Protocol H8H-MC-B010

Real-World Observational Study Using US Pharmacy Claims Data to Assess Safety Outcomes and Treatment Patterns in the US Among Migraine Patients Treated with REYVOW™ (Lasmiditan) Long Term

Confidential Information

Protocol Electronically Signed and Approved by Lilly: approval date provided below

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Post-Authorisation Safety Study (PASS) Information

Title	Real-World Observational Study Using US Pharmacy Claims Data to Assess Safety Outcomes and Treatment Patterns in the US Among Migraine Patients Treated with REYVOW™ (Lasmiditan) Long Term
Study Identifier	H8H-MC-B010
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Date of Last Version	See cover page
EU PAS Register No	Not available
Active Substance	REYVOW™ (lasmiditan)
Medicinal Product(s)	REYVOW™ (lasmiditan) 50 and 100 mg
Product Reference	LY573144
Procedure Number	N/A
Marketing Authorisation Holder(s)	Eli Lilly and Company
Joint PASS	No
Research Question and Objectives	The primary objectives of this study are to • assess REYVOW™ (lasmiditan) utilization and safety outcomes among patients treated with lasmiditan long term, and • describe patient demographics and clinical characteristics and treatment patterns of REYVOW™ (lasmiditan)-treated patients treated long term. The secondary objective of this study is to describe safety outcomes, including cardiovascular events, malignancy, and most frequently emerging categories of diagnoses among patients treated with REYVOW™ (lasmiditan) long-term, stratified by • patient demographic characteristics • comorbidities • number of prescriptions • duration of continuous treatment, and • concomitant medications.
Country of study	United States
Author	Lilly Global Patient Safety Pharmacoepidemiologist

Abbreviations: N/A = not applicable; PAS = Post-Authorisation Study; PASS = Post-Authorisation Safety Study.

Marketing Authorisation Holder

Marketing Authorisation Holder (MAH)	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 United States
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2. List of Abbreviations

Term	Definition
AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
CCAE	Commercial Claims and Encounters
CCSR	Clinical Classifications Software Refined
CGRP	Calcitonin gene-related peptide
CI	Confidence Interval
CNS	Central Nervous System
COBRA	Consolidated Omnibus Budget Reconciliation Act
CVD	Cardiovascular disease
ERB	Ethical Review Board
EU PAS	European Union post-authorisation study
HRT	Hormone Replacement Therapy
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICSR	Individual Case Safety Report
MDCR	Medicare Supplemental and Coordination of Benefits Database
NDC	National Drug Code
NSAID	Nonsteroidal Anti-inflammatory Drug
PASS	Post-Authorisation Safety Study
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event

3. Responsible Parties

Name, Degree(s)	Title	Affiliation	Address
PPD			

4. Abstract

Title: Real-World Observational Study to Assess Safety Outcomes in the US Among Migraine Patients Treated with REYVOW™ (Lasmiditan) Long Term

Rationale and background: Migraine is a leading cause of disability in the world, and patients may continue acute intermittent treatment for long periods of time. Given the inclusion and exclusion criteria and the limited duration of clinical trials, use of REYVOW™ (lasmiditan) long term (>1 year) has not been adequately studied. Long-term use is considered to be missing information that is worthy of further study.

Research question and objectives: This study aims to investigate the long-term safety and use of REYVOW™ (lasmiditan) in routine clinical practice by utilizing an administrative claims database.

The primary objectives of this study are to

- assess utilization and safety outcomes among patients treated with REYVOW™ (lasmiditan) long term, and
- describe patient demographics and clinical characteristics and treatment patterns of REYVOW™ (lasmiditan)-treated patients treated long term.

The secondary objective of this study is to describe safety outcomes, including cardiovascular events, malignancy, and most frequently emerging categories of diagnoses among patients treated with REYVOW™ (lasmiditan) long term, stratified by

- patient demographic characteristics
- comorbidities
- number of prescriptions
- duration of continuous treatment, and
- concomitant medications.

Study design: This is a descriptive retrospective cohort study that utilizes claims data from 31 July 2019 through 31 March 2025.

Population: This study includes US patients aged 18+ years with migraine who are treated with REYVOW™ (lasmiditan) for more than 1 year.

Variables: The exposure of interest is long-term use of REYVOW™ (lasmiditan), defined as least 1 NDC claim for lasmiditan occurring every 180 days after index for a minimum period of 366 days. The long-term safety outcomes of interest are cardiovascular adverse events, malignancy, serotonin syndrome, and all other diagnoses identified utilizing AHRQ CCSR groupings. Utilization variables include measures of the number and type of treatments identified, as well as prescriber information. Baseline variables include migraine type, comorbidities, concomitant medications, age, gender, insurance type, geographic location, and timing of first REYVOW™ (lasmiditan) use.

Data sources: IBM® MarketScan Commercial Claims and Encounters, Medicare Supplemental and Coordination of Benefits, and Medicaid databases will be utilized for this study.

Study size: All eligible REYVOW™ (lasmiditan)-exposed patients will be included, and the number of patients will depend on the uptake of REYVOW™ (lasmiditan) in the US. No minimum sample size is described.

Data analysis: All data will be summarized using descriptive statistics. Categorical variables will be presented using percentages and frequencies. Continuous variables will be presented as means and standard deviations. Rates will be presented in person-time, and 95% confidence intervals will be calculated.

Milestones:

The proposed milestones are as follows:

Milestone	Anticipated Due Date*
Start of data collection	Estimated for 31 December 2023
Final study report submission	31 December 2026

*These timelines are currently under discussion and are subject to change.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned Date
Start of data collection	Estimated for 31 December 2023
End of data collection	Estimated for 01 January 2026
Study progress report	N/A
Interim report submission	N/A
Registration in the EU PAS register	28 December 2023
Final report of study results submission	31 December 2026

Abbreviation: N/A = not applicable; PAS = Post-Authorisation Study.

7. Rationale and Background

Migraine is the second leading cause of disability in the world, with an estimated 1.04 billion individuals with the disease in 2016 (GBD 2018). It is a recurrent neurological headache disorder by painful attacks lasting 4 to 72 hours often accompanied by other symptoms, including nausea, vomiting, sensitivity to light and sound, and changes in vision (Katsarava et al. 2012). The clinical symptoms vary along a continuum from episodic migraine to chronic migraine. Migraine occurs more frequently in females (18%) than in males (6%) (Chandler et al. 2021).

Episodic migraine is characterized by no more than 14 headache days per month. Chronic migraine is characterized by 15 or more headache days per month for 3 or more months, of which 8 or more days either meet the criteria for migraine without aura or respond to migraine specific treatment (Katsarava et al. 2012), or both.

Chronic migraine is much less common than episodic migraine (Lipton et al. 2007; Buse et al. 2012). Migraine is 2 to 3 times more prevalent in women than in men (Vetvik and McGregor 2017), and its prevalence peaks in the middle of life in both sexes (GBD 2018). Migraine has been consistently associated with an increased risk of ischemic stroke and myocardial infarction, with a significantly higher risk among patients who had migraine with aura versus without and among women compared with men (Schurks et al. 2009; Mahmoud et al. 2018). The majority of patients with migraine use acute treatments such as triptans or nonsteroidal anti-inflammatory drugs for migraine attacks.

Migraine is a chronic condition, and it is anticipated that acute intermittent treatment will continue for long periods of time. Given the inclusion and exclusion criteria and limited duration of clinical trials, the use of REYVOW™ (lasmiditan) over a longer duration of time, that is, more than 1 year, has not been adequately studied. As such, long-term use is considered missing information and as such worthy of further study.

Phase 3 trials for lasmiditan generally followed patients for up to 1 year. The GLADIATOR trial evaluated intermittent use of lasmiditan for the acute treatment of migraine for up to 1 year (Brandes et al. 2020). This trial found that for patients treated long term (intermittent treatment for up to 1 year), the incidence of treatment emerging adverse events (TEAEs) decrease over time. The most frequently reported TEAEs were CNS related (Hou et al. 2020).

The goal of this PASS would be to collect more data on outcomes in a larger population of patients who are treated intermittently for longer periods of time than occurred in clinical development. If the data demonstrate that long-term use is associated with clinically meaningful adverse outcomes or morbidity, this could impact the benefit-risk in the context of acute treatment of a non-life-threatening condition such as migraine.

Administrative claims data contain information on millions of patients, including patients with migraine. These claims reflect

- routine clinical practice with diagnoses and procedures
- outpatient prescription drug use

- outpatient laboratory test result data, and
- healthcare utilization.

These data include patients who may not be referred to, or may choose not to participate in clinical trials, and can be readily used to investigate potential safety signals. This protocol outlines an observational study using claims data to fill the knowledge gap of the lasmiditan clinical trials. It is also important to understand the strengths and limitations of administrative claims data relative to the evaluation of the research questions for this study. Claims data come from reimbursement of healthcare visits and treatment.

REYVOW™ (lasmiditan) was approved in the US in October 2019 by the FDA for the acute treatment of migraine with or without aura in adults. REYVOW™ (lasmiditan) became available for prescription on 31 January 2020 (Lilly 2020). This PASS is planned to investigate the safety of lasmiditan treatment for longer than 1 year.

8. Research Question and Objectives

This study aims to investigate the long-term use and safety of REYVOW™ (lasmiditan) in routine clinical practice by utilizing an administrative claims database.

The primary objectives of this study are to

- assess REYVOW™ (lasmiditan) utilization and safety outcomes among patients treated with lasmiditan long term, and
- describe patient demographics and clinical characteristics and treatment patterns of REYVOW™ (lasmiditan)-treated patients treated long term.

The secondary objective of this study is to describe safety outcomes, including cardiovascular events, malignancy, and most frequently emerging categories of diagnoses among patients treated long term by REYVOW™ (lasmiditan), stratified by

- patient demographic characteristics
- comorbidities
- number of prescriptions
- duration of continuous treatment, and
- concomitant medications.

9. Research Methods

9.1. Study Design

This is a retrospective cohort study using secondary data from the IBM® MarketScan claims database to evaluate safety outcomes among patients treated with REYVOW™ (lasmiditan) long term. This study uses real-world data from patients in the US. This study will assess safety outcomes as well as describe treatment patterns and patient characteristics of those treated with REYVOW™ (lasmiditan) long term. Long-term use of REYVOW™ (lasmiditan) is defined as at least 1 NDC claim for lasmiditan occurring every 180 days after index for a minimum period of 366 days. Administrative claims data were chosen for this study because they reflect routine clinical practice and include

- diagnoses and procedures
- outpatient prescription drug use
- outpatient laboratory test result data, and
- healthcare utilization for millions of patients, including patients with migraine.

Administrative claims data allow the sample size for the study to be maximized. In addition, these data can provide long-term longitudinal data often not available in clinical trials.

This is a descriptive study of safety outcomes among patients treated with REYVOW™ (lasmiditan) long term. The events of interest include any cardiovascular AEs overall among patients treated with REYVOW™ (lasmiditan) long term, as well as specific cardiovascular AEs, malignancy, serotonin syndrome, and other diagnoses identified any time after 365 days post-index. Characteristics and treatment patterns of REYVOW™ (lasmiditan) patients treated long term also will be described.

9.2. Setting

This study will be conducted utilizing US administrative claims data from the IBM® MarketScan database. REYVOW™ (lasmiditan) was approved in the US in October 2019 by the FDA and became available for prescription on 31 January 2020 (Lilly 2020). As such, the use of REYVOW™ (lasmiditan) will be assessed from 31 January 2020 onward, and patients will be indexed at first filled REYVOW™ (lasmiditan) prescription date. Allowing for a 6-month baseline period, data from 31 July 2019 onward will be included in this study for the assessment of migraine diagnosis, as well as relevant comorbidities and concomitant medications at baseline. Patients will be considered long-term users provided they have a claim for REYVOW™ (lasmiditan) occurring every 180 days after index for a minimum period of 366 days. Safety outcomes will be assessed through 31 March 2025.

9.2.1. Study Population

Individuals in the REYVOW™ (lasmiditan) cohort will be indexed at first prescription date. The cohort will include all available patients who meet the following criteria:

Inclusion criteria:

- an initial NDC claim for REYVOW™ (lasmiditan) on 31 January 2020 or later
- at least 1 NDC claim for REYVOW™ (lasmiditan) occurring every 180 days after index for a minimum period of 366 days
- continuous medical and pharmacy coverage for at least 183 days before the index date to assess pre-index migraine characteristics and comorbidities
- a diagnosis of migraine within 183 days prior to index
- age 18 years or older at index, and
- at least 366 days continuous medical and pharmacy coverage after the index date.

Exclusion criterion:

- an initial NDC claim for REYVOW™ (lasmiditan) that occurs less than 366 days before the end of available data, as patients could not be considered long term within the defined study period.

9.2.1.1. Special Populations of Interest

None

9.3. Variables

9.3.1. Drug Exposure

The exposure of interest is long-term use of REYVOW™ (lasmiditan) defined as at least 1 NDC claim for lasmiditan occurring within 180 days after index for a minimum period of 366 days. For long-term users of REYVOW™ (lasmiditan), if more than 180 days pass after a filled REYVOW™ (lasmiditan) prescription without a subsequent filled prescription, the patient will be considered to have discontinued treatment. However, that patient will be followed for outcomes until end of insurance coverage, death, or end of study period, whichever comes first, upon which time that patient will be censored.

Filled prescriptions for REYVOW™ (lasmiditan) will be identified using the NDC codes as listed in Table 9.1. The REYVOW™ (lasmiditan) cohort of patients will be identified using a window from 31 January 2020 until 31 March 2024, with follow-up data available through 31 March 2025. Prescription fill patterns will be described, including the date of claim, pill count, and strength. Prescriber specialty for each REYVOW™ (lasmiditan) prescription will be identified and described. Refill patterns will be described, including time between prescription fills, pill count, and strength for each claim.

Table 9.1. REYVOW™ (Lasmiditan) National Drug Code List

Code	Strength	Route	Marketed Date
0002-4312-61	50 mg	Tablet	03 March 2021
0002-4312-08	50 mg	Tablet	31 January 2020
0002-4491-08	100 mg	Tablet	31 January 2020
0002-4491-61	100 mg	Tablet	31 January 2020

9.3.1.1. Safety Outcomes

Safety outcomes will be assessed through 31 March 2025. Events of interest include cardiovascular AEs, such as

- angina
- arrhythmia
- heart failure
- hemorrhagic stroke
- ischemic stroke
- myocardial infarction
- myocardial ischemia, and
- transient ischemic attack.

These cardiovascular outcomes will be combined and reported as an overall cardiovascular event and separately as individual events. Malignancy also will be assessed overall and by site. An additional safety outcome for investigation includes serotonin syndrome.

In addition to pre-specified AEs, CCSR groupings for ICD-10-CM as developed by AHRQ will be used to identify the most frequent categories of diagnoses arising at post-index Day 366 onward. CCSR aggregates more than 70,000 ICD-10-CM diagnosis codes into over 530 clinically meaningful categories, and the categories are organised across 21 body systems, which generally follow the structure of the ICD-10-CM diagnosis chapters (AHRQ 2022). Additional details will be outlined in the SAP. The categories not already included in pre-specified safety outcomes will be noted and rates of occurrence provided, although caution would be required in any interpretation of the implications of such results.

9.3.1.2. Utilization Variables

To address the primary objective of evaluating utilization and safety outcomes among patients treated long term, descriptive statistics for long-term REYVOW™ (lasmiditan) users will include measures of the number and type of treatments identified. These variables are outlined in Table 9.2. The coding algorithms using diagnosis, procedure, or drug codes for these covariates will be detailed in a separate SAP.

Table 9.2. Variables Identified during the Follow-Up Period

Variable	Description	Continuous or Categorical
Prescription frequency	The number of filled prescriptions for REYVOW™ (lasmiditan) during the study period	Continuous and categorical
Total treatment dose	Sum of the REYVOW™ (lasmiditan) doses for all claims	Continuous
Prescriber information	Prescribing physician specialty	Categorical
Pharmacy use	Description of the count of different pharmacies used to fill REYVOW™ (lasmiditan) prescriptions	Continuous
Duration of continuous treatment	Time between index and the date of last dispensing plus 180 days. Combination of treatment episodes	Continuous and categorical
Discontinuation	Occurs when >180 days pass between filled prescriptions for REYVOW™ (lasmiditan)	Categorical
Treatment episode	180 days for each filled prescription for REYVOW™ (lasmiditan)	Continuous
Persistence	Duration of continuous treatment	Continuous
Chronic use	Greater than 2 filled prescriptions for REYVOW™ (lasmiditan) within a 6-month period	Categorical
Strength	Strength of the drug product	Categorical
Package size	Quantity of pills for prescription fill	Continuous
Package count	Quantity of tablets for each filled prescription for REYVOW™ (lasmiditan)	Continuous

9.3.2. Baseline Variables and Other Covariates

To address the study's secondary objective of stratifying outcomes by patient characteristics, baseline demographic characteristics will be assessed at index (Table 9.3). These will include age, gender, insurance type, and geographic region of residence, as defined by US Census regions (US Census Bureau n.d.). Those for whom region is not available will have geography defined as "Unknown." The date of first REYVOW™ (lasmiditan) claim will also be noted.

Table 9.3. Demographic Characteristics

Variable	Description
Age (years)	Age at first filled prescriptions for REYVOW™ (lasmiditan) will be presented both as a continuous variable (mean and standard deviation) as well as a categorical variable with the following age categories: • 18-29 years • 30-49 years • 50+ years
Gender	Male, female, unknown
Insurance type	Commercial, Medicare, Medicaid
US geographic region	Northeast, Midwest, South, West, Unknown
Date	Month and year of first REYVOW™ (lasmiditan) claim

Patient clinical characteristics identified during the 6-month baseline period will be described as presented in Table 9.4. The coding algorithms using diagnosis, procedure, or drug codes to identify clinical characteristics will be detailed in a separate SAP.

Table 9.4. Clinical Characteristics Identified during the Baseline Period

Variable	Description
Migraine diagnosis	Migraine with and without aura.
Baseline comorbid conditions	All pre-specified diagnoses occurring during the 6-month baseline period, as well as the most common, will be reported.
Baseline concomitant medication (nonmigraine)	Concomitant medication during the observation period (including cholesterol-lowering medications, antihypertensive medications, antiplatelet agents, anticoagulants, antihistamines, oral contraceptives for women, postmenopausal hormone replacement therapy, anxiolytics/sedatives/hypnotics, and other most common medications identified).
Baseline concomitant medication (migraine)	Acute (triptans, gepants, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, non-NSAID analgesics, non-opioid analgesics, and ergotamines) and preventive (CGRP antagonists, anticonvulsants, antidepressants, antihypertensives, and botulinum toxins) medication.

Abbreviation: CGRP = calcitonin gene-related peptide.

Patient comorbid conditions and concomitant medications for migraine and nonmigraine will be reassessed and described at post-index Day 365 also.

9.4. Data Sources

The IBM® MarketScan databases capture longitudinal, individual-level administrative claims data from the US. Patients in the databases are

- active employees
- dependents
- retirees
- Consolidated Omnibus Budget Reconciliation Act (COBRA)
- recipients, and
- Medicare or Medicaid enrollees.

Data will be drawn from large employers, health plans, and public organisations in the US. The data included 3 components of MarketScan:

- the CCAE database
- the MDCR database, and
- the Medicaid database.

The CCAE database includes over 200 million enrollees annually who are covered by employer-sponsored private health insurance. The MDCR database includes health insurance programs for people aged 65 years or older, people aged under 65 years with certain disabilities, and people of all ages with end stage renal disease (CMS 2021). This database includes the Medicare Advantage Plan and supplemental plans. The Medicaid database includes data from multiple states for medical, surgical procedures, and prescription drugs. This includes data on approximately 50 million patients (IBM® MarketScan Research Databases page [WWW]).

9.5. Study Size

This is a descriptive study, and the available number of REYVOW™ (lasmiditan)-exposed patients will depend on the uptake of REYVOW™ (lasmiditan) in the US. No minimum sample size is described. In general, however, the accuracy of all estimates will rely heavily on the number of patients meeting criteria for inclusion. Table 9.5shows the corresponding standard errors of estimate for various different sample sizes based on possible background event rates.

Table 9.5. Standard Error of Estimates Based on Various Sample Sizes and Background Event Rate

	Sample Size Collected			
Background Event Rate	**100**	**250**	**500**	**1000**
10.0%	3.0%	1.9%	1.3%	0.9%
5.0%	2.2%	1.4%	1.0%	0.7%
2.5%	1.6%	1.0%	0.7%	0.5%
1.0%	1.0%	0.6%	0.4%	0.3%

9.6. Data Management

This analysis will use secondary data from the IBM® MarketScan database. Datasets and analytic programs will be kept on a secure server and archived per Eli Lilly and Company (Lilly) record retention procedures.

9.7. Data Analysis

SAS EG 7.15 (SAS Institute Inc., Cary, NC) and SQL Workbench Build 125 (Oracle Corporation, Austin, TX), or the most recent version available, will be the statistical software used for the analyses. All patients who fulfil the study selection criteria will be included. Study findings will be described as well as a summary of the literature to provide context. A flow diagram illustrating the selection of the study population will be presented. Analyses for safety outcomes will include all data up to the end of insurance coverage, end of study period, or death, upon which patients will be censored. Analyses for utilization will go through final treatment episode, end of insurance coverage, end of study period, or death, whichever occurs first. An example of a study period timeline is displayed in Figure 9.1.

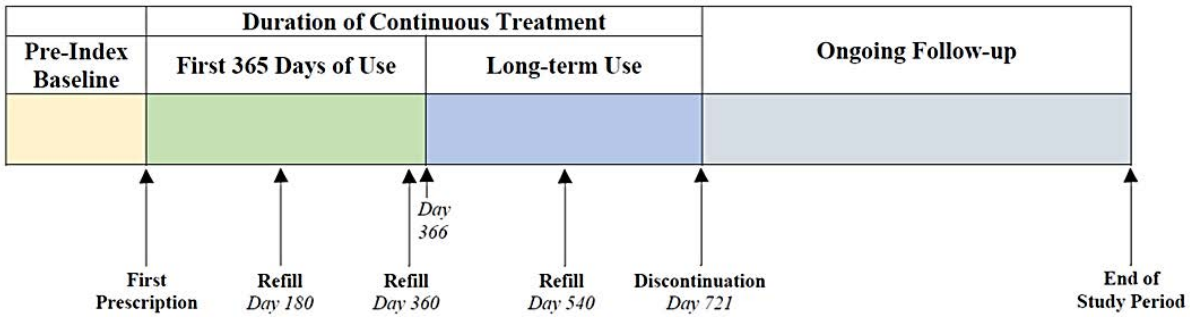

Figure 9.1. Sample study period timeline for long-term use.

9.7.1. Population Characteristics

Demographic information, migraine characteristics, whether with or without aura, and month and year of first claim for filled prescriptions for REYVOW™ (lasmiditan) will be collected during the baseline period and described for the study population. Categorical variables will be described in terms of frequencies and percentages. Continuous variables will be described in terms of means, standard deviations, medians, minimums, maximums, and interquartile range.

Prevalence of comorbid conditions and concomitant medications as assessed from the 6-month baseline period will be presented (Table 9.6). Migraine medications will be described in aggregate as "any preventive migraine medication" or "any acute migraine medication," as well as by specific medication.

To understand changes to the baseline characteristics over the first year of REYVOW™ (lasmiditan) use, analyses of population characteristics will be repeated for comorbid conditions and concomitant medications at post-index Day 365. Overall prevalence of comorbidities and concomitant medications from the 6-month baseline period through 1-year post-index will be described.

Table 9.6. Clinical Characteristics through One Year of REYVOW™ (Lasmiditan) Use

Variable	**Baseline Prevalence at Index**	**Overall Prevalence: Index to Post-index Day 365**
	n (%)	**n (%)**
Comorbid conditions		
Atherosclerosis		
Dyslipidaemia		
Hypertension		
Peripheral vascular disease		
Anxiety disorder		
Major depressive disorders		
Bipolar disorder		
Epilepsy		
Type 1 Diabetes		
Type 2 Diabetes		
Obese (as available in claims)		
Smoking (as available in claims)		
History of serotonin syndrome		
History of Malignancy[a]		
History of any CVD		
Angina pectoris		
Arrhythmia		
Heart failure		
Hemorrhagic stroke		
Ischemic stroke		
Myocardial infarction		
Myocardial ischemia		
Transient ischemic attack (TIA)		

Variable	Baseline Prevalence at Index	Overall Prevalence: Index to Post-index Day 365
Other most common comorbidities		
Concomitant medications (nonmigraine) Anxiolytics/sedatives/hypnotics Antihypertensive medications Antiplatelet agents Anticoagulants Cholesterol-lowering medications Oral contraceptives for women Postmenopausal HRT Other most common nonmigraine medications		
Concomitant medications (migraine) **Any Preventive** CGRP antagonists Anticonvulsants Antidepressants Antihypertensives Botulinum toxins **Any Acute** Triptans Gepants Nonsteroidal anti-inflammatory drugs (NSAIDs) Opioids Non-NSAID analgesics Non-opioid analgesics Ergotamines		

[a] Excluding non-melanoma skin cancer.

Abbreviations: HRT – Hormone Replacement Therapy; CVD – Cardiovascular disease; CGRP - Calcitonin gene-related peptide

9.7.2. Long-Term Safety Analysis

To address the primary objective related to long-term safety, safety outcomes of interest such as cardiovascular AEs, malignancy, and most frequently identified, as described in Section 9.3.1.1, will be assessed from post-index Day 366 onward for all cohort members. Rates of occurrence (percentage of patients with an event) and incidence rates will be calculated. Incidence rates will be calculated as the number of events of the safety outcomes of interest divided by the number of patient-years at risk, along with 95% CI per 1,000 patient-years, which will be calculated using the relationship between the Poisson distribution and chi-square distribution, as described in Dobson et al. (1991).

For each safety outcome, person-time will accrue for an individual from Day 366 until the first occurrence of that safety outcome or until end of insurance coverage, end of study period, or death, at which time that individual will be censored. That patient may continue follow-up for

other safety outcomes until such outcomes occur or until censoring. Events that occur prior to being treated long term will not be included.

To examine possible bias due to censoring, Kaplan Meier cumulative distribution functions for time-to-event will be provided for each safety outcome of interest.

9.7.3. Long-Term Utilization Analysis

To address the primary objective related to long-term utilization, utilization variables described in Table 9.2 will be assessed through final prescription date plus 180 days, end of insurance coverage, end of study period, or death, whichever occurs first. Categorical variables will be described in terms of frequencies and percentages. Continuous variables will be described in terms of means and standard deviations.

9.7.4. Stratified Analysis

All long-term REYVOW™ (lasmiditan)-treated patients will be included in the analyses described in Section 9.7.3, regardless of whether they have experienced the events of interest prior to the long-term safety follow-up (i.e., during baseline or the first year of lasmiditan treatment) to maximize the sample size for the lasmiditan treated population. However, it is noted that risk may be inherently different among patients based on baseline characteristics. As such, to address the study's secondary objective, rates of occurrence and incidence rates along with corresponding 95% CIs of pre-specified safety outcomes from Day 366 onward will be stratified by comorbidities, demographic variables, and concomitant medications as determined by their assessment on post-index Day 365. Incidence rate CIs will be constructed using the Dobsen et al. (1991) approach as done for the overall incidence rate, but separately for each stratum of interest. Comorbidities assessed at baseline are also outcomes of interest. For patients who have previously experienced such an event of interest, stratified analyses by comorbidities will allow for risk calculations by prior event status. For example, patients with no history of prior cardiovascular events, incidence rates and 95% CIs of cardiovascular outcomes will be calculated.

For patients who have previously experienced a cardiovascular event, rates of occurrence and incidence rates along with 95% CIs of cardiovascular outcomes will be presented separately from those with incident events described in Section 9.7.2. Timing of prior events for these patients will be described in terms of frequency and percentage as occurring either during the 6-month baseline period, during the first year of treatment, or both. The number of prior events experienced will be presented as means, standard deviations, medians, minimums, maximums, and interquartile range.

Stratification by REYVOW™ (lasmiditan) prescription characteristics will also occur, including by the number of prescriptions for lasmiditan and duration of continuous treatment at the time of event.

For this analysis, utilization variables will be presented as categorical, and this categorical presentation will be used to stratify rates of outcomes.

9.7.5. Missing Data

Missing values for baseline characteristics will be treated as unknown and will be reported as such. For the outcomes of interest, the absence of an associated code is assumed to mean the absence of the event.

9.7.6. Sensitivity Analysis

A sensitivity analysis repeating all analyses will be performed extending the baseline period from 183 to 365 days. In doing so, it may be possible to identify additional comorbidities and prior events of interest that may influence the stratified results. However, sample size may decrease given the requirement for a longer pre-index period of insurance coverage.

9.8. Quality Control

All data gathering and analyses will be overseen by 2 pharmacoepidemiologists experienced in the field of register-based research. Programming for this project will be conducted by a primary analyst and validated by a separate analyst, the validation analyst. For all data processing steps, the validation analyst will review the programme along with input and output datasets. For the analysis steps of the project, double-programming techniques to reduce the potential for programming errors will be employed.

9.9. Limitations of the Research Methods

Studies that use secondary data sources are subject to potential limitations, as the original purpose of the data may differ from the purpose of the designed study. For example, claims data are collected administratively for billing purposes. As such, the data may include relevant procedure and diagnoses codes for a payer but may not include all covariate data that could be pertinent to the researcher, such as over-the-counter medication use, and less severe outcomes for which a patient does not seek medical attention may not be captured. In addition, claims codes may be subject to inaccuracies, and ICD-10-CM code algorithm sensitivity and specificity for the identification of comorbidities and concomitant medications can lead to misclassification (Chandler et al. 2021). However, administrative claims data contain information on millions of patients and reflect routine clinical practice with

- diagnoses and procedures
- outpatient prescription drug use, and
- outpatient laboratory test result data.

These data can include extensive follow-up on patients who may not be included in clinical trials and can provide information on long-term or rare safety outcomes or both.

The IBM® MarketScan database contains commercially insured patients, as well as patients treated using Medicare and Medicaid; thus, there are limits to the generalizability of study findings to the uninsured population or those not covered under one of the included plans. In so far as their patterns of care, disease incidence and prevalence may differ from those seen in our study population, and results from this study may not hold true in these groups. Despite this, the chosen database is inclusive of more than 200 million enrolees from a variety of payers, thereby providing a large sample of diverse patients from which to conduct this study.

It is uncertain how many patients with migraine will use REYVOW™ (lasmiditan), as it is a new medication for migraine, and treatment patterns have yet to be fully elucidated. Additionally, data on migraine timing and frequency are not available for this study. Given that REYVOW™ (lasmiditan) is used as needed, it is therefore difficult to determine the true treatment frequency. For the purposes of this study, it is assumed that a 30-day supply will be used within 180 days, or approximately 6 months. This time frame is aligned with real-world analyses of other acute migraine treatments. For example, patients in the US who use triptans have been shown to have 2.5 prescription claims for triptans per year (Lee 2021). To provide a conservative estimate, this can be rounded down to approximately 2 prescriptions per year or 1 prescription every 6 months, similar to the estimated REYVOW™ (lasmiditan) time frames presented in this study.

One outcome of interest in the current study is the occurrence of malignancy in the REYVOW™ (lasmiditan)-treated population. However, malignancy can have a long latency period, and the maximum time a patient may be included in this study is approximately 5 years (January 2020 through March 2025), given the recent approval of REYVOW™ (lasmiditan). As such, it is possible that some malignancy events that occur over a longer period of time will not be identified in this study period.

Finally, the population prescribed REYVOW™ (lasmiditan) may not be fully representative of the treated episodic migraine population overall. Migraine has been consistently associated with an increased risk of ischemic stroke and myocardial infarction (Schurks 2009; Mahmoud 2018), and some migraine treatments such as triptans are contraindicated in individuals at high risk for cardiovascular events. These higher-risk patients may instead be prescribed REYVOW™ (lasmiditan), which has been shown to be devoid of vasoconstrictor activity (Rubio-Beltrán 2019). As such, REYVOW™ (lasmiditan)-treated patients may have a higher baseline risk for cardiovascular events than patients receiving other acute migraine treatments. As this study is not comparative, it is not possible to assess the impact of variations in characteristics between comparator treatment groups. Thus, its findings are applicable only to the REYVOW™ (lasmiditan)-treated population.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

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

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

11. Management and Reporting of Adverse Events/Adverse Reactions

11.1. Secondary Data Collection Study

This is a non-interventional study based on secondary data use, and therefore, no ICSR reporting is required. The study protocol-defined AEs include

- cardiovascular AEs, such as
  - hypertension
  - myocardial ischemia
  - myocardial infarction
  - angina pectoris
  - ischemic stroke
  - hemorrhagic stroke, and
  - transient ischemic attack
- malignancy
- serotonin syndrome, and
- all other identified events as defined by AHRQ CCSR level 2 groupings, as described in Section 9.3.1.1.

All protocol-defined AEs collected will be summarized in the final study report. No other AEs will be collected.

11.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (eg, mobile medical applications), and comparator product(s) used in postmarketing medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation and/or Lilly products not under evaluation but discovered in the course of the study, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

12. References

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Study title:

EU PAS Register® number: Not available Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	

[1]Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2]Date from which the analytical dataset is completely available.

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

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	
3.3 Does the protocol specify measures of occurrence? (e.g. rate, risk, prevalence)	☒	☐	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	

Comments:

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

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the	☐	☒	☐	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
pharmacokinetics and pharmacodynamics of the drug?				
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	

Section 7: Bias	Yes	No	N/A	Section Number
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates and other characteristics?	☒	☐	☐	
9.2 Does the protocol describe the information available from the data source(s) on:				

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

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.5 Does the plan describe methods for analytical control of confounding?	☒	☐	☐	
10.6 Does the plan describe methods for analytical control of outcome misclassification?	☒	☐	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____