NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Evaluation of satisfaction with rimegepant and triptans utilizing Migraine Buddy retrospective data
Protocol number	C4951073
Protocol version identifier	V1.0
Date	04 June 2024
Active substance	Analgesics, calcitonin gene-related peptide (CGRP) antagonists. ATC code: **N02CD06**
Medicinal product	Rimegepant (Nurtec 75mg ODT)
Research question and objectives	***Primary objective:*** This study aims to assess the holistic benefit of rimegepant as compared to triptans, particularly in relation to patients' satisfaction with regards to medication efficacy, tolerability and migraine-induced cognitive impact. ***Research questions:*** 1. How does satisfaction with pain intensity compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine? 2. How does satisfaction with attack duration compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine? 3. How does satisfaction with speed of action compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine? 4. How does satisfaction with migraine-induced cognitive impact compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine? 5. How does satisfaction with tolerability compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine? 6. How does satisfaction with relief of other symptoms compare between adults diagnosed with migraine who are using

	Nurtec or triptans as an acute treatment for migraine? 7. How do clinical characteristics (for eg, migraine severity, current migraine prophylactic treatment use) impact patients' satisfaction with regards to medication efficacy, tolerability and migraine-induced cognitive impact in those who are using Nurtec or triptans as an acute treatment for migraine.
Country(ies) of study	United States (US)
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADH	Aptar Digital Health
AE	Adverse Event
CGRP	Calcitonin Gene-related Peptide
CM	Chronic Migraine
CV	Cardiovascular
EM	Episodic Migraine
EMA	European Medicines Agency
HCP	Healthcare Professional
HIPPA	Health Insurance Portability and Accountability Act
HT	Hydroxytryptamine
ICJME	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MHD	Monthly Headache Day
MMD	Monthly Migraine Day
NRDL	National Reimbursement Drugs List
ODT	Orally Disintegrating Tablet
QoL	Quality of Life
RCT	Randomized control trial
SD	Standard Deviation

Abbreviation	Definition
US	United States of America

3. RESPONSIBLE PARTIES

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4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Milestone	Planned Date
Initiation of data analysis	09 June 2024
Completion of data analysis	10 June 2024
Abstract	14 June 2024

6. RATIONALE AND BACKGROUND

Migraine is a common, often disabling neurologic disease characterized by recurrent attacks of head pain that are typically unilateral, throbbing, and associated with a range of symptoms that may include photophobia, phonophobia, nausea, and vomiting.[1-3] Migraine can be classified as episodic or chronic based on the frequency of the migraine or headache: episodic migraine (EM) is characterized by one to 14 monthly headache days (MHDs) or monthly migraine days (MMDs), while chronic migraine (CM) is characterized by 15 or more MHDs for at least three months, with at least eight days a month on which the headaches and associated symptoms meet diagnostic criteria for migraine.[1,3,4] Migraine is a clinically complex disorder, and in addition to its direct clinical burden, patients experience a greater number of comorbidities compared to those without migraine.[5]

While treatment goals vary by region, guidelines from both the US and France (the most recently published treatment goals in Europe) for acute migraine treatment suggest these are rapid and sustained freedom from pain, improvement in other migraine symptoms, and minimal or no adverse events (AEs).[6,7] There is significant need for effective and tolerable treatments for migraine sufferers, especially those who experience at least four migraine days per month. In these patients, preventive treatment is recommended to reduce migraine-related disability and the overuse of acute therapies and rescue medication.[6] Both US and European guidelines note the importance of reduced attack frequency, reduction or maintenance (no escalation) of acute treatment use, and an improvement in quality of life (QoL).[6,7] Current migraine treatments leave millions of people who have migraine with unmet needs due to lack of and/or insufficient efficacy, AEs, and contraindications.[8,9]

Treatment strategies aim to abort episodic symptoms and reduce the frequency of attacks, with "triptans" (5-hydroxytryptamine [5-HT]1b/1d receptor agonists) being the most commonly used prescription medications for acute treatment.[10] However, their effectiveness is not universal, and due to vasoconstrictive effects, they are contraindicated in patients with known cardiovascular disease (CV). Recent advancements have introduced 2 novel classes of acute migraine medications: selective 5-HT1F agonists ("ditans") and CGRP antagonists ("gepants"), with the U.S. Food and Drug Administration approving Lasmiditan, Ubrogepant, and rimegepant for the acute treatment of migraine in adults.

Rimegepant (VYDURA®/NURTEC® ODT), a next-generation, small molecule oral selective and potent calcitonin gene-related peptide (CGRP) receptor antagonist, is the first and only migraine treatment approved for both the acute treatment of migraine with or without aura in adults and for the preventive treatment of EM in adults who have at least four

migraine attacks per month. Prior to rimegepant, there was no single medication proven to be safe and effective for both acute and preventive treatment of migraine. Rimegepant was approved in the US for the acute treatment of migraine in February 2020, and for preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month in May 2021. It was approved by the EMA for both indications in April 2022.

There is a lack of published studies comparing directly triptans which are the most commonly used prescription medications for acute treatment with rimegepant. Existing indirect comparisons between the randomized controlled trials (RCTs) of rimegepant and triptans are confounded by high levels of heterogeneity leading to biased results.

This study will utilize retrospective data collected with the Migraine Buddy Mobile application to evaluate satisfaction of treatment with rimegepant and triptans. The primary motivation for the study is to generate evidence to support a submission to the National Reimbursement Drugs List (NRDL) in China, but it is anticipated that results will also be of relevance to health care providers and payers outside of China.

7. RESEARCH QUESTION AND OBJECTIVES

Primary objective: The objective of this study is to assess the holistic benefit of rimegepant as compared to triptans, particularly in relation to patients' satisfaction with regards to medication efficacy, tolerability, and migraine-induced cognitive impact.

Research questions:

1. How does satisfaction with pain intensity compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

2. How does satisfaction with attack duration compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

3. How does satisfaction with speed of action compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

4. How does satisfaction with migraine-induced cognitive impact compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

5. How does satisfaction with tolerability compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

6. How does satisfaction with relief of other symptoms compare between adults diagnosed with migraine who are using Nurtec or triptans as an acute treatment for migraine?

7. How do clinical characteristics (for eg, migraine severity, current migraine prophylactic treatment use) impact patients' satisfaction with regards to medication efficacy, tolerability and migraine-induced cognitive impact in those who are using Nurtec or triptans as an acute treatment for migraine.

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective analysis of cross-sectional data collected in the Migraine Buddy app between 20 October 2023 and 20 May 2024 from US users.

Migraine Buddy users reporting current use of an acute treatment for their migraine attacks completed a survey assessing their satisfaction with the acute migraine drugs being used. Data from users reporting use of Nurtec and/or a triptan (and Rizatriptan in particular) will be extracted for analysis.

The primary endpoint is the level of satisfaction on several dimensions of migraine characteristics. Survey questions ask specifically about satisfaction with Nurtec or the triptan. The level of satisfaction with Nurtec will be compared to the level of satisfaction with triptans.

The strength of this design is the real-life setting of the data collected. Users were using the Migraine Buddy app for tracking their migraines in real life.

8.2. Setting

Migraine Buddy is an app available on iOS and Android. It's used by people interested in tracking their headaches and other symptoms. It generates reports that users are able to share with their doctors to help them establish a diagnosis and/or optimize treatment. The app has been downloaded more than 3.7 million times across 190 countries.

The study population for this study is Migraine Buddy users in the US who answered a survey about their acute treatments, displayed on the home page of the app. For the purpose of this retrospective study, only questions related to treatment satisfaction will be analyzed.

Users complete the satisfaction questions only once for each current acute migraine treatment. The survey becomes visible on the home page after users have recorded in the app at least one migraine attack treated with that specific acute treatment (via a survey about this medication in particular eg, "Are you satisfied with Nurtec?"). Once completed, the survey is removed from the home page unless the user switches or initiates a new acute migraine treatment. If a patient is using more than one acute treatment, they will be able to complete satisfaction questions for each acute treatment. Approximately two-thirds of the app users are currently using both rimegepant and triptans to acutely treat their migraine attacks. Questions are worded such that they ask specifically about the particular acute treatment eg, Nurtec. For the surveys used in the 7-month time frame of this retrospective study, feasibility assessment showed that participants answered the satisfaction questions for a specific acute medication

only once, in 97% of the cases. For the few users who responded to 2 or more waves of identical surveys, the most recent answer will be used for the analysis.

Data was gathered between 30 October 2023 & 20 May 2024 from users of the Migraine Buddy app through the "diary tracking" and the satisfaction questions were administered via survey and via the interactive data collection tool named "Taylor". All the data will be extracted from the Aptar Digital Health (ADH) platform existing database in order to perform the analysis described in this protocol.

8.2.1. Inclusion Criteria

Patients who used Nurtec and/or triptans as an acute treatment for migraine, with or without a background of preventive treatment (anti-CGRP, Botox or oral migraine preventive medications).

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

1. Male or female participants with migraine
2. Having consented to the anonymous use of their data for research
3. Currently using Nurtec and/or triptans to treat migraine attacks

8.2.2. Exclusion Criteria

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

1. Users who did not report using either medication for which they complete the survey within 60 days prior to the survey.

8.3. Variables

For this retrospective study, the only variables collected are the self-reported satisfaction of Migraine Buddy users via a questionnaire accessible from the home screen of the app. Satisfaction with Nurtec or triptans was asked in relation to several dimensions: pain intensity, attack duration, speed of action, cognitive impact of Migraine, tolerability, and other symptoms.

Variable	**Role**
Current acute treatment (s)	Patient treatments
Current prevention treatment (s)	Patient treatments
Monthly migraine Days	Clinical Characteristics
Satisfaction with treating pain	Outcome
Satisfaction with reducing attack duration	Outcome
Satisfaction with speed of pain relief	Outcome
Satisfaction with reduction of migraine-	Outcome

Variable	Role
cognitive impact	
Satisfaction with tolerability	Outcome
Satisfaction with relief of other symptoms	Outcome

8.4. Data Sources

Data source is the Migraine Buddy app responses to questions in the satisfaction survey. The Migraine buddy app and its database is owned by ADH, after the acquisition of Healint. The satisfaction levels refer to the medication in general. They are not tied to specific attacks. To avoid a recall bias, data from users answering the survey more than 60 days after the last time they reported using Nurtec or a triptan will be discarded.

This questionnaire asked the level of satisfaction with their treatment on a 7-levels Lickert scale. (1 = extremely dissatisfied to 7 = extremely satisfied). Based on their responses, the respondents will be stratified into those who were dissatisfied (reporting 1 = extremely dissatisfied to 3 = somewhat dissatisfied), neutral (4=neither dissatisfied nor satisfied) or satisfied (reporting 5 = somewhat satisfied to 7 = extremely satisfied) with the treatment. Data will be reported for the overall cohort, no individual data will be shared.

8.5. Study Size

The available number of patients (sample size) for this study is approx. 700 for the Nurtec group and 800 for the triptan group. By definition some users may have responded to both satisfaction surveys, ie, both groups of patients may overlap. Descriptive statistics will be used to summarize the study variables.

8.6. Data Management

This retrospective observational study involves the use of real-world data that exists in anonymized structured format and does not contain patient personal information. If identifiable information is available, this will be removed by ADH in accordance with HIPPA standards to protect participants privacy.

ADH is the developer and distributor of the Migraine Buddy app. This app is used by people who wish to track their migraine attacks for their own usage and/or share reports with their doctor. Occasionally, users answers surveys to improve their journey with the app. The source of data for this retrospective study is the Migraine Buddy app. The data used for this study was collected independently from the protocol. There is no CRF. The survey data are simply extracted as csv files via a python code.

8.7. Data Analysis

The study analysis population will include patients who received Nurtec and/or triptans as an acute treatment currently for their migraine.

The feasibility of subgroup analyses will be explored (eg, by migraine severity, currently using prophylactic treatment). Feasibility will evaluate if there is sufficient sample size for meaningful comparisons. All outcomes will remain blinded for the feasibility assessment.

The mean, standard deviation (SD), median, 25th and 75th percentiles and minimum and maximum values will be reported for numeric variables, whilst relative frequencies and percentages will be reported for categorical variables.

To compare the outcome measures (Section 7) between adults diagnosed with migraine who are using either Nurtec or triptans as an acute treatment for migraine, appropriate tests (eg, t-test, chi-square test) will be used based on the distribution of the measure. The alpha level will be 0.05, 2-sided. No adjustments for multiple comparisons will be made.

The real-world nature of the Migraine Buddy app means variables may contain different proportions of missing data. We would expect the non-missing observations (the 'base') of patients to vary from variable to variable. The base relevant to each analysis will be reported in any data tables provided. This study will use a 'complete case analysis' approach to handle missing values, ie, there will be no imputation of missing data. Where missing values are found in a particular variable, any patients with missing values will be removed from all pieces of analysis where that variable is used. However, patients removed from one piece of analysis are still eligible for inclusion in other analyses.[11]

8.8. Quality Control

As this is a retrospective study, issues of quality control at study sites, eg, data queries, do not apply. Analysis is programmed according to the specifications in this protocol.

Data will be cleaned to address missing values, outliers and inconsistencies.

No open field questions are used in the survey, participants simply check boxes. Programming prevented users from selected multiple answers to single-choice questions. The number of variables is low. No specific encoding (C-DISC etc) is needed.

8.9. Limitations of the Research Methods

While Migraine Buddy users self-report as having migraine has been shown to be reliable, it is possible that they have been misdiagnosed or are currently receiving a triptan to assist an HCP with determining a diagnosis of migraine.[12] This would potentially reduce the response to migraine-specific drugs such as triptans or rimegepant.

The answers from users can be recorded at different time in relation to a migraine attacks: before, during, just after or up to 60 days after an attack. Those timings can impact the perception of relief/outcome. Therefore, the results presented should only be considered in the scope of a comparison between 2 drugs and not as absolute values expressing a proportion of attacks on which the said drug will provide a positive outcome.

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 contains 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)

It is the responsibility of ADH to obtain an IRB-approved waiver which provides legal protection and institutional endorsement of the study. All correspondence with the IRB/EC should be retained by ADH. Copies of IRB/EC waivers should be forwarded to Pfizer.

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 Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, the Good Outcomes Research Practices issued by ISPOR (formerly known as the International Society for Pharmacoeconomics and Outcomes Research) and the International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data will be analyzed to produce an abstract to be submitted for a presentation at the PAINWeek meeting in September 2024. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. [13]

In the event of any prohibition or restriction imposed (eg, 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.

12. REFERENCES

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13. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medication Journals, 2019.

13. LIST OF TABLES

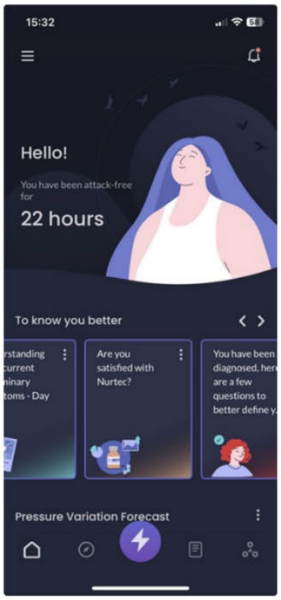
None.

14. LIST OF FIGURES

None.

Appendix 1. Screenshots of the Survey as Seen by the Participants

Screenshots of the questionnaires presented to participants



The survey appears on the Migraine buddy app home screen of users who have reported using the medication at least once in their diary
e.g. “are you satisfied with Nurtec?”
Or ”are you satisfied with Maxalt (Rizatriptan)”? Etc…