NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Evaluating reduction of opioid and barbiturate use following rimegepant initiation in the United States
Protocol number	C4951089
Protocol version identifier	1.0
Date	12 November 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000755
Active substance	Analgesics, calcitonin gene-related peptide (CGRP) antagonists. ATC code: N02CD06
Medicinal product	Rimegepant (Nurtec 75mg ODT)
Research question and objectives	Research question Among US adults with migraine and prior use of opioids or barbiturates, how does the use of opioids and barbiturates change following rimegepant initiation? Specific study objectives include: Primary Objective 1. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant. Secondary Objectives 2. To describe the pre-treatment characteristics of new rimegepant users, including demographics, comorbid conditions, and prior medication use. 3. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals using at least one preventive treatment for migraine 4. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals with

	problematic opioid use (≥ 3 opioid prescriptions and/or morphine milligram equivalents [MME] above 75th percentile during pre-index period)
Country of study	United States
Author	Redacted

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMPP	American Migraine Prevalence and Prevention
CaMEO	Chronic Migraine Epidemiology and Outcomes
CGRP	Calcitonin Gene Related Peptide
CPT	Current Procedural Terminology
EC	Ethic Committee
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedural Coding System
HIPPA	Health Insurance Portability and Accountability Act
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MME	Morphine milligram equivalents
MOH	Medication Overuse Headache
NDC	National Drug Codes
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PASS	Post-Authorization Safety Study
RWD	Real World Data
RWE	Real World Evidence
Rx	Prescription
SD	Standard Deviation
US	United States

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Title: Changes in opioid and barbiturate use following initiation of rimegepant for migraine in the United States

Version and date: 1.0, 12 November 2025

Main author: Redacted (Pfizer Inc.)

Rationale and background: Although opioids and barbiturates are not recommended in treatment guidelines for migraines, they are nevertheless often prescribed to individuals with migraine, despite the risks of dependence and other harms associated with these medications. Prescribing a migraine-specific treatment (e.g., rimegepant) could reduce the use of opioids and barbiturates among individuals with migraine.

Research question and objectives: Among US adults with migraine and prior use of opioids or barbiturates, how does the use of opioids and barbiturates change following rimegepant initiation? The primary objective is to evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant. Secondary objectives are: (1) to describe the pre-treatment characteristics of new rimegepant users, including demographics, comorbid conditions, and prior medication use; (2) to evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals using at least one preventive treatment for migraine; (3) to evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals with problematic opioid use (≥ 3 opioid prescriptions and/or morphine milligram equivalents [MME] above 75th percentile during pre-index period)

Study design: This is a retrospective, observational, noninterventional, cohort study using commercially available real-world data (RWD) of adjudicated medical and pharmacy claims from closed-network health insurers in the US. The study will examine data from September 1, 2019, to March 31, 2023.

Population: This study will be conducted among adults in the study database diagnosed with migraine who filled a prescription for rimegepant. The population in this database is broadly representative of those in the US covered by commercial, managed Medicare, or managed Medicaid health plans.

Variables: The primary exposure is initiation of rimegepant, defined by the first prescription fill between March 1, 2020, and October 1, 2022. Outcomes include changes in opioid and barbiturate utilization patterns before and after rimegepant initiation, measured by prescription fills, quantity dispensed, average dose, duration of use, and discontinuation. Key covariates are demographic and clinical characteristics (age, sex, region, comorbidities, chronic pain, prior preventive treatments) assessed during the baseline period.

Data sources: This study will analyze the IQVIA PharMetrics® Plus longitudinal health plan database, which includes anonymized, medical and pharmacy claims from closed-network, third-party payers in the US. This database includes commercial, managed Medicare, and managed Medicaid health plans.

Study size: The study database includes 52,591,063 individuals. It is estimated that 45,051 (0.86%) have an eligible first prescription for rimegepant and 4,049 (0.0077%) meet all eligibility criteria.

Data analysis: Number of fills and quantity dispensed (in MMEs for opioids and milligrams for barbiturates) will be assessed in the 180 days before and after the index fill for rimegepant. Changes in key outcomes will be analyzed using generalized linear mixed models adjusted for age, sex, region, chronic pain, comorbidities, and use of preventive treatment for migraine. Subgroup analyses will be conducted among individuals using ≥1 preventive treatment and individuals with problematic opioid use (≥3 fills or MMEs above 75th percentile).

Milestones: This study was initiated in 2023. Analyses were completed in 2024. A manuscript based on this study was accepted for publication in 2025.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned Date
Start of data collection	21 August 2023
End of data collection	04 September 2023
Registration in the HMA-EMA Catalogues of RWD studies	15 December 2025
Final study report	01 March 2026

6. RATIONALE AND BACKGROUND

Overall harms of opioids

The harms associated with opioid use are a well-established, global problem[1, 2]. The US Food and Drug Administration (FDA) requires all opioid medications, including immediate release/short-acting and extended release/long-acting formulations, to carry a boxed warning on the label stating the risk for addiction, dependence, abuse, and misuse, which can lead to overdose and death[3, 4].

Opioids for migraine

Opioid use for individuals with migraine is associated with negative outcomes[5]. Frequent use (≥10 days/month for >3 months[6]) of opioids is associated with medication overuse headache (MOH) and an increased risk of progression from episodic to chronic migraine[7-10]; MOH is associated with impaired quality of life[11], greater disability[12], and higher healthcare resource utilization[13, 14]. Evidence also suggests that opioids are not effective for the acute treatment of migraine and their use can impair the effectiveness of other medications used for the acute treatment of migraine (e.g., triptans)[15, 16]. Clinical practice guidelines for the management of migraine recommend against the use of opioids for the acute treatment of migraine, except in limited circumstances[3, 17-20]. Nevertheless, patients with migraine are frequently prescribed opioids[9, 21-24] or use opioids prescribed for other pain conditions to treat their migraines.

Individuals with migraine are more than twice as likely to receive opioids compared with non-migraine controls[21-25]. In the American Migraine Prevalence and Prevention (AMPP) study, ~30% of respondents with migraine reported current or previous opioid use[5]. In a retrospective claims analysis of 147,832 people with migraine who initiated preventive treatment, 77.4% also received an opioid for acute treatment during the follow-up period of up to 5 years[26]. Emergency department visits for migraine frequently result in administration of opioids or their prescription – 20% in Australia[24] and 59% in the US[27] – and this is associated with increased future health resource utilization[28]. Nearly 20% of patients presenting to a tertiary care headache center reported they first received opioids in the emergency department[29].

Barbiturates for migraine

Barbiturates – primarily butalbital – are often found in analgesics used for headache or migraine, usually in combination with aspirin, acetaminophen, or codeine. A survey of 9128 respondents with episodic migraine in the US found that 6% were using analgesics that contained barbiturates[30]. Analyses of 3121 respondents in the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study found that 12.8% used analgesics that contain barbiturates[22]. Similar to opioids, barbiturates can also lead to dependence[31], contribute to MOH, increase the risk of progressing to chronic migraine[16, 32], and are not recommended by clinical practice guidelines for migraine[18, 19].

Rimegepant for migraine

Rimegepant is an orally administered calcitonin gene related peptide (CGRP) receptor antagonist approved by the US FDA in February 2020 for the acute treatment of migraine and in May 2021 for the prevention of episodic migraine. Several studies support the effectiveness of rimegepant for the acute treatment[34-38] and prevention[39] of migraine. A previous analysis suggested that individuals who may be using opioids or barbiturates for the acute treatment of migraine might decrease such use after initiating a migraine-specific treatment such as rimegepant[33].

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The study aims to address the following research question: Among US adults with migraine and prior use of opioids or barbiturates, how does the use of opioids and barbiturates change following rimegepant initiation? Specific study objectives include:

Primary Objective

1. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant.

Secondary Objectives

2. To describe the pre-treatment characteristics of new rimegepant users, including demographics, comorbid conditions, and prior medication use.

3. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals using at least one preventive treatment for migraine

4. To evaluate changes in opioid and barbiturate utilization patterns after the initiation of rimegepant in the subset of individuals with problematic opioid use (≥ 3 opioid prescriptions and/or morphine milligram equivalents [MME] above 75th percentile during pre-index period)

8. RESEARCH METHODS

8.1. Study Design

This is a non-interventional, retrospective, observational, cohort study that will assess changes in opioid and barbiturate utilization after initiation of rimegepant among adults in the US. This study will analyze an administrative claims database (IQVIA PharMetrics® Plus) with information on

individuals in the US with commercial, managed Medicare, or managed Medicaid health plans. This database includes information captured in medical and pharmacy claims (e.g., dates of service, diagnosis codes, procedure codes, medications dispensed, demographics, health plan enrolment)[40].

This study aims to characterize, in a real-world setting, the use of opioids and barbiturates among individuals with migraine before and after initiating rimegepant. Individuals will be grouped according to their use of 5 medications prior to rimegepant initiation (index date): 1. opioids, 2. barbiturates (i.e., butalbital), 3. alprazolam, 4. rescue inhalers, or 5. statins. The latter three groups will be used as controls to represent medications intended for continuous use and episodic use.

Rimegepant is approved for both the acute treatment of migraine and the prevention of episodic migraine. For the acute treatment of migraine, rimegepant is taken as needed. For the prevention of episodic migraine, rimegepant is taken every other day. Since the same medication is approved for 2 indications, assumptions must be made about the intended use when analyzing real world data.

Rimegepant is commonly dispensed in packages of 8 tablets. When 2 packages (16 tablets) are dispensed, it is assumed that rimegepant is intended for the prevention of episodic migraine. When 1 package (8 tablets) are dispensed, it is assumed that rimegepant is intended for the acute treatment of migraine.

For each medication of interest, outcome measures will include the total number of prescriptions filled/dispensed, the total quantity dispensed (number of tablets or other medication units), the average dispensed per fill (calculated for opioids in MME and for butalbital and alprazolam in mg), the total duration of use (days supplied), and the proportion of individuals with discontinuation (defined as the absence of any prescription fill in after rimegepant initiation).

This study design is appropriate to the study objectives and allows for the evaluation of real-world prescription medication use patterns in a large group of individuals broadly representative of patients in the US taking rimegepant without influencing patient or provider behavior. Pharmacy claims databases are often used for this purpose, supplemented by medical claims to provide diagnosis codes to help understand why medications are being used and the comorbidities of individuals taking those medications[41,42]. By utilizing an administrative claims database, the study can efficiently examine the use of prescription medications dispensed by retail pharmacies and similar outlets in a large and diverse population of adults in the US with commercial health plans[42,43].

The pre- vs. post- study design is commonly used in non-interventional studies using real world data and allows researchers to examine outcomes of interest before and after an event occurs[44]. Such study designs are unable to establish a causal relationship between the event and outcome and researchers must be cautious to minimize bias and confounding. The use of multiple control groups for medications intended for continuous or episodic use (alprazolam, rescue inhalers, statins) provides relevant comparators and enhances the validity of the findings observed. Study findings might inform future studies focused on how the use of rimegepant for migraine might impact the use of other, suboptimal medications (opioids/barbiturates) often used for migraine.

8.2. Setting

Population

This study will use data from a large, commercially available, database of adjudicated medical and pharmacy claims from closed-network health insurers in the US. The population in this database is broadly representative of those in the US covered by commercial, managed Medicare, or managed Medicaid health plans[40].

Care setting

Medical claims in this database represent all care settings (e.g., physician office, hospital outpatient, hospital inpatient) and all health care provider services (e.g., evaluation and management, diagnostic procedures, nonsurgical procedures, surgical procedures) commonly reimbursed by third-party payers. Pharmacy claims in this database are primarily from retail pharmacies.

Time period

The study will examine data from September 1, 2019, to March 31, 2023. The first date of rimegepant initiation during this period will be defined as the index date.

The pattern of opioid and barbiturate utilization will be assessed 180 days before (pre-index) and 180 days after (post-index) the index date. The study baseline will be defined as the pre-index period plus the index date. Each outcome measure will be calculated separately for 12 consecutive 30-day periods (study months), starting 6 months before and ending 6 months after the index date.

Baseline clinical characteristics and comorbidities will be assessed based on diagnosis codes in inpatient or outpatient medical claims. Medication use will be identified from National Drug Codes (NDC) in pharmacy claims or Healthcare Common Procedural Coding System (HCPCS) codes in medical claims. Migraine medications will be categorized as those intended for acute treatment, prevention of, or both, based on their common usage for migraine.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Have an index ("first") prescription fill for rimegepant between March 1, 2020, and October 1, 2022; the date of this index fill defines the index date
    a. The end date of cohort eligibility is 6 months prior to the end of data availability to ensure sufficient follow-up for all patients prior to the end of data availability. For the 12-month sensitivity analysis, the end of cohort eligibility will be April 1, 2022.
2. Have an index fill quantity for rimegepant of 8 tablets (ie, intended use for acute treatment of migraine).
3. Have ≥180 days of rimegepant use from index date to last fill date +30 days
    a. The period of rimegepant use is measured as the number of days from the index date, or first observed rimegepant fill, to the last observed rimegepant fill date +30 days.
4. Be ≥ 18 years of age on the index date

5. Have ≥180 days of continuous enrollment in commercial health plans with both medical and pharmacy benefits prior to and following the index date, defined as the pre-index period and post-index period, respectively

6. Have a diagnosis of "migraine" (ICD-10-CM code: G43.xx) at *any point* during the pre- or post-index periodsHave ≥1 prescription fill during the pre-index period for one of the following drugs of interest: opioids, barbiturates (butalbital), alprazolam, rescue inhalers, or statins

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Prior use of other novel agents for acute treatment of migraine (i.e., ubrogepant or lasmiditan) in the pre-index period

2. Diagnosis of malignant neoplasm (cancer) during the pre or post-index periods

8.3. Variables

The study variables and its operational definition are listed in Table 1.

Table 1. Variables description

Variable	Role	Data source(s)	Operational definition
Demographic characteristics			
Age	Baseline characteristic	Enrollment files	Continuous: Mean/SD
Age categories	Baseline characteristic	Calculated	Categorical: 18-34, 35-54, 55-64, 65+
Age 55 category	Baseline characteristic	Calculated	Categorical: 18-54, 55+
Sex	Baseline characteristic	Enrollment files	Categorical: Male, Female, Unknown
Region	Baseline characteristic	Enrollment files	Categorical: Northeast, South, West, Midwest
Prior migraine treatments during pre-index period			
Triptans	Baseline characteristic	Rx claims	Binary (any use)
Ergotamines	Baseline characteristic	Rx claims	Binary (any use)
NSAIDs	Baseline characteristic	Rx claims	Binary (any use)
Acetaminophen	Baseline characteristic	Rx claims	Binary (any use)

Beta blockers	Baseline characteristic	Rx claims	Binary (any use)
Tricyclic antidepressants	Baseline characteristic	Rx claims	Binary (any use)
Antidepressants	Baseline characteristic	Rx claims	Binary (any use)
Anticonvulsants	Baseline characteristic	Rx claims	Binary (any use)
Anti-CGRP monoclonal antibodies	Baseline characteristic	Rx and medical (HCPCS) claims	Binary (any use)
Onabotulinumtoxin A	Baseline characteristic	Rx and medical (HCPCS) claims	Binary (any use)
Isometheptene combinations	Baseline characteristic	Rx claims	Binary (any use)
Antiemetics (migraine)	Baseline characteristic	Rx claims	Binary (any use)
Antiemetics (other)	Baseline characteristic	Rx claims	Binary (any use)
Used ≥1 conventional oral prevention agent during pre-index	Baseline characteristic	Calculated	Binary (any use)
Used ≥1 of any prevention agent during pre-index	Baseline characteristic	Calculated. Includes the above variable + anti-CGRP mabs + onabotulinumtoxinA	Binary (any use)
Comorbid conditions			
Elixhauser comorbidities	Baseline characteristic	Medical claims	Binary
Elixhauser weighted index	Baseline characteristic	Calculated	Discrete
Elixhauser index categories	Baseline characteristic	Calculated	Categorical: 0, 1, 2-3, 4-5, ≥6
Other chronic pain	Baseline characteristic	Medical claims	Binary (ICD-10)
Chronic migraine	Baseline characteristic	Medical claims	Binary (ICD-10)
Any chronic pain (includes chronic migraine + other chronic pain)	Baseline characteristic	Calculated	Binary

Any injury	Baseline characteristic	Medical claims	Binary (ICD-10)
Any surgical procedure	Baseline characteristic	Medical claims	Binary (CPT)
Outcome Measures			
Total number of fills dispensed	Outcome measure	Rx claims	Count
Total quantity dispensed	Outcome measure	Rx claims	Count
Average dose (MME or mg) within time period	Outcome measure	Calculated	Continuous (calculated): Mean/SD
Total duration of use (days)	Outcome measure	Calculated	Continuous (calculated)
Discontinuation	Outcome measure	Rx claims	Binary (no prescription fills during post-index period)
Additional measures for opioid use group:			
Type of opioid used	Outcome measure	Rx claims	Binary
Total number of Rx opioid agents used (mean)	Outcome measure	Rx claims	Count
Total number of Rx opioid agents used	Outcome measure	Rx claims	Categorical: 1, 2, ≥3

CGRP: Calcitonin Gene-Related Peptide; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedural Coding System; ICD10: International Classification of Diseases, 10th Revision; MME: Morphine Milligram Equivalents; NSAIDs: Nonsteroidal anti-inflammatory drugs; Rx: Prescription; SD: Standard Deviation

8.4. Data Sources

This study will use the IQVIA PharMetrics® Plus longitudinal health plan database with medical and pharmacy claims adjudicated by third-party payers managing commercial health plans. Individuals in this database are a geographically representative sample of the US commercially insured population[40]. The database contains information on patient demographics, plan enrollment, inpatient and outpatient medical claims, and outpatient pharmacy claims. These data were used as presented by the data source, without recoding. The primary outcomes in this study are based on observed pharmacy fills for the medications of interest (opioids, barbiturates, alprazolam, rescue inhalers, or statins) for any reason, so minimal interpretation or reliance on clinical coding accuracy is required. The data are de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPPA)[40]. This data source has been used extensively in pharmacoepidemiology research[45-49].

8.5. Study Size

Since this is a retrospective study of existing and commercially available data, no formal sample size calculation was performed. The study database includes 52,591,063 individuals. It is estimated that 45,051 (0.86%) have an eligible first prescription for rimegepant and 4,049 (0.0077%) meet all eligibility criteria.

8.6. Data Management

All data for this study will be extracted from the IQVIA PharMetrics® Plus longitudinal health plan database. IQVIA is the data vendor and data store, providing access to a structured, de-identified dataset of adjudicated medical and pharmacy claims from a geographically representative sample of individuals with commercial, managed Medicare, or managed Medicaid health insurance in the United States.

Data will be obtained directly from IQVIA by Pfizer's Real World Evidence (RWE) team under an active data use license. The extraction process will follow Pfizer's standard operating procedures for secondary data studies. The RWE team will submit a formal data extraction request to IQVIA, specifying all required variables, inclusion and exclusion criteria, and the study timeframe. The data will be delivered in a secure, structured format (e.g., CSV or SAS datasets) and transferred to Pfizer's secure analytics environment for processing and analysis. The data extract will be limited to patients meeting the study's inclusion and exclusion criteria (e.g., adults with a diagnosis of migraine, first prescription fill for rimegepant between March 1, 2020, and October 1, 2022, continuous enrollment, etc.) and will occur once.

The technical specifications for the data extract—including all variable definitions, coding, and inclusion/exclusion parameters—are detailed in the study's data dictionary (see ANNEX 1. LIST OF STANDALONE DOCUMENTS). It provides detailed definitions, coding algorithms, and operational logic for all variables, exposures, outcomes, and covariates used in the study. This includes:

- Demographics: Definitions and coding for age, sex, and region.
- Comorbidities: Algorithms and ICD-10 codes for identifying chronic pain, migraine, and other relevant conditions.
- Medication Exposures: Lists of generic names, NDC/HCPCS codes, and logic for identifying study medications (e.g., opioids, barbiturates, migraine preventives, rescue inhalers, statins).
- Surgical and Injury Variables: CPT and ICD-10 code mappings for identifying major surgical procedures and injuries.
- Outcome Measures: Algorithms for calculating prescription fills, quantity dispensed, average dose (MME or mg), duration of use, and discontinuation.
- Operational Definitions: Clear instructions for how each variable is derived from claims data, including data sources (pharmacy or medical claims) and measurement periods.

All data are de-identified and compliant with the Health Insurance Portability and Accountability Act (HIPAA). Data management, storage, and analysis will be performed exclusively by authorized Pfizer personnel in accordance with internal quality standards and regulatory requirements.

8.7. Data Analysis

The workflow below will be applied to conduct data analysis.

1. First, all individuals who meet all study eligibility criteria (study population) will be identified.
2. Second, all data for the study population will be extracted from the study database into an analytical file that will be used for all subsequent analyses.
3. Third, all required study variables will be identified or calculated in the study population.

   The Center for Center for Medicare & Medicaid Services (CMS) Opioid Oral MME Conversion Factors Table (available at the US department of Health and Human Services portal) will be used to standardize opioid dose measurements in MME (ie, for each prescription, the daily dose will be multiplied by the corresponding opioid conversion factor and then divided by days supplied; MMEs will be summed across all opioid prescriptions).
4. Fourth, all required subgroups will be created in the study population.
5. Fifth, study outcomes will be summarized across study subgroups, which are determined by the pharmaceutical form of each medication as summarized in the table below:

Table 2. Study subgroups

	Opioids	Barbiturates	Alprazolam	Rescue Inhalers	Statins
Number of Rx fills (mean, SD, % change)	X	X	X	X	X
Tablets/quantities dispensed (mean, SD, % change)	X	X	X	X	X
Milligrams dispensed (mean, SD, % change)		X	X		
Morphine milliequivalents (MME) (mean, SD, % change)	X				

Days supplied (mean, SD, % change)	X	X	X	X	X
Discontinuation in post-index (mean, SD, % change)	X	X	X	X	X

Subgroups vary according to the dosage form of each medication. Rx: prescription

6. Sixth, statistical comparisons will be conducted according to the Statistical Analysis Plan, described below.

8.7.1. Statistical analysis plan

1. Among each medication use group, a report with descriptive statistics of the demographic and clinical baseline characteristics as well as medication use prior to rimegepant will be created.

2. Next, a patient-level dataset containing crude counts of the five utilization outcome measures for each 30-day window (W1-W12) of the pre- and post-index periods will be created.

3. To measure changes in utilization outcome measures across the pre-index to post-index period, two aggregated measures for each outcome based on time during the pre- (W1-W6) or post-index (W7-W12) period will be created. Using these aggregate measures, the pre and post-index mean outcome values and determine the percent change (%Δ) will be presented.

4. In order to determine the association between rimegepant initiation and reduction of other acute treatments, a generalized linear mixed models for each outcome will be applied. Mixed effects models account for within-person correlation due to the repeated measurement of outcomes over time in longitudinal studies. The main independent (exposure) variable will be a binary indicator of time during the pre-index period (0) vs. post-index period (1). For modeling the continuous and count outcomes—number of fills, quantity dispensed, average dose, and duration of use—first the distribution of each utilization outcome measure within the dataset will be determined in order to specify the appropriate distributions and link functions for their mixed model. The discontinuation outcome is a binary outcome, observed at one point in time. Hence, a logistic regression model to examine any association to rimegepant initiation will be applied. For each model, for pre-index demographic and clinical characteristics, including age, sex, region, presence of any chronic pain (migraine or non-migraine), Elixhauser weighted index, and pre-index use of any prevention agent will be adjusted.

5. To determine the robustness of the outcome measures and association estimates, two subgroups and two sensitivity analyses will be performed as described below. The sensitivity analyses only apply to the total cohort, and not the additional subgroups.

    a) Subgroup analysis #1: Identify all individuals from the total cohort with use of ≥ 1 prevention agent during the pre-index period, presented by medication use group.

b) Subgroup analysis #2: Identify individuals form the opioid use group having potentially problematic opioid use. This subgroup is a composite of problematic opioid use defined in two ways. Patients meeting either measurement definition will be included.

   i. The first method will identify individuals in the cohort with ≥3 opioid prescriptions during the pre-index period.

6. The second method will calculate quartiles of opioid dose in MMEs and identifies individuals within the fourth quartile (76th to 100th percentile) during the pre-index period.

c) Sensitivity analysis #1: Increase the duration of the pre-index and post-index periods from 180 days each to 360 days each.

d) Sensitivity analysis #2: Exclude all patients having a major surgical procedure or injury diagnosis at any point during the study period.

8.8. Quality Control

To ensure the highest standards of data quality and integrity, this study implements a comprehensive quality control framework, drawing on established procedures from both Pfizer's Real World Evidence (RWE) team and the IQVIA PharMetrics® Plus database.

Database Owner Procedures

IQVIA PharMetrics® Plus implements robust data quality assurance protocols, including standardized data collection, adjudication, and multi-step validation processes. Data are sourced from closed-network, third-party payers and are subjected to systematic checks for completeness, internal consistency, and plausibility before being released for research use. These processes are detailed in IQVIA's official documentation and have been described in peer-reviewed literature as industry standards for claims database management[40,41,50].

Mechanisms to Ensure Data Quality and Integrity

The protocol will be interpreted by a primary statistical programmer with expertise in Real World Data (RWD). The primary programmer will develop working definitions for all study variables, outcomes, and subgroups in consultation with study investigators. The primary programmer will develop and execute a programming plan and share draft results with the study team as they become available.

The study team will provide feedback on draft results and discuss any unexpected, unclear, or contradictory findings until such issues are clarified or addressed by modifying methods and issuing updated draft results. Once the draft results are accepted by the study team, a secondary statistical programmer with expertise in RWD will perform quality control by reviewing all programs, related files (i.e., logs), and output developed by the primary programmer.

This review will first focus on identifying and addressing any errors in the program, related files, or output, and will then identify and address any issues in the interpretation of the protocol by the primary programmer. As needed, the secondary programmer may develop their own programs to run against the study database to replicate key findings (e.g., number of individuals who meet all eligibility criteria).

As needed, the study statistician may also review programs, related files, and output from the primary and secondary programmers to provide additional quality control.

8.9. Limitations of the Research Methods

As an observational, noninterventional, study using commercially available, existing RWD, this study will have several limitations, including:

1. Its population includes only adults with commercial health insurance in the US observed during a limited time period; findings may not be generalizable beyond that group or time period [50];

2. It relies on the limited sociodemographic information provided by third-party payers (e.g., age, sex, census region), which is likely insufficient to characterize all relevant sociodemographic confounders (e.g., education, income, wealth, household, lifestyle)[50-52;]

3. It relies on ICD-10 diagnosis codes to identify migraine, which is likely insufficient to fully characterize its presentation (e.g., severity, frequency, symptoms, history, response to medications)[53];

4. It relies on ICD-10 diagnosis codes to identify comorbidities, which is likely insufficient to fully characterize overall health (e.g., physical function, mental function)[53];

5. It relies on information reported by health care providers to third-party payers, which is limited, transactional, intended to facilitate reimbursement, not intended for research purposes, and may represent potential diagnoses or health conditions that are later ruled out[53];

6. It relies on pharmacy claims reimbursed by third-party payers, which contain limited information about over-the-counter medications, nutritional supplements, low-cost prescription medications not submitted for reimbursement, prescription medications purchased with group discounts (e.g., GoodRx), or medications not covered by health plans;

7. It does not consider access to medications not reimbursed during the study period (e.g., left over from a previous prescription) or obtained from other sources (e.g., family member);

8. It relies on prescriptions filled by retail pharmacies as a proxy for medication use, which does not include any information about if, how, or when the dispensed medication was used, why the medication was prescribed or its intended use, any instructions from the health care provider beyond medication name, quantity, and strength, or any information about discontinued medications;

9. It does not include any patient-reported outcomes to indicate how the patient responded to a medication (e.g., effectiveness, safety);

10. Its findings cannot be attributed to a specific cause

11. Because rimegepant has 2 approved indications with different dosing regimens, assumptions must be made about its intended use based on the quantity of tablets dispensed (ie, 8 tablets = acute treatment, 16 tablets = prevention). It's possible that some individuals who received 16 tablets of rimegepant were using it for the acute treatment of migraine, resulting in the misclassification and exclusion of otherwise eligible individuals from our study population. However, the likelihood of this occurring seems low since most individuals using rimegepant for the acute treatment of migraine use only 2-5 tablets/month.[54].

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

As this study uses only deidentified information from a commercially available database that is certified by the vendor to comply with applicable privacy regulations (e.g., 21 CFR 45), it is viewed as exempt from review by an IRB or EC since no research subjects are involved.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be submitted to a congress/conference as an abstract and developed into a manuscript for a peer-reviewed publication.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	V3	15 November 2023	C4951089_ Reduction of Opioid Barbiturate Use_Data Dictionary
2	V1	15 November 2023	C4951089_Reduction of Opioid Barbiturate Use_Table Shells

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	C4951089_NIS protocol_V1.0_12Nov2025
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Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	19-Nov-2025 13:07:14	Final Approval
Purdie,David	19-Nov-2025 16:27:11	Manager Approval