NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Comparing Patient-Reported Outcomes Between Rimegepant and Triptan Users with Migraine in the United States
Protocol number	C4951076
Protocol version identifier	1.0
Date	04 October 2024
Active substance	Analgesics, calcitonin gene-related peptide (CGRP) antagonists. ATC code: N02CD06
Medicinal product	Rimegepant (Nurtec 75mg ODT)
Research question and objectives	The goal of this research is to assess patient-reported outcomes (PROs), specifically treatment satisfaction, healthcare resource use (HCRU), quality of life (QoL), work productivity loss, and migraine-specific disability of Rimegepant users, relative to triptan users, among US adults diagnosed with migraine. Secondarily, a sensitivity analysis will be conducted, applying a more restrictive definition for the Rimegepant acute user cohort, to corroborate the initial set of results. Findings from these analyses may be used to inform communications with payers regarding reimbursement of Rimegepant.
Country of study	United States (US)
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AAN	American Academy of Neurology
AE	Adverse event
ATT	Average treatment effect of treated
CGRP	Calcitonin gene-related peptide
ER	Emergency room
FDA	Food and Drug Administration
GCS	Global composite score
HCRU	Health care resource use
HRQoL	Health related quality of life
IEC	Independent ethics committee
IP	Internet Protocol
IPTW	Inverse probability of treatment weighting
IRB	Institutional review board
mAb	Monoclonal Antibody
MCS	Mental composite score
MIDAS	Migraine Disability Assessment Scale
NHWS	National Health and Wellness Survey
NSAID	Non-steroidal anti-inflammatory drugs
OLS	Oracle Life Sciences
OTC	Over the counter
PCS	Physical composite score
PRO	Patient-reported outcome
QoL	Quality of life

US	United States of America
WPAI-GH	Work Productivity and Activity Impairment – General Health

3. RESPONSIBLE PARTIES

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4. ABSTRACT

None.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Minimum requirements:

Milestone	Planned Date
Initiation of data analysis	05 October 2024
First draft of abstract	10 October 2024
Final abstract	15 October 2024
Completion of data analysis	20 November 2024
First draft of poster content	01 March 2025
Final poster content	15 March 2025

7. RATIONALE AND BACKGROUND

Triptans, also known as serotonin receptor agonists, are considered as a standard treatment for acute migraine and have been widely prescribed in the United States [1]. A systematic review showed that standard dose (taken orally or intranasally) of triptans alleviated pain within 2 hours in 42 to 76% of patients and provided sustainable headache relief at 24 hours in 29% to 50% of patients [2]. However, triptans are not for preventing migraine and are associated with numerous adverse events including nausea, dizziness, and coronary vasoconstriction [3].

Rimegepant, an oral medication which works by blocking the calcitonin gene-related peptide (CGRP) receptors, was approved by the Food and Drugs Administration (FDA) in February 2020, as an alternative method for the acute treatment of migraine in adults [4]. Rimegepant relieves pain as well as incommodious symptoms and can prevent migraine when given the proper dose [5]. However, nausea, urinary tract infection, and dizziness were adverse events reported for Rimegepant [6].

Both triptans and Rimegepant are commonly prescribed for acute migraine but have different efficacy and side effects. Triptans showed better pain relief compared to gepants, whereas gepants were associated with fewer adverse events compared with triptans [1]. Recent research also showed Rimegepant being more effective in the acute treatment of migraine in adults with a history of insufficient response to 1 or ≥2 triptans among and in current triptan users [7].

As patients with migraine tend to experience worse health status, reduced health-related, reduced work productivity, the impact of treatment in improving patient reported outcomes is critical [8,9]. Among triptan users, the HRQoL and work productivity were significantly impacted in those with insufficient response to triptans [10]. In addition to the reduction in migraine frequency, Rimegapant was associated with improvement in HRQoL over time [11]. However, few studies have comprehensively examined patient reported outcomes among Rimegepant users compared with triptan users. As such, the purpose of this study was to assess patient-reported outcomes (PROs) including treatment satisfaction, healthcare

resource use (HCRU), quality of life (QoL), work productivity loss, and migraine-specific disability of Rimegepant users, relative to triptan users.

8. RESEARCH QUESTION AND OBJECTIVES

The primary aim of this analysis is to assess PROs, specifically treatment satisfaction, HCRU, QoL, work productivity loss, and migraine-specific disability of Rimegepant users, relative to triptan users, among US adults diagnosed with migraine.

Secondarily, a sensitivity analysis will be conducted, applying a more restrictive definition for the Rimegepant user cohort, to corroborate the initial set of results. Findings from these analyses may be used to inform communications with payers regarding reimbursement of Rimegepant.

9. RESEARCH METHODS

9.1. Study Design

This is a cross-sectional study using the 2023 US (N=75,007) National Health and Wellness Survey (NHWS) data. People who use Rimegepant will be compared with those who use triptan on treatment satisfaction, HCRU, QoL, work productivity loss, and migraine-specific disability outcomes. The cross-sectional design allows us to compare the Rimegepant vs. triptan users on multiple outcomes in a relatively quick and inexpensive way.

9.2. Setting

All data from the NHWS are reported by the respondent. NHWS participants are recruited through an existing, general-purpose (i.e., not health care-specific) web-based consumer panel via opt-in e-mails, co-registration with panel partners, e-newsletter campaigns, banner placements, and affiliate networks. All panelists explicitly agree to be a panel member, register with the panel through a unique e-mail address, and complete an in-depth demographic registration profile. A stratified random sampling procedure is implemented to ensure that the demographic composition of the final NHWS sample is representative of the general adult population in the US. In each year the NHWS is fielded, data from the International Database of the US Census Bureau are used to identify the relative proportions of adults by age, race/ethnicity, and gender; these proportions are then mimicked during the recruiting of panel members.

9.2.1. Inclusion Criteria

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

1. Patients who have consented to the anonymous use of their data for research purpose.
2. Aged 18 or older.
3. Self-reported a diagnosis of migraine by physician.
4. Currently on Rimegepant or triptan (via oral route) use at time of survey.

5. In addition, patients to be included in the sensitivity analysis need to meet the following criteria:
    - Currently on acute Rimegepant use (<12 days using Rimegepant per month), or triptan (via oral route) use at time of survey.

9.2.2. Exclusion Criteria

Patients meeting the following criteria will not be included in the study:

1. Currently on both Rimegepant and triptan use at time of survey.

9.3. Variables

The NHWS includes self-reported data on demographics, health characteristics, disease history, and health outcomes. The Table 1 below provides further details on the specific variables that will be assessed in the study.

Table 1. Study Variables

Variable	Role	Operational Definition
Rimegepant vs. triptan use	Exposure	Current Rimegepant users (for sensitivity analysis restricted to acute Rimegepant users with <12 days use per month) vs. triptan users (no OTC, oral route only).
Outcomes: Migraine treatment use and treatment satisfaction		
Migraine medication type (drug or OTC)	Outcome	Defined as drug only, OTC only and both drug and OTC, based on current use of migraine medication classes
Migraine treatment type (acute or prevention)	Outcome	Defined as acute only, prevention only and both acute and prevention, based on current use of migraine medication classes
Total number of acute migraine agent drug (continuous)	Outcome	Total number of acute agent classes (both drug and OTC) used
Total number of acute migraine agent drug (categorical)	Outcome	Including 1 drug class, 2 or more drug classes, and 3 or more drug classes based on the total number of acute agent (both drug and OTC) classes used
Total number of prevention migraine agent drug (continuous)	Outcome	Total number of prevention agent classes (only drug) used
Total number of prevention migraine agent drug (categorical)	Outcome	Including 1 drug class, 2 or more drug classes, and 3 or more drug classes based on the total number prevention agent classes (only drug) used
Current migraine treatments (drugs)	Outcome	Defined as yes or no for current migraine treatments on drug classes including: Rimegepant, triptans, NSAIDs, opioids, barbiturates, ergots, gepants (acute, including Rimegepant), ditan, combination analgesics, other acute drugs, anticonvulsants, beta-blocker, antidepressant, CGRP mAb, botox, and gepant (prevention, including Rimegepant)
Treatment satisfaction (drugs)	Outcome	Treatment satisfaction of drug classes of: Rimegepant, all acute agents, triptans, NSAIDs, opioids, barbiturates, ergots, gepants (acute), ditans, combination analgesics, other acute treatment, all prevention agents,

		anticonvulsants, beta-blockers, antidepressants, CGRPs mAb, botox, and gepant (prevention) Categorized into 7 categories: extremely dissatisfied, very dissatisfied, somewhat dissatisfied, neither dissatisfied nor satisfied, somewhat satisfied, very satisfied, extremely satisfied
Current migraine treatments (OTC)	Outcome	Defined as yes or no for current migraine treatments on OTC classes of analgesics (acetaminophen only), analgesics (combinations), NSAIDs, other OTCs
Treatment satisfaction-analgesics (acetaminophen only)	Outcome	Treatment satisfaction of OTC classes of analgesics (acetaminophen only), analgesics (combinations), NSAIDs, and other OTCs Categorized into 7 categories: extremely dissatisfied, very dissatisfied, somewhat dissatisfied, neither dissatisfied nor satisfied, somewhat satisfied, very satisfied, extremely satisfied
Outcomes: HRQoL		
RAND-36	Outcome	PCS, MCS, and GCS index scores of the RAND-36 [12]
EQ-5D-5L	Outcome	Health state utilities and the EuroQoL Visual Analog Scale (EQ-VAS) [13]
WPAI-GH	Outcome	Absenteeism (% of work time missed because of one's health in the past 7 days), presenteeism (% impairment experienced while at work in the past 7 days because of one's health), overall work impairment (combination of absenteeism and presenteeism), and activity impairment (% impairment in daily activities because of one's health in the past 7 days) among total population, employed, unemployed, and disabled [14]
MIDAS	Outcome	Total score, categorical (grade I-IV), and item scores (1-7) of MIDAS [15]
Outcomes: HCRU		
ER visits	Outcome	Visited ER in past 6 months (yes or no); number of ER visits in past 6 months among total population and participants with ER visits
Hospitalizations	Outcome	Was hospitalized in past 6 months (yes or no); number of hospitalizations in past 6 months among total population and participants with hospitalizations
General practitioner/family practitioner visits	Outcome	Visited general practitioner/family practitioner in past 6 months (yes or no); number of general practitioner/family practitioner visits in past 6 months among total population and participants with general practitioner/family practitioner visits
Cardiologist visits	Outcome	Visited cardiologist in past 6 months (yes or no); number of cardiologist visits in past 6 months among total population and participants with cardiologist visits
Neurologist visits	Outcome	Visited neurologist in past 6 months (yes or no); number of neurologist visits in past 6 months among total population and participants with neurologist visits
Traditional healthcare provider visits	Outcome	Visited traditional healthcare provider in past 6 months (yes or no); number of traditional healthcare provider visits in past 6 months among total population and participants with traditional healthcare provider visits
Covariates adjusted through IPTW		
Age (continuous)	Potential confounder	Age of participants in years

Sex	Potential confounder	Male vs. female
Race	Potential confounder	Categorized as black, white, and other
Hispanic/Latino	Potential confounder	Yes vs. no
Marital status	Potential confounder	Single/ not living with partner vs. married/ living with partner
Health insurance	Potential confounder	Categorized as private insurance, public insurance, no insurance, and unsure
University education	Potential confounder	Less than university education vs. university education or higher
Annual household income	Potential confounder	Categorized as below median income (<50,000), median income ($50,000-$74,999), above median income (≥$75,000), and decline to answer
Employed	Potential confounder	Yes (full-time/ part-time/ self-employed) vs. no
Charlson comorbidity index	Potential confounder	Charlson comorbidity index scores with and without patients of score 0 and categories based on scores: 0, 1, 2, 3, and 4+
Body mass index	Potential confounder	Body mass index in kg/m^2
Alcohol use	Potential confounder	Currently drink alcohol vs. currently do not drink alcohol
Smoking status	Potential confounder	Categorized as current smoker, former smoker, and never smoked
Exercise	Potential confounder	Number of days exercise per months
Contraindications	Potential confounder	Ever experienced each of contraindications (angina, arrythmia, atrial fibrillation, congestive heart failure, heart attack, left ventricular hypertrophy, mini-stroke/transient ischemia attack, peripheral arterial disease /poor circulation, Peripheral vascular disease, stroke, and unstable angina/chest pains)
Cardiovascular risk factors	Potential confounder	Ever experienced each of cardiovascular risks (high blood pressure, high cholesterol, current smoker, type 2 Diabetes, and obesity)
Any contraindications	Potential confounder	Ever experienced any contraindications listed above
Any cardiovascular risk factors	Potential confounder	Ever experienced any cardiovascular risks factors listed above
Any contraindications or cardiovascular risk factors	Potential confounder	Ever experienced any contraindications or cardiovascular risks factors listed above
Time since migraine diagnosis	Potential confounder	Time since migraine diagnosis in years
Monthly migraine days (continuous)	Potential confounder	Number of days experienced migraine in past 30 days
Monthly headache days (continuous)	Potential confounder	Number of days experienced headache in the past 30 days
Medication overuse (migraine only)	Potential confounder	Yes or no, for migraine-specific medications only
Other covariates that will be evaluated for balance between exposure groups		
Age (categorical)*	Potential confounder	Categorized based on age of participants in years: 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89
Monthly migraine days (categorical)*	Potential confounder	Categorized based on number of days experienced migraine in past 30 days: <4, 4-9, 10-14, and ≥15
Monthly headache days (categorical)*	Potential confounder	Categorized based on number of days experienced headache in past 30 days: <4, 4-9, 10-14, and ≥15
Experience migraines related to menstrual cycle	Potential confounder	Yes vs. no, female participants only

*Categorical age, monthly migraine days, and monthly headache days will be included in inverse probability of treatment weighting (IPTW) adjustment if their distributions are not balanced (standardized mean difference >0.1) after IPTW.

Abbreviations: OTC: over the counter; NSAID: non-steroidal anti-inflammatory drugs; CGRPs mAb: calcitonin gene-related peptide antibodies monoclonal antibodies; HRQoL: health related quality of life; PCS: physical composite score; MCS: mental composite score; GCS: global composite score; WPAI-GH: the Work Productivity and Activity Impairment – General Health; MIDAS: Migraine Disability Assessment Scale; HCRU: health care resource utilization; ER: emergency room; IPTW: inverse probability of treatment weighting

9.4. Data Sources

This study will use self-reported data sourced from the NHWS. The NHWS is an annual, cross-sectional, internet-based survey of adults conducted across several countries annually. The current study will use data from the 2023 US (N=75,007) NHWS.

9.5. Study Size

Sample size estimates, based upon preliminary feasibility, are provided below, in Table 2. The sample size for this study is fixed by the number of patients in the NHWS database who meet the imposed criteria.

Table 2. Estimated Sample Sizes

Patient Cohorts	n
Overall NHWS sample	75,007
Diagnosed with migraine	8,439
Triptan users (oral route only, no OTC) without Rimegepant use	1,340
Rimegepant users without triptan use	144
Rimegepant users (acute only) without triptan use*	112

*For sensitivity analysis.

Abbreviations: NHWS: National Health and Wellness Survey; OTC: over the counter

A sample size of 1) 130 and 2) 100 in each group (1:1 allocation) will have 80% power to detect an effect size of at least 1) 0.35 standard deviation (SD) units (indicative of at least a "small-to-medium" effect) and 2) 0.4 SD units (indicative of a medium effect), respectively, using a 2-group t-test with a 5% 2-sided significance level. We will have a sample size much greater than 130 in one of our groups, resulting in higher statistical power compared to the 1:1 allocation mentioned above. A total sample size of 100 will have 80% power to detect an effect size from a chi-square distribution of at least 0.33 (indicative of at least a "small-to-medium" effect) using a chi-square test with a 5% 2-sided significance level and 3 degrees of freedom. There will be sufficient power to detect a "small-to-medium" effect of Rimegepant user vs. triptan use on the outcomes in the main analysis, and sufficient power to detect a medium effect in the sensitivity analysis with acute Rimegepant users only.

9.6. Data Management

This study will use previously collected data that have been deidentified, processed, and cleaned. Prior to initiating the study programming, procedures were implemented to assess the quality of responses including, but not limited to, response ranges, consistency, and skip patterns. Data entry was completed instantaneously as the respondent answered the survey questions. Therefore, there are no paper surveys to house or destroy, and no manual data entry is required. The database that houses the questionnaire responses allows for direct exportation into statistical software. Identifying information about panel members will not be released other than a single panel identification number. Therefore, the working data files contain no identifying information, apart from the panel identification number. Specifically, the dataset does not include names, addresses, or any other information that can personally identify the respondents.

Quality checks were implemented on the dataset before it became final. These checks included Internet Protocol (IP) address checks (i.e., ensuring the respondent resided within the country stated and that a single IP address was not associated with multiple panel accounts), completion times (ensuring a respondent did not complete the survey in a timeframe that was too short, implying inattentiveness), illogical/inconsistent data responses, etc. At the discretion of the data management team, respondents who failed these checks were excluded from the final dataset.

The statistical software package that will be used for the study is R 4.3.1 (R Project for Statistical Computing).

9.7. Data Analysis

The average treatment effect of treated (ATT) will be measured to evaluate the effects of Rimegepant vs. triptan among current Rimegepant users.

Based on clinical relevance, we will prespecify a list of variables to adjust for the comparison.

Inverse probability of treatment weighting (IPTW) will be conducted to adjust for confounding by the covariates. The propensity score for each participant will be estimated by logistic regression and by including the prespecified list of variables to adjust for. Weights for ATT will be calculated for both exposed (Rimegepant users) and unexposed group (triptan users) [16]. Stabilized weights will be used to address extreme weight values.

To confirm that the IPTW procedure is successful, the weighted Rimegepant users and triptan users will be compared on the covariates using standardized mean difference (SMD) to ensure both groups are adequately balanced across all weighting criteria. While there is no definitive cut-off for identifying imbalance in IPTW, as a rule of thumb, a standardized mean difference (SMD) that is >0.10 is indicative of imbalance [17]. This threshold will be applied to determine the quality of the weighting.

Once the weighting is confirmed to be successful, bivariate analyses will be conducted to compare the weighted cohorts on treatment satisfaction, HCRU, QoL, migraine-specific

disability, and work productivity loss. Specifically, categorical variables will be analyzed using chi-square tests or Fisher's exact tests for small samples; continuous variables will be analyzed using 2-sample t-tests. Non-parametric tests may be considered for comparisons on skewed variables (e.g., HCRU) when the sample size is small (e.g., <30). For bivariate comparisons, p-values <0.05, 2-tailed, will be considered statistically significant. If there are covariates that are unbalanced after weighting (i.e., SMD >0.1), those covariates will be adjusted for in the regression analysis of outcomes. Generalized linear models will be fit depending on the distributions of outcomes.

As a sensitivity analysis, the aforementioned IPTW and bivariate comparisons will be replicated after restricting the Rimegepant user cohort to the subset of those presumed to be acute treatment users (<12 days using Rimegepant).

A sensitivity analysis will be conducted by incorporating NHWS sampling weights into the IPTW process. Sampling weights will be applied in the logistic regression to predict the propensity score, and the final weight will be the product of the propensity score weight and the sampling weight. Bivariate comparisons will then be replicated after using these newly derived weights for the participants.

9.8. Quality Control

This is a non-interventional retrospective study, so issues of quality control at study sites, e.g., data queries, do not apply. The following programming specifications will be used:

- NHWS survey includes single select questions, multi select multiple choice questions, as well as open-ended questions (e.g., asking participants to type in the types of over-the-counter medications they were taking).

- NHWS data to be used in this study will be downloaded from the Oracle server and saved as a separate data file. This data file will be stored in a secure folder on the Oracle server, which is backed up in multiple iterations on a regular basis.

- Programming code will be created for data management. This programming code will include the creation of cohort variables or any other derived variables.

- All analyses will be performed using R 4.3.1 (R Project for Statistical Computing). For quality assurance purposes, a second independent researcher will review the programming code to be used for analysis.

- Programming code used for data management and programming code used for analysis will be stored on the Oracle server and will be backed up on a regular basis.

- Data will be reviewed for quality control prior to data analysis by OLS. For example, if a respondent entered the same number for most responses, or followed a pattern in their responses, they would be considered for removal from analysis. In addition, prior to data analysis, all variables are cleaned and checked for outliers and inconsistencies by OLS.

9.9. Limitations of the Research Methods

The data from the NHWS are self-reported; thus, independent, or clinical verification of responses will not be possible. Due to the self-reported nature of the data, recall error or other response biases may potentially introduce measurement error. However, many of the measures included in the study were developed solely for the purposes of patient self-report (RAND-36, EQ-5D-5L, WPAI-GH, MIDAS), and self-report is a valid and appropriate methodology for assessing subjective outcomes. Because of the cross-sectional nature of the data, causal inferences cannot be drawn, and longitudinal fluctuations in the relationships between study variables cannot be determined. While IPTW will be used to control for potential confounders, it is possible there are other variables that could not be included in the analyses that may at least partially explain any relationships observed in the current study. Finally, while the NHWS is designed to reflect the demographic composition of the general adult population in each country in which it is fielded, it is possible that the data may not be representative of the specific patient subpopulations examined in this study.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

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

10.2. 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.

10.3. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

IRB/IEC is not required for this study. However, the protocols and questionnaire associated with the original fielding of the 2023 US NHWS were reviewed by Pearl Institutional Review Board (Indianapolis, IN; Protocol Number: 2023-0121) and granted exemption from expedited or full ethical review. The granted exemption is stored on the Oracle server.

10.4. 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 Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[18].

11. 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study results will be disseminated in the form of abstract submissions and poster presentations at the American Academy of Neurology (AAN) meeting in May 2025. For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship.

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 (i.e., Oracle Life Sciences) 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.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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