analyses will summarize associations between the claims and survey data.

7.5.1.5 Analysis of Non-Migraine (Control) Cohort

Analyses involving the non-migraine (control) for Cohorts 1 and 3 will involve both estimation of parameters for measures within non-migraine patients (e.g., attitudes toward people with migraine) and comparisons between the non-migraine (control) and migraine populations (e.g., demographic, comorbidities, HRCU, quality of life). The non-migraine (control) cohort will be characterized with point estimates and 2-sided 95% confidence intervals as for other analyses. Comparisons for measures between the non-migraine (control) and migraine cohorts will be conducted using t-test/chi-square tests or non-parametric analyses as appropriate.

7.5.2. Safety Analyses

Lack of drug effect will be evaluated as a safety measure based on survey responses. Descriptive statistics will be conducted. Continuous variables will be summarized as means with standard deviations, or medians and ranges, as appropriate. Categorical variables will be summarized as frequencies and percentages. Analyses will be conducted according to specification documents.

7.5.3. Subgroup Analyses

This study will involve numerous between-subject and within-subject comparisons. All comparisons will be outlined *a priori* in specification documents (see Attachment 13).

Specific group comparisons include, but are not limited to the following:

1. Class-level comparison of CGRP mAbs vs. the four SOC medications that are indicated and approved in the US for the prevention of migraine (divalproex sodium, propranolol, timolol, and topiramate)
    a. In addition, and if sample size allows, additional comparisons will be made in the subgroup of patients with chronic migraine (e.g., anti-CGRP mAbs vs. botulinum toxin)
2. Class-level comparison of novel acute medications vs. standard of care medications that are indicated and approved in the US for the treatment of acute migraine (triptans, ergotamines)
3. Class-level comparison of novel acute medications vs. OTC medications (analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids) that are used for the treatment of acute migraine

It should be noted that all comparisons highlighted in #1-3 are conditional on their introduction to market and sample size.

No subject withdrawal criteria is required rather there will be loss-to-follow-up of participants not participating in subsequent survey waves.

7.5.4. Interim Analyses

No interim analyses are planned for this study as each survey wave represents a completed 'mini' study. After each survey wave, data will be cleaned and locked, and all analyses will be conducted according to specification documents.

8. Safety Evaluations

8.1. Adverse Events

The study personnel will collect via OVERCOME patient surveys all protocol-defined adverse events (AEs), 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. The protocol-defined AEs include lack of drug effect.

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

Adverse events collected will be summarized in the interim safety 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 (for example, 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

Serious adverse events (SAEs) are not actively collected, as this is a closed survey, and there is no opportunity for respondents to report SAEs.

8.1.2. Nonserious Adverse Events

The study personnel will record any **nonserious** protocol-defined AE arising in temporal association with the Lilly product(s) under evaluation within 30 days of awareness of the event via electronic data entry. 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 package insert.

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 subject is based solely on the investigator's routine or usual practice in the provision of care to subjects with migraine.

As this is an observational study and does not impose any form of intervention, the subject 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 subject information will be maintained.

Although this observational study also uses data previously collected (healthcare claims data linkage) and does not impose any form of intervention, the data will be de-identified to protect subject privacy. Whereas generally, a formal Consent to Release Information form is not required, the study will have include a Consent to Release Information given that it is generating data via Primary Data Collection activities (survey).

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 Pharmacoepidemology 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

Subject data are recorded on electronic 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.

All information about this observational study and individual subject 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.

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). For the purposes of protecting a patient's identity, a unique code will be assigned to each respondent, such as a series of numbers and/or letters (for example, CA180330-0001-00001). The data that are recorded with the respondent's assigned code is called "key-coded data". Key-coded study data will be managed by the sponsor and/or its delegates in a study-specific electronic database (the "study database"). Only the investigator and the site staff have access to the link between patient's assigned code and the patient's identity. However, in case of an audit or inspection, subject to local laws and regulations, government officials, IRB/EC representatives and sponsor representatives may access this information at the study site. Data that could directly identify the respondent will not be collected in the "study database".

The study may be evaluated by Lilly internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. Lilly audit reports will be kept confidential.

The investigator must notify Lilly promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to Lilly.

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact Lilly prior to destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

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Attachment 1. Observational Study Protocol Migraine Eligibility Critieria

Current headache or migraine in the past 12 months and either:

1. Validated migraine cohort eligibility screener (Lipton et al, 2016) using modified ICHD-3 criteria in regard to the person's most severe type of headache (must fulfill both #1 and #2):
    a. Answers at least two of the following symptoms as "less than half of the time" or "half the time or more":
        i. The pain is worse on just one side
        ii. The pain is pounding, pulsating or throbbing
        iii. The pain has moderate or severe intensity
        iv. The pain is made worse by routine activities such as walking or climbing stairs
    b. Answers to either one or both symptoms as "less than half of the time" or "half the time or more":
        i. "You feel nauseated or sick to your stomach" OR “you vomit”
        ii. "Light bothers you (more than when you do not have headaches)" AND "Sound bothers you (more than when you do not have headaches)"
2. Self-reported medical diagnosis of migraine from a healthcare provider regardless of ICHD-3 qualification status from #1

Attachment 2. Observational Study Protocol Amendment 2017-6229 Summary US Population-Based Longitudinal Survey in Migraine: ObserVational survey of the Epidemiology, tReatment and Care Of MigrainE (OVERCOME)

Summary of Amendments

Amendment	Description
1	Inclusion of a non-migraine (control) group alongside the second migraine cohort was removed from the study design.
2	Analysis of the migraine cohort will include comparisons by monthly headache day categories (e.g., 0-3, 4-7, 8-14, and 15+) assuming sample size allows.
3	The current study analysis will now compare people with migraine treated with CGRP monoclonal antibody medications versus people using other approved treatments for migraine prevention (including divalproex sodium, propranolol, timolol, and topiramate) and other recommended (SOC based on AHS/AAN guidance) medications for migraine prevention.
4	Removal of the exploratory objective describing the demographic, clinical profile and HCRU of people with other headache disorders (e.g., tension-type headache, post-traumatic headache (PTH), cluster headache) or other pain conditions (e.g., chronic low back pain (CLBP) and osteoarthritis).
5	Change in approach for the second longitudinal survey from 2020-2022 to 2019-2021.
6	Updated **inclusion** criteria to that people with migraine can be included if they have had a headache or migraine in the past 12 months. Also, remove the criteria for inclusion of those who are currently taking preventive medication.
7	Updated the **exclusion** criteria to include those with all headaches in the past 12 months due to hangover or illness.
8	Add language to the study design sampling approach that stratification by monthly headache days (0-3 and 4+) would occur 'if needed' in order to ensure sufficient sample size in key demographic groups for calculating estimates with appropriate precision and understanding the impact of CGRPs as a class.
9	Updated the planned respondent selection Figure 2.
10	Updated planned respondent selection Figure 3

11	Updated timing of survey collection Figure 4
12	Revise language for analysis plan from statistical analysis plan (SAP) to specification documents.
13	Revised and updated variables tables
14	Added the mention that in the longitudinal analysis, changes in comorbidities or co-existing conditions will not be examined
15	Attachment 1 - Data collection schedule now removed
16	Revise language to Kantar
17	Revise Safety section
18	Revise Adverse Event section
19	Revised study design to include (1) a third cohort of respondents with migraine followed every 6 months for 2 years and (2) an additional non-migraine cohort
20	Updated overall study design Figure 1
21	Clarified description of sampling
22	Additional panels and/or change in panel names used for survey respondent recruitment
23	Refined description and figure of planned respondent selection
24	Exclusion criteria of cluster headache from Cohort 3
25	Figure 4 removed due to redundancy
26	Revised/updated study variables Table 1
27	Revised/updated study variables Table 2
28	Revised assumptions in Table 3
29	Revised assumptions for sample size
30	Added text to address sample size
31	Added text and table for precision and power assessments

Amendment 1:

Inclusion of a non-migraine (control) group alongside the second migraine cohort was removed from the study design.

Change from original language:

Original text – "Study size: Two migraine cohorts, N=~20,000 each, 2 year longitudinal follow-up (5 web-based survey completions at 6-month intervals); two non-migraine (control) cohorts, N=10,000 each, cross-sectional survey."

Revised text – "Study size: Two migraine cohorts, N=~20,000 each, 2 year longitudinal follow-up (5 web-based survey completions at 6-month intervals); non-migraine (control) cohort, N=10,000, cross-sectional survey."

Rationale:

Collection of data for a second non-migraine (control) group was no longer considered necessary to meet the study objectives. Specifically, the objective of the first non-migraine cohort to provide a comparator group for the migraine cohort was accomplished using the first cohort. The additional objective of the non-migraine cohort to provide information on stigma towards people with migraine was provided using the first non-migraine cohort and changes over time between the two collection periods (1-year) were expected to be minimal.

Protocol sections:
Abstract – study size
Section 6.1 Description of overall study design
Section 6.4 Description of the planned study population
Section 6.5 Description of cohort collected at each time periods

Amendment 2:

Analysis of the migraine cohort will include comparisons by monthly headache day categories (e.g., 0-3, 4-7, 8-14, and 15+) assuming sample size allows.

Change from original:

Additional text added: "In addition, and if sample size allows, additional comparisons will be made for monthly headache day categories including those with episodic migraine (combined or separate for those with 0-3, 4-7, 8-14 monthly headache days) and chronic migraine (15+ monthly headache days)."

Rationale:

This grouping was added to examine the varying burden of disease among persons with episodic headaches (<15 monthly headache days).

Protocol sections:
Section 5.1 Primary objectives
Section 5.2 Secondary objectives
Section 6.4.2 Subject groups

Amendment 3:

The current study analysis will now compare people with migraine treated with CGRP monoclonal antibody medications versus people using other approved treatments for migraine prevention (including divalproex sodium, propranolol, timolol, and topiramate) and other recommended (SOC based on AHS/AAN guidance) medications for migraine prevention.

Change from original:

Additional text added to comparison groups: " We will compare outcomes for people … and other recommended (SOC based on AHS/AAN guidance) medications for migraine prevention"

Rationale:

The study analyses and comparison groups now reflect the newly published AAN/AHS guidelines (2018 AHS Consensus Statement, Headache 2019;59:1-18):

Table 4.—Treatments With Evidence of Efficacy in Migraine Prevention (Adapted from Silberstein et al[19])

Established efficacy[†]	Probably effective[‡]	Possibly effective[§]
Antiepileptic drugs[‖]	Antidepressants	ACE inhibitors: Lisinopril
Divalproex sodium[‖]	Amitriptyline	Alpha-agonists
Valproate sodium[‖]	Venlafaxine	Clonidine
Topiramate[‖]	Beta-blockers	Guanfacine
Beta-blockers	Atenolol	Antiepileptic drugs: Carbamazepine
Metoprolol	Nadolol	Beta-blockers
Propranolol		Nebivolol
Timolol		Pindolol
Triptans: Frovatriptan[¶]		Antihistamines: Cyproheptadine
OnabotulinumtoxinA[32]		Angiotensin receptor blockers: Candesartan

ACE, angiotensin-converting enzyme.
[†]More than 2 Class I trials based on AAN Scheme for Classification of Evidence.[33]
[‡]One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence.[33]
[§]One Class II study based on AAN Scheme for Classification of Evidence.[33]
[‖]Not for use in women of childbearing potential who are not using an appropriate method of birth control.[34,35]
[¶]Short-term prevention of menstrual migraine.
[‡‡]For prevention of chronic migraine.

Protocol sections:
Section 5.2 Secondary objectives
Section 6.4.2 Subject groups

Amendment 4:

Removal of the exploratory objective describing the demographic, clinical profile and HCRU of people with other headache disorders (e.g., tension-type headache, post-traumatic headache (PTH), cluster headache) or other pain conditions (e.g., chronic low back pain (CLBP) and osteoarthritis).

Change from original:

Original text: "Describe the demographic, clinical profile and HCRU of people with other headache disorders (e.g., tension-type headache, post-traumatic headache (PTH), cluster headache) or other pain conditions (e.g., chronic low back pain (CLBP) and osteoarthritis)."

Revised text: None.

Rationale:

Other headache disorders and other chronic pain are no longer a focus of this study.

Protocol sections:
Section 5.3 Exploratory objectives

Amendment 5:

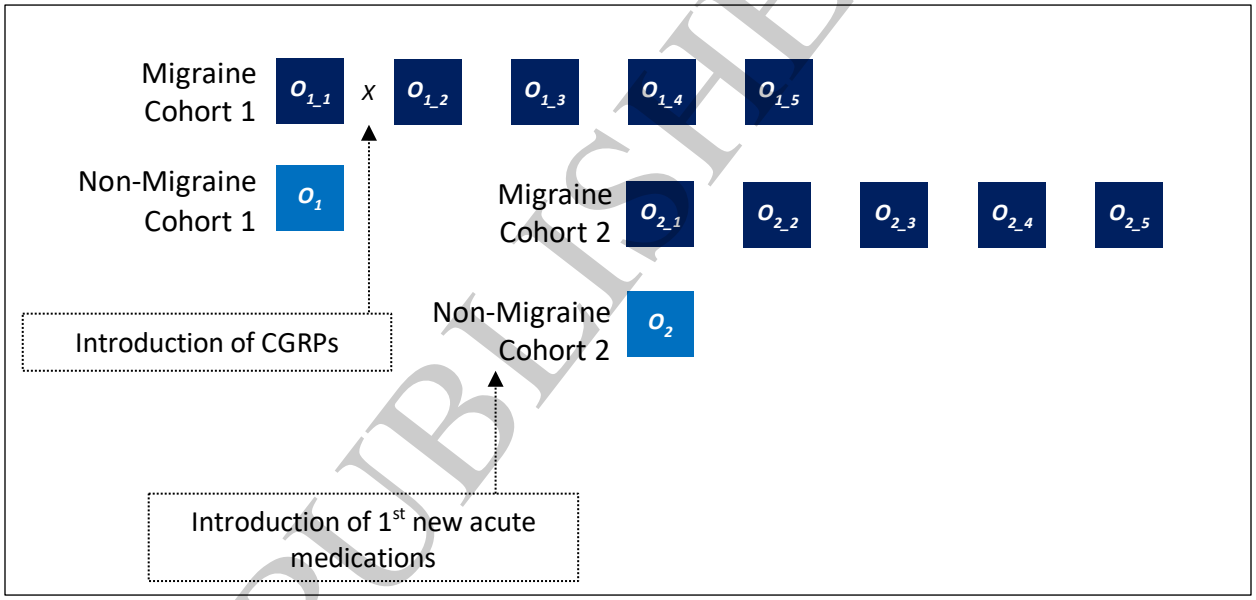
Change in approach for the second longitudinal survey from 2020-2022 to 2019-2021.

Change from original:

Original text – "Approach: Longitudinal study with 5 web-based survey completions at 6-month intervals (cohort 1: 2018-2020; cohort 2: 2020-2022)"

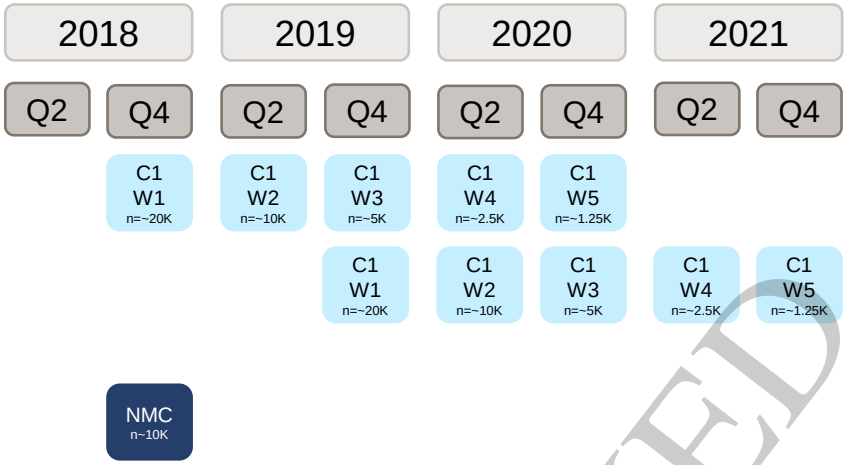
Revised text – "Approach: Longitudinal study with 5 web-based survey completions at 6-month intervals (cohort 1 (C1): 2018-2020; cohort 2 (C2): 2019-2021)"

Original figure -



Revised figure

Time Periods and Estimated Population Per Survey



C = Cohort; W = Wave; NM = Non-Migraine

Rationale:

The staggering of the two longitudinal surveys from two to one years between baseline surveys was changed following the high attrition between the first and second wave of the first cohort. In order to insure sufficient sample size to allow for the surveillance of the migraine population at all 6-months intervals during the entrance of CGRPs into the market, the second cohort's data collection was moved up. Also, this allowed for the possibility of creating an annual OVERCOME survey.

Protocol sections:

Section 6.1 Summary of research design

Amendment 6:

Updated **inclusion** criteria to that people with migraine can be included if they have had a headache or migraine in the past 12 months. Also, remove the criteria for inclusion of those who are currently taking preventive medication. The summary of research design was also updated to reflect these changes.

Change from original:

1. Original text – "Respondents will be screened for migraine (or for preventive medication use and well-controlled migraine)"

   Revised text – "Respondents will be screened for migraine (current headache/migraine and identified as having migraine EITHER via a validated screener and/or self-reported diagnosis of migraine from a healthcare provider"

2. Original text – "Persons with migraine…based on the modified ICHD-3 screening criteria (with a frequency of half the time or more with their severe headaches, report 2 or more of 4 pain symptoms (the pain is worse on just one side, the pain is pounding, pulsating, or throbbing, the pain has moderate or severe intensity, The pain is made worse by routine activities such as walking or climbing stairs) and report either nausea or both photophobia and phonophobia) or are well-controlled on a preventive medication (see Attachment 2)"

   Revised text – "Persons reported having a headache or migraine (any type) in the last 12 months AND identified as having migraine based EITHER on the modified ICHD-3 screening criteria (with a frequency of less than half the time, half the time or more with their severe headaches, report 2 or more of 4 pain symptoms (the pain is worse on just one side, the pain is pounding, pulsating, or throbbing, the pain has moderate or severe intensity, the pain is made worse by routine activities such as walking or climbing stairs) and report either nausea or vomiting, or both photophobia and phonophobia) OR self-reported physician diagnosis of migraine"

3. Original Text – "Among the remaining 14,000 target participants, most will be identified according to their ICHD-3 criteria then according to frequency (0-3 monthly headache days). It is possible that some people with migraine may have their disease well-controlled, because they are on an evidence-based preventive medicine and may not qualify for the study because they do not meet all ICHD-3 criteria or they have 0-3 monthly headache days. As this is a population of interest, people who are screened out (excluded) for either of these reasons will undergo a further screening (inclusion) criterion to identify and include people with migraine on a current preventive medication. Thus, the quota for 0-3 monthly headache days will be reduced in such circumstances."

   Revised text – "Among the remaining 14,000 target participants, most will be identified according to their ICHD-3 criteria then according to frequency (0-3 monthly headache days)."

Rationale:

Following a review of the soft-launch data from the first baseline cohort (C1W1) several types of respondents were raised as issues that led to changes in the inclusion criteria:

1. Issue 1 – In the original inclusion criteria respondents were included if they had a physician diagnosis, met symptoms for migraine (ICDH3), or were on a preventive medication. At soft launch, the respondent profiles were examined. There were respondents with the following characteristics:

   - Have had a headache in past 12 months
   - Headaches not all due to hangover/illness
   - Do not meet ICHD3
   - Report physician diagnosis of migraine or cluster
   - Are NOT on preventive therapy

➔ Decision: In order to ensure that a person with a migraine diagnosis was also a current migraine patient, the inclusion criteria were updated to include all respondents with a current headache or migraine (question S12)

2. Issue 2 – In the original inclusion criteria respondents were included if they had a physician diagnosis, met symptoms for migraine (ICDH3), or were on a preventive medication. At soft launch, the respondent profiles were examined and there were inconsistencies for those reporting taking migraine prevention medication (note, current headache/migraine was not an inclusion criteria):

- Only 17% (12/69) of those reporting taking a preventive medication also passed the ICHD-3 criteria
- Only 17% (12/69) reported having a headache/migraine in the past 12 months and all of these failed the ICHD-3 criteria
    - >90% (11/12) did not report a migraine dx either in M25_2, _3, _7 or _8.

➔ Decision: Do not rely on 'current use of preventive medication' as an inclusion criteria as this group may reflect people with headaches who are treated similarly to those with migraines, but do not pass the ICDH-3 criteria.

Protocol sections:

Section 6.4.1 Selection criteria

Section 6.1 Summary of Research Design

Amendment 7:

Updated the **exclusion** criteria to include those with all headaches in the past 12 months due to hangover or illness.

Change:

Original exclusion criteria –

Excluded from the study are participants who are:

1. Unwilling or unable to provide electronic informed consent

Revised exclusion criteria -

Excluded from the study are participants who are:

1. Unwilling or unable to provide electronic informed consent

Excluded from the Migraine cohort:

2. Anyone with all headaches in the past 12 months due to hangover or illness (see Attachment 12)

Rationale:

This exclusion criteria was used for survey but not documented previously in the protocol.

Protocol sections:

Section 6.4.1 Selection criteria

Amendment 8:

Add language to the study design sampling approach that stratification by monthly headache days (0-3 and 4+) would occur 'if needed' in order to ensure sufficient sample size in key demographic groups for calculating estimates with appropriate precision and understanding the impact of CGRPs as a class. Further, this sampling approach (i.e., oversampling of those with 4+ monthly headache days) would potentially require re-weighting the data to represent the US migraine population. Therefore, 'if needed' is now also applied to the adjustment by weighting.

Change from original:

Added to original text (in underline) –

"In addition, if needed, the sample will be stratified into groups based on the number of monthly headache days (0-3 vs 4+) in order to ensure adequate representation of people who may be eligible for preventive medications (4+ monthly headache days)"

"The latter consideration is enhanced by the stratification approach to be used if needed, with over-selection of the cohort according to monthly headache days such that an increased number of patients with 4+ monthly headache days, and therefore more likely to receive anti-CGRP therapy, will be included if needed"

"Indeed, given the oversampling of persons according to the frequency of monthly headache days, we anticipate re-weighting the final included population so that it is representative of the US migraine population. However, we note that weighting the data will be determined following the data fielding and performed if needed.

If perfomed, weights may be derived from the empirical distribution of monthly headache daysfor age and sex groups from other population-based studies of migraine (e.g., NHWS, AMPP)… As noted above (section 7.2.1), weighting will be used to adjust prevalence rates if needed, since, by design, the study design is biased to overrepresents persons with 4+ monthly headache days."

Rationale:

This language allows for the removal of the sample according to quotas for monthly headache days in the event that the sample drawn from a representative population would provide a sufficiently large sample of those in the 4+ monthly headache group (i.e. > 6000). Ideally this option is preferred since it would avoid the latter need for weighting.

Protocol sections:

Section 6.1 Summary of research design

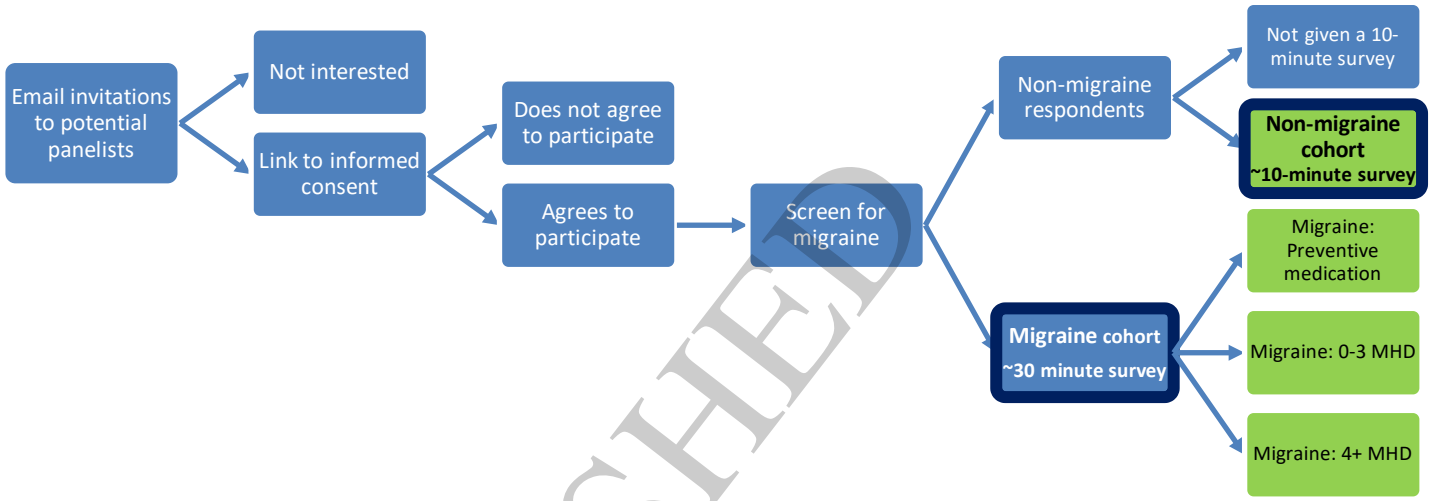
Section 7.2.2 Approach to adjust for bias/confounding

Section 7.5.1.1 Analysis of cross-sectional cohorts

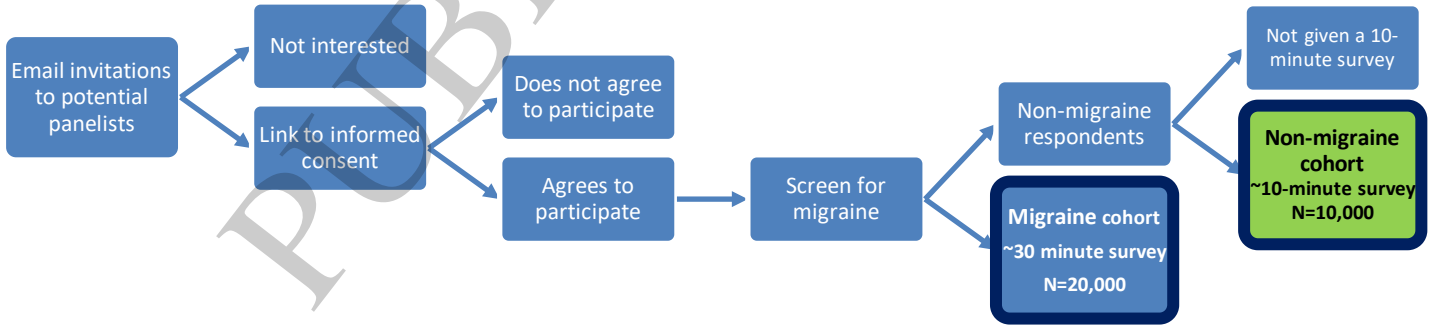
Amendment 9:

Updated the planned respondent selection Figure 2.

Change:
Original figure –



Revised figure –



Rationale:
Figure 2 was updated to correspond with the updated inclusion/exclusion criteria and the non-migraine cohort selection for cohot 1 only.

Protocol sections:

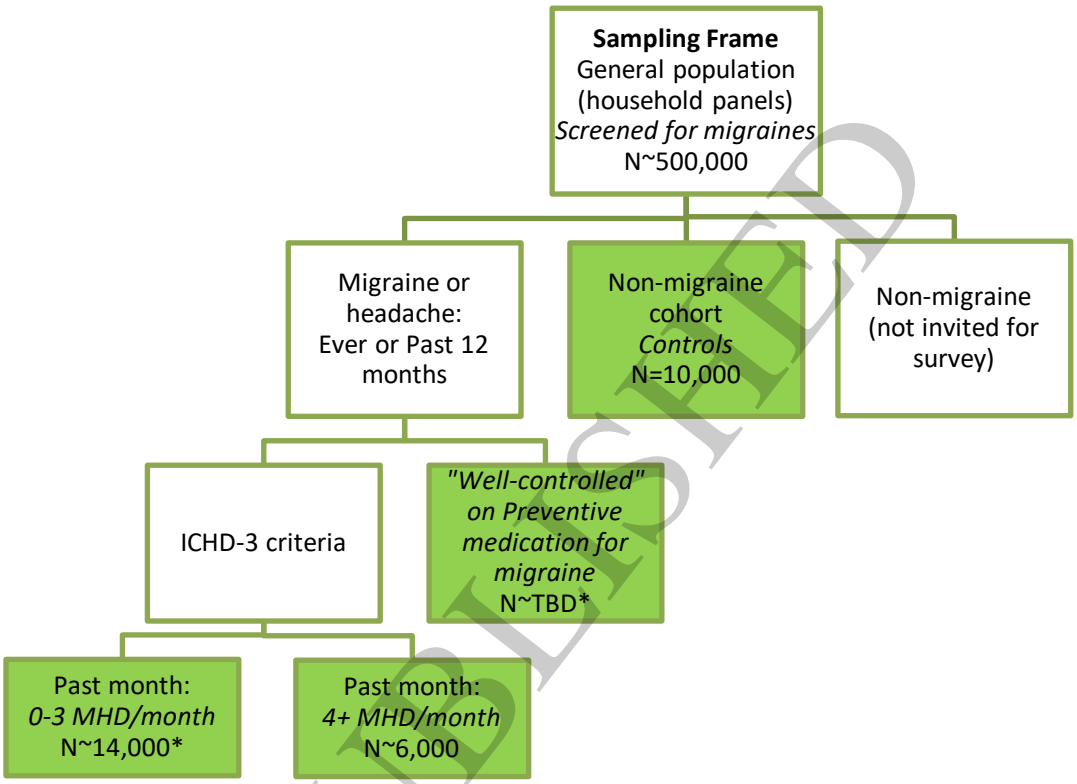
Section 6.2 Data source
Figure 2

Amendment 10:

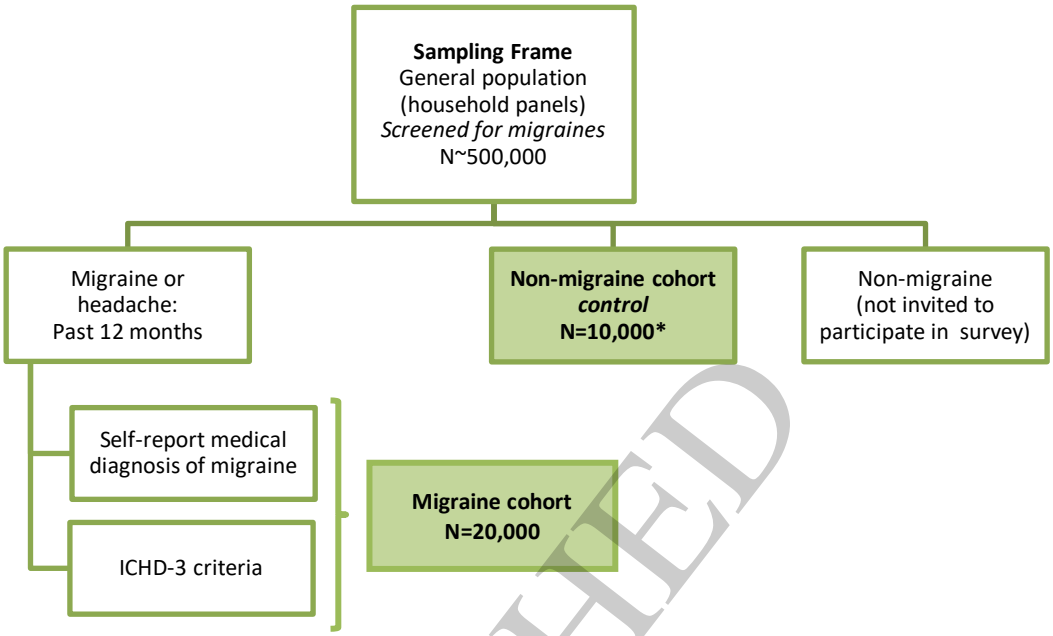
Updated planned respondent selection Figure 3.

Change:

Original figure



Revised figure – Added footnote and change regarding non-migraine cohorts (from "Non-migraine cohort controls" to "...control")



*Non-migraine cohort will be collected during for cohort 1

Rationale:
Figure 3 was updated to correspond with the updated inclusion/exclusion criteria and the non-migraine cohort selection. The stratification or potential quota sampling by monthly headache days was removed as that would only be performed 'if needed. Also, now note that non-migraine is for cohot 1 only. See ammendmends 1, 6, and 8.

Protocol sections:

Section 6.4 Study population
Figure 3

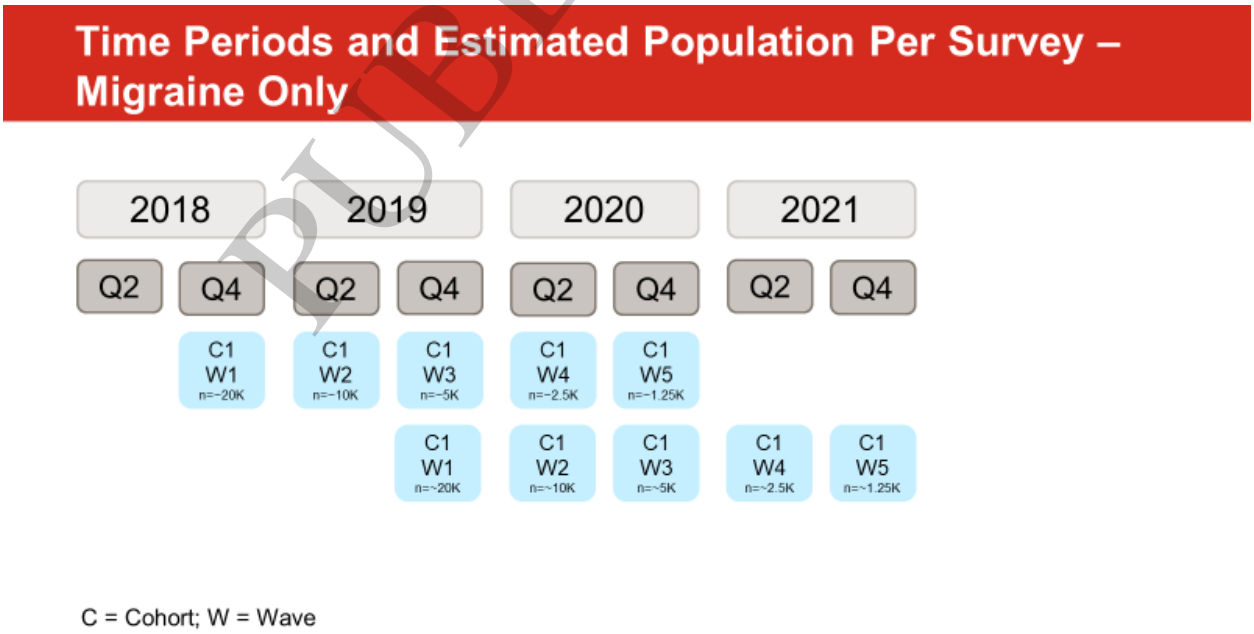
Amendment 11:

Updated timing of survey collection Figure 4

Change:

Original figure

Revised figure



C = Cohort; W = Wave

Amendment 12:

Revise language for analysis plan from statistical analysis plan (SAP) to specification documents.

Change:

Original text – 'statistical analysis plan' or 'SAP'

Revised test – 'specification documents'

Rationale:

After consultation with Lilly statisticians, the use of SAPs are not required for observational studies. Further, since in these studies the protocol outlines the overall analyses and the specifications documents detail the analysis, Lilly decided that specification documents was more appropriate language.

Protocol sections:

Section 6.4.2 Subject groups
Section 7.5.1 Outcomes analyses
Section 7.5.3 Subgroup analyses
Section 7.5.4 Interim analyses

Amendment 13:

Revised and updated variables tables

Change:

Revised and abridged original tables 1 and 2

Rationale:

Due to the large number of measures included in the OVERCOME surveys, the original table was replaced with a more succinct overview.

Protocol sections:

Section 6.7 Variable measures
Table 1
Table 2

Amendment 14:

Added the mention that in the longitudinal analysis, changes in comorbidities or co-existing conditions will not be examined.

Additional text (in underline):

"We will compare the subset of patients providing longitudinal data versus those who do not. We note that changes in comorbidities or co-existing conditions will not be examined."

Rationale:

The study objectives do not include examining incidence of comorbidities or co-existing conditions for the migraine population. However, subsequent waves ask respondents about current comorbidities in order to describe the population (i.e. potential confounders, medical history).

Protocol sections:

Section 7.5.1.3 Longitudinal analysis

Amendment 15:

Attachment 1 - Data collection schedule now removed.

Change

Attachment removed

Rationale:

This table no longer relevant or helpful

Protocol section:

Attachment 1

Amendment 16:

Revise language to Kantar.

Change:

Original text – 'Kantar Health'

Revised test – 'Kantar'

Rationale:

Kantar brands now use the company name only and are differentiated according to their divisions, e.g., Kantar, Health Division.

Protocol sections:

Global change

Amendment 17:

Revise Safety section

Change:

Original text – “Not applicable”

Revised test – "Lack of drug effect will be evaluated as a safety measure based on survey responses. Descriptive statistics will be conducted. Continuous variables will be summarized as means with standard deviations, or medians and ranges, as appropriate. Categorical variables will be summarized as frequencies and percentages. Analyses will be conducted according to specification documents."

Rationale:

Regulators have requested information on lack of drug effect as an adverse event, thus this information is considered a safety measure/outcome.

Protocol sections: Section 7.5.2 Safety Analyses

Amendment 18:

Revise Adverse Event section

Change:

Original text – "Adverse events (AEs) will not be actively collected because this study does not have a safety objective and there are no identifiable AEs. Study personnel are requested to report any suspected adverse reactions (SARs) with any drug to the appropriate party as required in normal practice."

Revised text –

The study personnel will collect via OVERCOME patient surveys all protocol-defined adverse events (AEs), 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. The protocol-defined AEs include lack of drug effect.

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

Adverse events collected will be summarized in the interim safety 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 (for example, 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.

Serious adverse events (SAEs) are not actively collected, as this is a closed survey, and there is no opportunity for respondents to report SAEs.

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

Original text: Protocol Defined Adverse Event Reporting Timing (Primary Data Collection Only) section. "Adverse events (AEs) will not be actively collected because this study does not have a safety objective and there are no identifiable AEs Study personnel are requested to report any suspected adverse reactions (SARs) with any drug to the appropriate party as required in normal practice.

Revised text: Whole section deleted

Rationale:

Regulators have requested information on lack of drug effect as an adverse event, thus this information is considered a safety measure/outcome. Adverse event language has been updated to reflect this change.

Protocol sections:

Section 8.1 Adverse Events

Section 8.2 Protocol Defined Adverse Event Reporting Timing (Primary Data Collection)

Amendment 19:

Update background section to reflect the approval timing of the newer classes of migraine-specific medications.

Change:

Original text:

A new class of mechanism-based preventive medications – calcitonin gene-related peptide (CGRP) monoclonal antibody (mAb) antagonists (referred to as CGRP mAbs or anti-CGRP herein)– are expected to be approved in 2018. Following on those approvals, new acute migraine medications, such as serotonin 5-HT1F agonists (ditans) and oral CGRPs antagonists (also can be referred to as anti-CGRP), are expected to enter the market in 2019+.

Revised text:

New classes of migraine-specific medications – monoclonal antibodies (mAbs) that target calcitonin gene-related peptide (CGRP; referred to as CGRP mAbs or anti-CGRP herein), small

molecule CGRP receptor antagonists, and serotonin 5-HT1F agonists)– began gaining approval in the US beginning in 2018.[23–29]

Rationale:

To more accurately reflect the timing of the approvals.

Protocol sections:
Section 4. Background and Rationale

Amendment 20:

Revised study design to include (1) a third cohort of respondents with migraine followed every 6 months for 2 years and (2) an additional non-migraine cohort.

Change:

Original text:

1. To set a 'baseline' by characterizing the population of people with migraine prior to the introduction of novel acute and preventive treatments for migraine
    a. Approach: Cross-sectional study – the first wave of each of the two cohorts (2018 and 2019) will serve to characterize the population of people with migraine at each point in time
2. To create a reference group of people without migraine (controls) from the general population in order to have a reference group to compare with migraine group (e.g., HCRU, comorbidities) and understand attitudes of people without migraine towards those with migraine
    a. Approach: Cross-sectional study – during first (cohort 1 (C1): 2018) of the longitudinal study
3. To collect longitudinal data (up to 2 years) for people with migraine
    a. Approach: Longitudinal study with 5 web-based survey completions at 6-month intervals (cohort 1 (C1): 2018-2020; cohort 2 (C2): 2019-2021)

Revised text:

1. To set a 'baseline' by characterizing the population of people with migraine prior to the introduction of novel acute and preventive treatments for migraine
    a. Approach: Cross-sectional study – the first wave of each of the three cohorts (2018, 2019 and 2020) will serve to characterize the population of people with migraine at each point in time
2. To create a reference group of people without migraine (controls) from the general population in order to have a reference group to compare with migraine group (e.g., HCRU, comorbidities) and understand attitudes of people without migraine towards those with migraine

    a. Approach: Cross-sectional study – during first wave of the first (cohort 1 (C1): 2018) and third (cohort 3 (C3): 2020) cohorts
3. To collect longitudinal data (within each cohort for up to approximately 2 years) for people with migraine
    a. Approach: Longitudinal study with 5 web-based survey completions at 6-month intervals (cohort 1 (C1): 2018-2020; cohort 2 (C2): 2019-2021; cohort 3 (C3): 2020-2022)

Additional text (background): "Additionaly, it is valuable to observe the change in treatment landscape as new products enter into the market."

Rationale:

To capture new products as they enter the market and to see the changes in the treatment landscape over time.

Protocol sections:

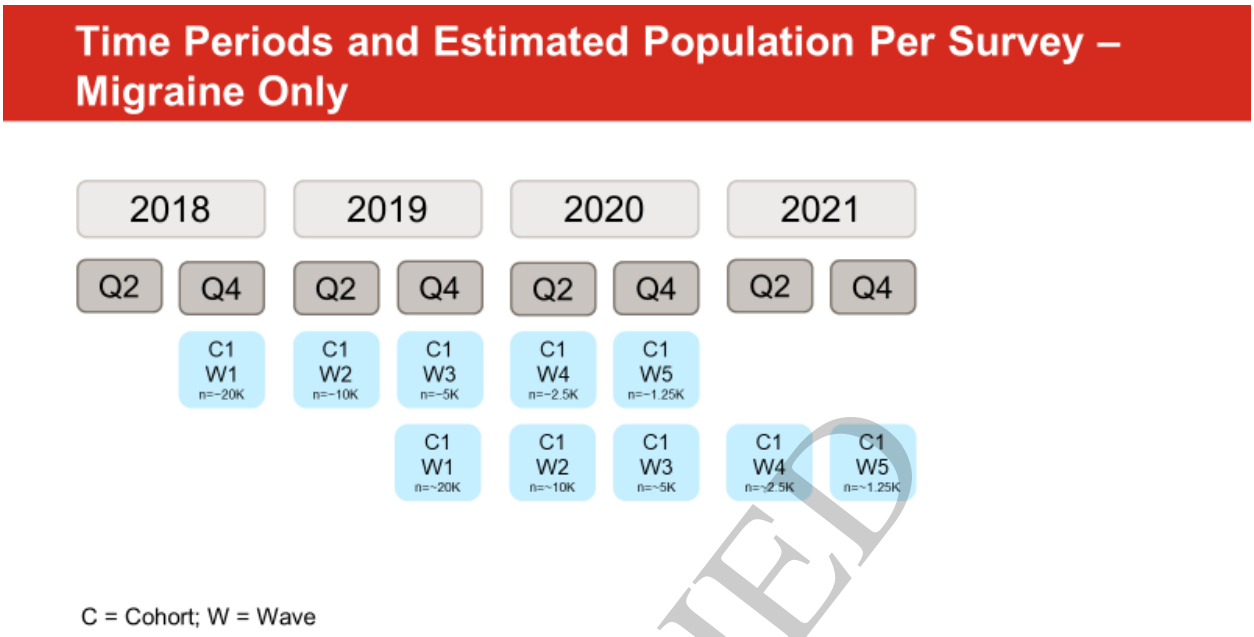
2. Abstract
4. Background
5.1 Primary Objective
6.1 Summary of Research Design
6.4 Study Population
Figure 1
Table 3
7.5.1.1 Analysis of cross-sectional cohorts
7.5.1.2 Analysis of changes between cohorts
7.5.1.5 Analysis of non-migraine (control) cohort

Amendment 21:

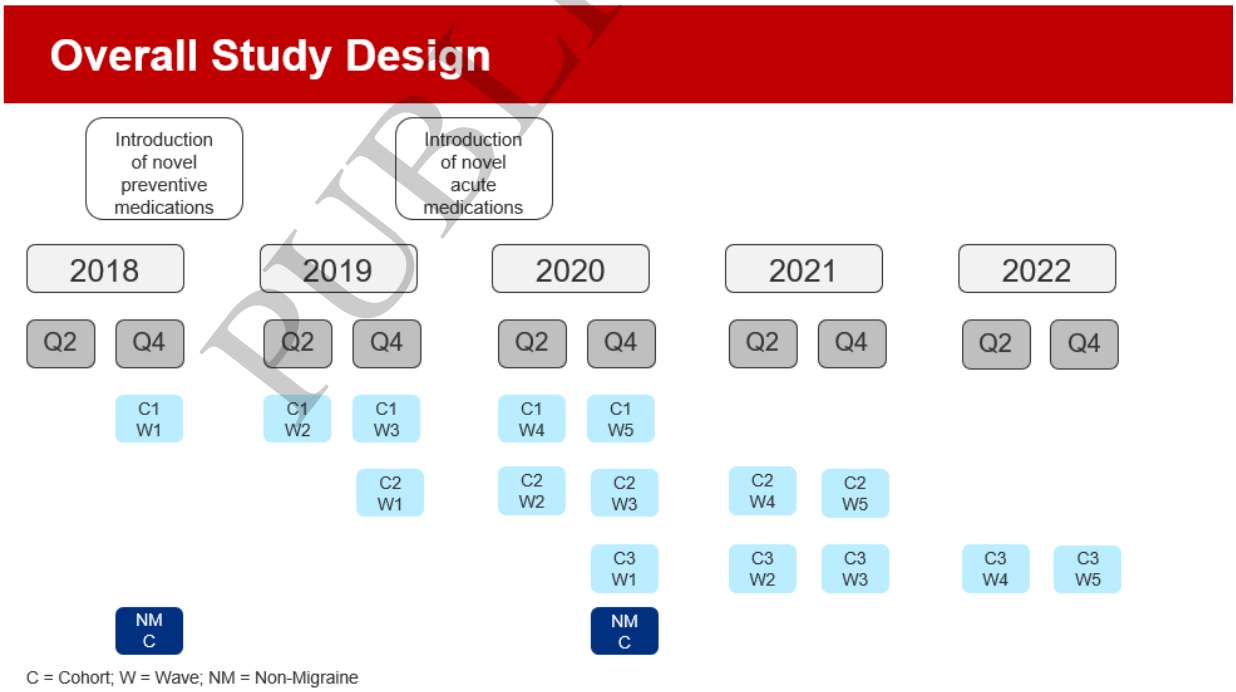
Updated overall study design Figure 1

Change:

Original figure



Revised figure



Rationale:

To reflect the additional cohort (migraine and non-migraine).

Protocol sections:

6.1 Summary of Research Design

Amendment 22:

Clarified description of sampling

Change:

Original text:

Eli Lilly and Company wishes to conduct two web-based panel studies of adults to accomplish our study objectives using a stratified random sample. To the extent possible, the study sample will represent the US adult population in terms of key demographic characteristics (age, gender, race/ethnicity). *If needed*, the sample will be stratified into groups based on the number of monthly headache days (0-3 vs 4+) in order to ensure adequate representation of people who may be eligible for preventive medications (4+ monthly headache days). This will be accomplished by oversampling respondents with 4 or more monthly headache days from an anticipated N~4,000 (based on the known distribution of monthly headache days in people with migraine) to N~6000. Among the remaining 14,000 target participants, most will be identified according to their ICHD-3 criteria then according to frequency (0-3 monthly headache days).

Revised text:

Eli Lilly and Company wishes to conduct three web-based panel survey studies of adults to accomplish our study objectives. To the extent possible, the study sample will represent the US adult population in terms of key demographic characteristics (age, gender, race/ethnicity, geography). Respondents with migraine will be identified from this demographically representative sample and, *if needed*, the sample will be stratified into groups based on the number of monthly headache days (0-3 vs 4+) in order to ensure adequate representation of people who may be eligible for preventive medications (4+ monthly headache days). This will be accomplished by oversampling respondents with 4 or more monthly headache days from an anticipated N~4,000 (based on the known distribution of monthly headache days in people with migraine) to N~6000. Among the remaining 14,000 target participants, most will be identified according to their ICHD-3 criteria then according to frequency (0-3 monthly headache days). Respondents without migraine will be collected using targeted sampling to represent the US adult population in terms of key demogaphic characteristics (age, gender, race/ethnicity, geography)

Rationale:

To better describe the sampling method, which first used targeted sampling to create a representative sample and also allowed for random sampling of this representative sample. Also we now note that geography was used in all cohorts to create the US representative sample.

Protocol sections:

6.1 Summary of Research Design

Amendment 23:

Additional panels and/or change in panel names used for survey respondent recruitment

Change:

Original text:

Data for the study will be obtained using responses from a customized web-based survey of invited consumers who meet inclusion and exclusion criteria and who agree to participate. Consumers will initially be recruited from Lightspeed Research (LSR) which is wholly owned by Kantar, with supplemental panels obtained from LSR partners Global Market Insite, MarketCube, Research Now, Active Measure, and Empanel, EMI, if needed.

Revised text:

Data for the study will be obtained using responses from a customized web-based survey of invited consumers who meet inclusion and exclusion criteria and who agree to participate. Consumers will initially be recruited from Lightspeed Research (LSR) which is wholly owned by Kantar, with supplemental panels obtained from LSR partners Global Market Insite, MarketCube, Dynata (Research Now), Disqo (Active Measure), Empanel, EMI and Mfour, if needed.

Rationale:

Update new and re-named panels used in study

Protocol sections:

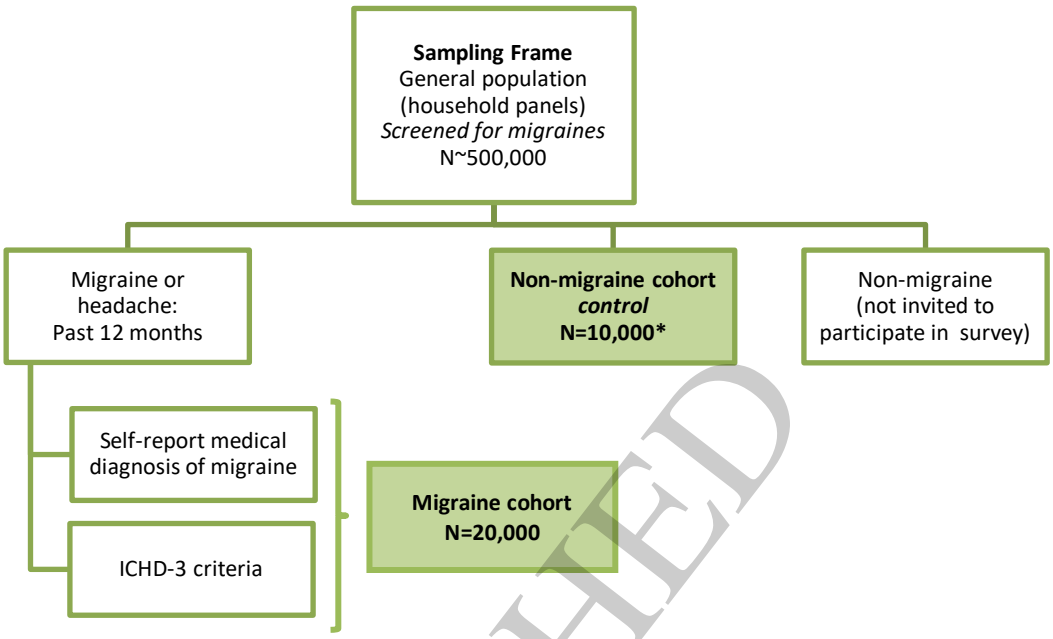
6.1 Summary of Research Design

Amendment 23:

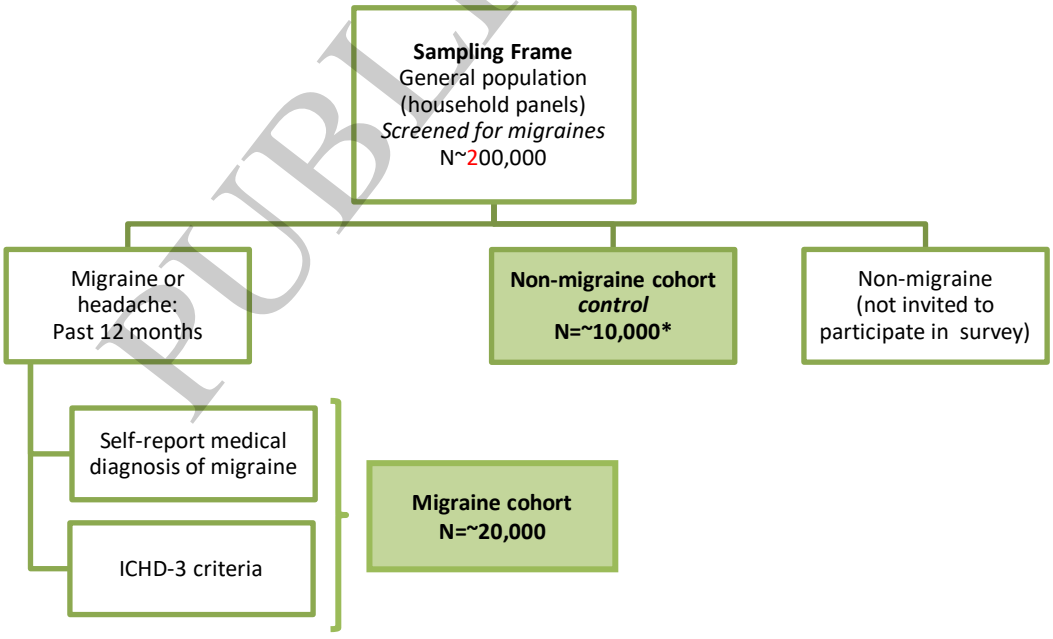
Refined description and figure of planned respondent selection

Change:

Original figure:



Revised Figure:
Adjusting "Screened for migraines" from ~500,000 to ~200,000.



Rationale:

To reflect more accurate screened for migraine sample number.

Protocol sections:

6.4 Study population

Amendment 24:

Exclusion criteria of cluster headache from Cohort 3

Change:

Original text:

Excluded from the study are participants who are:

1. Unwilling or unable to provide electronic informed consent

Excluded from the Migraine cohort:

1. Anyone with all headaches in the past 12 months due to hangover or illness

Revised text:

Excluded from the study are participants who are:

1. Unwilling or unable to provide electronic informed consent
2. [For cohort 3] Having a self-reported medical diagnosis of cluster headache with no other self-reported medical diagnosis for migraine

Excluded from the Migraine cohort:

1. Anyone with all headaches in the past 12 months due to hangover or illness
2. [For cohort 3] Having a self-reported medical diagnosis of cluster headache with no other self-reported medical diagnosis for migraine

Rationale:

Respondents with cluster headache were excluded post-data collection from Cohort 1 and 2, therefore it was decided to exclude these respondents a priori.

Protocol sections:

6.4.1 Selection Criteria

Amendment 25:

Removal of Figure 4 due to redundancy

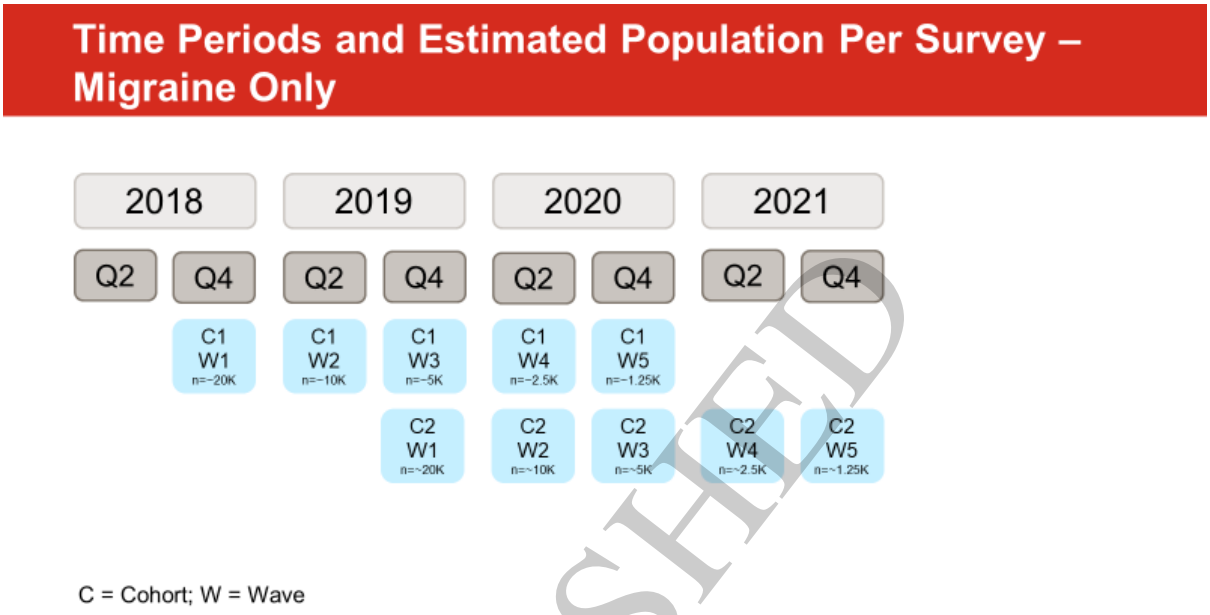
Change:

Original text:

Figure 4 illustrates the planned study time periods comprising respondent enrollment for baseline and follow-up surveys. While it is not shown in the Figure, we will also have administer a survey

to a subset of N=10,000 people from the general population without migraine as a control group at the time of the cohort 1 baseline survey. Timelines are approximations.

Figure 4 Study time periods – respondents with migraine only.



*Estimated re-contact rate is 50% at 6-month intervals

Revised text:

Figure 1 above illustrates the planned study time periods comprising respondent enrollment for baseline and follow-up surveys (see Table 3 below). Timelines are approximations.

Rationale:

Respondents with cluster headache were excluded post-data collection from Cohort 1 and 2, therefore it was decided to exclude these respondents a priori.

Protocol sections:

6.4.1 Selection Criteria

Amendment 26:

Revised and updated study variables Table 1

Change:

1. Original – Confirmation of eligibility: Confirmation of selection criteria

   Revised – Confirmation of eligibility: Confirmation of selection criteria (see 6.4.1)

2. Revised addition – Prevention medication: When and why prevention medication is used

3. Revised addition – HCRU: HCP communication type
4. Revised addition – QOL/burden/Impact: IMPAC scale

Rationale:

Clarified the selection criteria and added the new questions to better understand medication use, HCRU, and burden.

Protocol sections:
6.1 Variables/Measures Table 1

Amendment 27:

Revised and updated study variables Table 2

Change:

Original – Confirmation of eligibility: Confirmation of selection criteria

Revised – Confirmation of eligibility: Confirmation of selection criteria (see 6.4.1)

Rationale:

Clarified the selection criteria

Protocol sections:
6.1 Variables/Measures Table 2

Amendment 28:

Revised assumptions in Table 3

Change:

Original table:

Study	Estimated N	Estimated % of primary cohort
Migraine Cohort (C)1_Wave (W)1 – Baseline	20,000	100%
Non-migraine Cohort 1	10,000	na
Migraine C1W1 – claims	2,000-3,000	10-15%
Migraine C1W2 – 6 months post-baseline	10,000	50.0%
Migraine C1W3 – 12 months post-baseline	5,000	25.0%
Migraine C1W4 – 18 months post-baseline	2,500	12.5%
Migraine C1W5 – 24 months post-baseline	1,500	7.5%
Migraine C2W1 – Baseline	20,000	100%
Migraine C2W2 – 6 months post-baseline	10,000	50.0%
Migraine C2W3 – 12 months post-baseline	5,000	25.0%

Migraine C2W4 – 18 months post-baseline	2,500	12.5%
Migraine C2W5 – 24 months post-baseline	1,500	7.5%

Revised table:

Study	Estimated N	Estimated % of primary cohort
Migraine Cohort (C)1_Wave (W)1 – Baseline	20,000	100%
Non-migraine Cohort 1	10,000	na
Migraine C1W1 – claims	2,000-3,000	10-15%
Migraine C1W2 – 6 months post-baseline	10,000	28.0%
Migraine C1W3 – 12 months post-baseline	4,000	20.0%
Migraine C1W4 – 18 months post-baseline	2, 000	10.0%
Migraine C1W5 – 24 months post-baseline	1, 000	5.0%
Migraine C2W1 – Baseline	20,000	100%
Migraine C2W2 – 6 months post-baseline	7,000	35.0%
Migraine C2W3 – 12 months post-baseline	4,000	20.0%
Migraine C2W4 – 18 months post-baseline	2,000	10.0%
Migraine C2W5 – 24 months post-baseline	1,000	5.0%
Migraine Cohort (C)3_Wave (W)1 – Baseline	20,000	100%
Non-migraine Cohort 3	10,000	na
Migraine C3W2 – 6 months post-baseline	7,000	35.0%
Migraine C3W3 – 12 months post-baseline	4,000	20.0%
Migraine C3W4 – 18 months post-baseline	2,000	10.0%
Migraine C3W5 – 24 months post-baseline	1,000	5.0%

Rationale:

Assumptions have been updated based on current experience.

Protocol sections:
7.1.1 Assumptions

Amendment 29:

Revised assumptions for sample size

Change:

1. Added text regarding new acute and preventive migraine medications available in the market (assumption #4)

   New acute and preventive medications for migraine increased by 85% from Q2 2019 to 2020.[29]

2. Updated text related to expected panel survey participation over time (assumptions #5)

Original text – Longitudinal completion rates at each 6-month intervals would be approximately 50% (i.e., loss-to-follow-up of active panel participants of will be approximately 50% at each survey wave) resulting in ~6% completing all 5 visits, with the desire to have at least 1,250 patients available at that time (2 years). The 50% loss is a conservative estimate, based in part on the CaMEO study experience (58% return at the first timepoint and smaller percentage decreases at later time points)19 and Kantar's prior experience. In all likelihood, we will have a far better retention rate than 6% at 2 years (CaMEO was >30%), but we have been conservative in our estimation given the differences in study populations – CaMEO is all chronic migraine, so participation rates in that study may be expected to be greater.

8. Revised text – Longitudinal participation rates at each 6-month interval of the original cohort (i.e., respondents for each wave are identified from baseline cohort regardless of prior wave participation) are expected to vary between approximately 5%-35%. We note that there is an expected loss-to-follow-up of active panel participants at each survey wave). Estimated percentage of respondents in each cohort that will complete a survey for all 5 visits is <5%; with the desire to have at least 1,000 patients available at that time (2 years).

Rationale:

Clarified the selection criteria

Protocol sections:
6.1 Variables/Measures
Table 2

Amendment 30:

Added text to address determination of sample size

Change:

The sample size was selected to provide 90% power for a) detecting an effect size of at least 0.11 for the 1 year difference within a longitudinal cohort; b) 90% power to detect individual factors associated with at least a 9.7% difference for the change in a pre-defined binomial attribute (eg change in opiod use) within a longitudinal cohort; c) 90% power to detect at least a 3.0% difference between Cohort 1-1 and Cohort 2-1 (or Cohort 2-1 and Cohort 3-1) in percentage of patients exhibiting a pre-defined binomial attribute. Additionally, the sample size will allow precision of at least 5.7% in the estimate for the percentage of migraine patients exhibiting a pre-defined binomial attribute.

Rationale:

The estimated sample size at the last time point has been reduced since the original protocol was approved without impact on precision/power. Section 7.1 has been added to clarify the current assumptions. The team also felt that upon further review more details could be provided to clarify what was driving the original sample size decisions.

Protocol sections:
7.1 Determination of Sample Size

Amendment 31:

Added text and table to precision and power assessments to consider Cohort 3

Change:

- Added 'and/or Migraine Cohort 3_1' to the comparison with Migraine Cohort 1_1.
- Added estimate of percent preventive eligible of ~30%
- Updated participation rate from 50% to 5-35% (see amendment 29)
- Added:

The following table shows the estimated lower bound for power at 12 months and 24 months to detect a specified change from the baseline percentage for binomial endpoints (for example, 5% corresponds to 50% changing to 55%).

Population	**Change (x 100%)**	**Power**	
		12-month change from baseline	**24-month change from baseline**
Full migraine	5%	99%	61%
	10%	≈100%	99%
	15%	≈100%	≈100%
Preventive eligible	5%	66%	22%
	10%	≈100%	66%
	15%	≈100%	95%

Rationale:

To estimate the power to detect a difference over time considering the additional third cohort

Protocol sections:
Section 7.1.2

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[redacted]

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