NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Evaluation of the reliability of effect of rimegepant or triptans for the acute treatment of migraine across multiple attacks
Protocol number	C4951066
Protocol version identifier	Final, V2.0 (amendment 1)
Date	23 April 2024
Active substance	Analgesics, calcitonin gene-related peptide (CGRP) antagonists. ATC code: N02CD06
Medicinal product	Rimegepant (Nurtec 75mg ODT)
Research question and objectives	The objectives of this study are to 1) explore reliability of effect with acute use of rimegepant or triptans; 2) evaluate satisfaction with rimegepant or triptans; 3) evaluate willingness to continue using rimegepant or triptans; 4) explore proportion optimized on treatment with rimegepant or triptans. **Research questions:** 1. What is the reliability of effect of rimegepant or triptans in the real world over multiple migraine attacks when taken PRN? 2. How satisfied are patients with rimegepant ortriptans to treat their migraine attacks? 3. How willing are patients to continue taking rimegepant or triptans to treat their migraine attacks? 4. What proportion of those treating acutely with rimegepant or triptans are adequately responding and well managed? 5. When do patients administer rimegepant or triptans when treating an acute attack?

Author	PPD , CPsychol, PPD PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AIDS/HIV	Acquired Immunodeficiency Syndrome/Human Immunodeficiency Virus
ARW	Adelphi Real World
BMI	Body Mass Index
CGRP	Calcitonin Gene-related Peptide
CM	Chronic Migraine
COVID-19	Coronavirus Disease 2019
CV	Cardiovascular
DSP	Disease Specific Programme™
EC	Ethics Committee
ED	Emergency Department
EM	Episodic Migraine
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Market Research Association
GI	Gastrointestinal
IBM	International Business Machines Corporation
IBS	Irritable Bowel Syndrome
ICJME	International Committee of Medical Journal Editors
ICSR	Individual Case Safety Reports
IRB	Institutional Review Board

Abbreviation	Definition
MHD	Monthly Headache Day
MMD	Monthly Migraine Day
m-TOQ6	Migraine Treatment Optimization Questionnaire
NASH	Nonalcoholic Steatohepatitis
NSAIDs	Non-steroidal Anti-inflammatory Drugs
ODT	Orally Disintegrating Tablet
PCP	Primary Care Physician
PRF	Patient Record Form
PRN	Pro Re Nata
PRO	Patient-reported Outcome
PSC	Patient Self Completion
QoL	Quality of Life
RWD	Real World Data
Rx	Prescription
SAP	Statistical Analysis Plan
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
SUNCT	Short-lasting, Unilateral, Neuralgiform headache attacks with Conjunctival injection and Tearing
TIA	Transient Ischemic Attack
US	United States of America
YLD	Years Lived with Disability

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
PPD			

4. ABSTRACT

Stand alone document.

AMENDMENTS AND UPDATES

Amendment 1

This amendment is to add a descriptive analysis of triptans compared to rimegepant for the acute treatment of migraine attacks.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Version 2.0	23 April 2024	Administrative	3. Responsible parties	PIs updated	Clinical scientist joined the team, and changes to vendor team
Version 2.0	23 April 2024	Administrative	6. Milestones	Timelines for additional analyses & reporting added	Provide data for China NRDL submission
Version 2.0	23 April 2024	Substantial	8 – Research Objectives 9.2 Setting 9.2.1 Inclusion criteria 9.2.2 Exclusion criteria 9.3 Variables 9.6 Data analysis 9.6.1 Analysis Plan 9.6.2 Analysis Plan for Objective 1 9.6.3 Analysis Plan for Objective 2 9.6.4 Analysis Plan for Objective 3 9.6.5 Analysis Plan for Objective 4	Addition of triptans as treatment of interest. For descriptive analysis only.	Provide data for China NRDL submission
Version 2.0	23 April 2024	Substantial	9.5 Study size	Sample size updated to include triptan population.	Provide data for China NRDL submission

5. MILESTONES

Milestone	Planned Date
Protocol/SAP (Version 1.0)	7 Dec 2023
Data collection started (Version 1.0)	2 Jan 2024
Data collection completed (Version 1.0)	3 Jan 2024
Final study tables (Version 1.0)	29 Jan 2024
Protocol/SAP (amendment V.1.)	23 Apr 2024
Final study tables (Phase V1.1)	30 April 2024
Final report	02 Dec 2024
Abstract 1	17 Feb 2024
Abstract 2	17 May 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]

In 2019, an estimated 1.1 billion people in the world suffered from migraine, causing 42.1 million years lived with disability (YLD).[6] Women are two to three times more likely than men to be affected by migraine.[7-9] The global age-standardized prevalence of migraine was 14.1% in 2019, which is an increase of 1.7% since 1990. There were 87.6 million incident cases of migraine globally in 2019, resulting in an incidence of 11.4%, which was an increase of 2.1% since 1990.[6]

In the US, migraine accounted for $36 billion in both direct and indirect costs in 2016.[10] The three most common locations for migraine care are primary care, neurologist, and emergency department (ED) settings, with approximately 1.2 million ED visits in the US annually due to migraine attacks.[11] Indirect costs related to work productivity impairment are commonly incurred in patients with migraine, with presenteeism accounting for the majority of work-related productivity loss.[12,13] Annual costs due to migraine-related lost productivity in the US were estimated at $2.1 million for the manufacturing sector and $2.9 million for the service sector (per 10,000 individuals).[14] Patients with refractory migraine have higher mean annual frequency of outpatient visits, ED visits and admissions, and a higher intensity of care vs. patients with migraine and those without migraine.[15]

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).[16,17] 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.[16] 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).[16,17] Current migraine treatments leave millions of people who have migraine with unmet needs due to lack of and/or insufficient efficacy, AEs, and contraindications.[18,19]

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.

The Adelphi Real World (ARW) Migraine Disease Specific Programme™ (DSP) 2022 surveys provide an opportunity to examine physician and patient perspectives for rimegepant in the US. This protocol describes the analysis of ARW Migraine VII DSP™ as a secondary real-world data (RWD) source to address the research questions.

7. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are to 1) explore reliability of effect with acute use of rimegepant or triptans; 2) evaluate satisfaction with rimegepant or triptans; 3) evaluate willingness to continue using rimegepant or triptans; 4) explore proportion optimized on treatment with rimegepant or triptans.

Research questions:

1. What is the reliability of effect of rimegepant or triptans in the real world over multiple migraine attacks when taken PRN?

2. How satisfied are patients with rimegepant or triptans to treat their migraine attacks?

3. How willing are patients to continue taking rimegepant or triptans to treat their migraine attacks?

4. What proportion of those treating acutely with rimegepant or triptans are adequately responding and well managed?

5. When do patients administer rimegepant or triptans when treating an acute attack?

8. RESEARCH METHODS

8.1. Study Design

A cross-sectional study design using physician and patient survey data drawn from the ARW Migraine VII DSP will be employed to assess the acute use of, satisfaction with, willingness to continue use and treatment optimization of rimegepant or triptans in patients with migraine. Participants were recruited into the Migraine VII DSP in the US between May 2022 and November 2022. This study comprises a secondary data analysis of DSP data.

The full DSP methodology has been published and validated and the illustration below outlines the main phases of the DSP].[20,21,22] The DSP was conducted across a number of countries including the EU5 and US. Given the timing of the data collection, only data from the US will be utilized as rimegepant was available on the US market at the time of administration, unlike for other countries.

The ARW DSP™ are made available to subscribers upon the strict condition that all information remains the intellectual property of ARW and should not be divulged to any third party except with the written prior permission of ARW. Pfizer has subscribed to access the ARW Migraine VII DSP and so cannot be considered as the Study Sponsor.

8.2. Setting

ARW works with field partners across the US with the same principle of physician-based recruitment for all DSPs. Both physician-level and patient-level data are available for analyses of the migraine DSP (see Figure 1).

The study population will comprise of consulting patients included in the Migraine VII DSP between May 2022 and November 2022; namely, consulting adult patients diagnosed with migraine and prescribed rimegepant or triptans as an acute treatment for their migraine in the US.

DSP physician participants for the migraine DSP in the US were neurologists and general physicians identified from public lists of healthcare professionals and meeting the following criteria:

- Physicians identified as a PCP or neurologist.
- PCPs must make treatment decisions for at least 10 patients with migraine and neurologists must make treatment decisions for at least 20 patients with migraine.

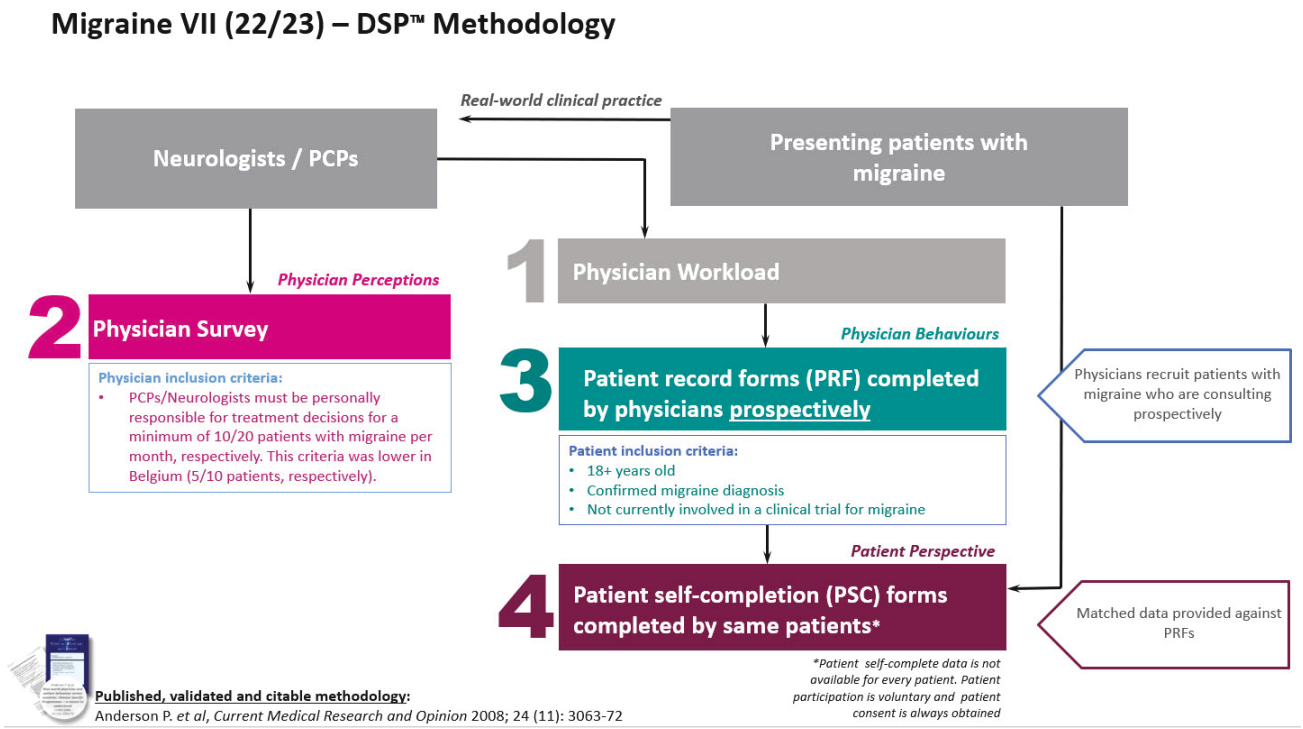
Candidate respondents were screened online and those who met the predefined eligibility criteria were invited to participate (see Section 8.2.1 and Section 8.2.2).

Each participating physician was asked to provide patient data for up 8 patients with migraine. Patient data for the migraine DSP was based on patients aged 18 years or older with a diagnosis of migraine and not involved in a clinical trial.

As described in Figure 1, during the US survey period (May–November 2022), physicians involved in the management of migraine patients were recruited to complete an online survey (Physician Survey) of their attitudes and behaviors regarding the treatment of migraine. Each physician then completed an electronic Patient Record Forms (PRFs) on 8 consecutive consulting patients with migraine, regardless of the reason for the visit. The consecutive approach to recruitment was stressed to each participating physician to remove the element of selection bias. A generic copy of the data collection forms for Physicians is included in APPENDIX 2. COPIES OF PATIENT RECORD FORM (PRF), PATIENT SELF COMPLETION (PSC) QUESTIONNAIRES and PHYSICIAN SURVEY QUESTIONNAIRES: ENGLISH LANGUAGE VERSION.

The patients were then asked if they would be willing to complete a pen-and-paper Patient Self-Completion (PSC) questionnaire about their experiences of having migraine. This allows a unique view of the disease from both the patient and physician perspective. Completion of the PSC by the patient was voluntary.

Figure 1. Migraine DSP Data Collection Methodology



8.2.1. Inclusion Criteria

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

1. Patients who have episodic and/or chronic migraine
2. Patients age >18
3. Currently prescribed rimegepant OR triptans for the acute treatment of migraine

8.2.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be included in the study population for analysis:

1. Currently prescribed rimegepant for prevention of migraine or for both the acute treatment & prevention of migraine
2. Rimegepant group: currently prescribed an acute treatment for migraine other than rimegepant
3. Triptan Group: currently prescribed an acute treatment for migraine other than triptans

8.3. Variables

The variables of interested captured in the data collection forms are summarized in Table 1:

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
Physician provided Patient Report Form (PRF)			
Patient age	Patient demographics	PRF AQ1	
Patient biological sex		PRF AQ2	Male, Female, Intersex
Patient BMI		PRF AQ3/4	
Patient ethnicity		PRF AQ6	White / African American / Native American / Asian (Indian subcontinent) / South-East Asian / Asian (other) / Hispanic / Middle Eastern / Other
			Working fulltime / part-time / retirement / student /

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
Employment Status		PRF AQ8	unemployed / long-term sick / home maker / don't know
		PRF AQ9	Part-time / retirement / student / unemployed / long-term sick due to migraine: yes/no
		PRF AQ10	Days off work due to migraine
Insurance Type		PRF AQ14	Medicaid / medicare / commercial / exchange plan / cobra / non-medicare retired benefit / tricare/veterans / other / no insurance / don't know
Migraine diagnosis- chronic?	Patient clinical characteristics	PRF CQ5	Yes / No
Number of migraine related headache days in last 3 months		PRF CQ4bi	
Severity of attacks over last 3 months		PRF CQ7a	Very mild / Mild / Moderate / Severe / Very Severe
Current migraine symptoms/most bothersome symptom		PRF CQ6a/6b	Pain on one side of the head / Pain that moves from one side of the head to another/ Pain on both sides of the head at the same time / Pulsating/throbbing pain / Pain worsened by activity / Photophobia / Sensitivity to smell / Visual aura / Light-headedness / Speech changes / Sensory aura / Nausea / Vomiting / Allodynia / Watery/swollen/red eyes / Facial swelling / Runny nose/nasal congestion / Ear congestion / Kinesiophobia / Muscle weakness / Mood changes / Changes in appetite / Other / Unknown
		PRF CQ10	Hours/days
Duration of attack without treatment		PRF CQ3	Tension type headache / Medication overuse headache / Cluster headache / SUNCT /

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
Other headache conditions		PRF KQ2/LQ1	Hemicrania continua / New daily persistent headache / Primary stabbing headache / Primary exercise headache / Primary thunderclap headache / Hypnic headache / Secondary headaches / Other headache conditions / None
Current comorbidities			Myocardial infarction / Ischaemic stroke / Haemorrhagic stroke / TIA / Cerebrovascular disease / Hypertension / Hypotension / Ischaemic heart disease / Congestive heart failure / Atrial fibrillation / Arrhythmia / Angina / Deep vein thrombosis / Cardiomyopathy / Coronary artery disease / Peripheral vascular disease / Mitral valve disease / Reynaud's disease / Type 1 diabetes (with and without complications / Type 2 diabetes (with and without complications) / Obesity / Thyroid disease / Hyperlipidaemia / Dyslipidaemia / Mild/Moderate/Severe renal disease / Mild/Moderate/Severe liver disease / NASH/ Depression / Anxiety / Stress / Vascular dementia / Alzheimer's disease / Other dementia / Epilepsy / Parkinson's disease / Obsessive compulsive disorder / Panic disorder / Sleeping disorders / Seizures / Vertigo / Chronic pulmonary disease / Asthma / Chronic sinusitis / Connective tissue disease / Hemiplegia/Paraplegia / Rheumatologic disease / Arthritis / Neuropathic pain / Osteoporosis / Neck pain / Back

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
			pain / Fibromyalgia / Trigeminal neuralgia / Muscle weakness / Any malignancy / Metastatic solid tumour / Tumour without metastases / Gastrointestinal problems / Peptic ulcer disease / Lupus / Anorexia / Alcoholism / Menstrual disorders / IBS / Glaucoma / AIDS/HIV / Erectile dysfunction / Long term effects of COVID-19 / Other / None
Patient received prior acute treatment(s) Time spent on Rimegepant or triptans (currently receiving)	Patient current & prior acute treatments	PRF DQ10 PRF DQ2a	Triptan(s) including combinations / NSAID(s) including combinations / Anti-CGRP gepants / Opioid analgesics including combinations / Non-opioid analgesics including combinations / Ergotamines and Derivatives / Serotonin 5-HTIF agonist (ditan) / Other / No drug treatment Days / Don't know
Patient current preventive treatment(s) Patient prior prevention treatment(s)	Patient current & prior preventive treatment (s)	PRF EQ1 PRF EQ3 PRF EQ10	Yes / No but previously / Never
Failure to achieve pain freedom within 2 hours post dose (physician perspective)	Outcome-Objective 1	PRF DQ18	Yes / No / Unknown
Reason for choice of current acute treatment- 'consistency of response after repeated use' (physician perspective)	Outcome-Objective 1	PRF FQ1a	Complete pain freedom after 2 hours / Pain relief after 2 hours / Relieves most bothersome migraine symptom / Fast onset of action / Relieves even the most severe migraine attacks /

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
			Prolonged pain relief/long duration of action / Avoids the need for a second dose or rescue treatment / Low headache recurrence (within 24 hours of attack) / Tends to work across all patients / Consistency of response after repeated use / Dual use treatment- a single drug to achieve acute and preventive treatment effects / Ability to prescribe a stronger initial dose, rather than multiple additional doses / Ability to take additional doses for non/partial response / Available as a table/capsule / Available as a melt / Available as a patch / Available via nasal administration / Available as an injection / Ability to prescribe for consecutive days (eg, for menstrual migraine and other trigger events / Allows repaid return to function / Patient can continue activities and honour commitments / Patient can enjoy recreational/leisure activities / Reduces number of days missed from school/work / Improves patient's quality of sleep / Patient can maintain relationships / Low risk of medication overuse headaches with repeated use / Lower risk of paraesthesia (abnormal sensation(s) of the skin) / Lower risk of palpitations/flushing / Lower risk of other CV side effects / Lower risk of nausea/vomiting / Lower risk of other GI side effects / Lower risk of memory/concentration problems / Lower risk of drowsiness/sedation / Lower risk of dizziness / Lower risk of fatigue / Lower risk of liver damage / Lower risk of weight

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
			problems / Lower risk of depression / Lower risk of allergic reaction / Lower risk of breathing difficulties / Lower/no risk of injection site reaction / Lower risk of addiction/abuse / Suitable for adjunctive/add-on therapy / Lack of interaction with other drugs / Safe for long term use / Efficacious in patients who have failed prior acute migraine treatments / Suitable for patients with moderate/high CV risk / Safe in patients with cardiac/circulatory disorders / Suitable for vomiting/nauseous patients / Suitable for patients with menstrual migraine / Suitable for women of child bearing age / Suitable for women of child bearing age / Suitable for physically active patients / Suitable for use in career orientated professionals / Approved for migraine / Good patient adherence / Patient convenience / Patient request/preference for therapy / Cost effective treatment / Persona; experience prescribing this drug / On local/national formulary / Clinical trial/publication evidence / Other selected for rimegepant or triptans
Satisfaction with current acute treatment (physician perspective)	Outcome-Objective 2	PRF IQ1a	Extremely satisfied / Satisfied / Slightly Satisfied / Neither satisfied nor dissatisfied / Slightly dissatisfied / Dissatisfied / Extremely dissatisfied

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
Drivers for lack of satisfaction with current acute treatment (physician perspective)	Outcome-Objective 2	PRF IQ1b	Lack of efficacy / Slow onset of action / Efficacy diminished over time / Number of side effects experienced / Severity of side effects experienced / Mode of administration / Complicated dosing regimen / The number of prescribed acute treatments / The treatment is costly for the patient / Other
Patient Self-Completion Form (PSC)			
Number of migraine attacks acute treatment achieves pain freedom within 2 hours post dose (patient perspective)	Outcome-Objective 1	PSC HQ6	0 out of every 5 attacks / 1 out of every 5 attacks / 2 out of every 5 attacks / 3 out of every 5 attacks / 4 out of every 5 attacks / 5 out of every 5 attacks
Satisfaction with current acute treatment (patient perspective)	Outcome-Objective 2	PSC HQ18a	Extremely satisfied / Satisfied / Slightly Satisfied / Neither satisfied nor dissatisfied / Slightly dissatisfied / Dissatisfied / Extremely dissatisfied
Drivers for lack of satisfaction with current acute treatment (patient perspective)	Outcome-Objective 2	PSC HQ18b	It only reduces my migraine pain by half / IT reduces my migraine pain by less than half / It does not work quickly enough / It does not work as well as it used to / The number of side effects I experience / The severity of the side effects I experience / I am not happy with the way I have to take it / I find it difficult to know when to take it / I have too many different acute treatments to take / I worry about becoming dependent on it / It costs me too much money / Other
Patient willingness to continue use of acute treatment (patient perspective)	Outcome-Objective 3	PSC HQ18c	Definitely yes / Probably yes / Do not know / Probably note / Definitely not

Table 1. Variables

Variable	Purpose	Data Source(s)	Operational Definition
Migraine Treatment Optimization Questionnaire (m-TOQ6)	Outcome-Objective 4	PSC Section I- m-TOQ6	Reported by item and total score.
When patient takes acute Rx treatment	Outcome – Objective 5	PSC HQ3	Before any sign of a migraine attack, but in anticipation of one starting / At the first sign of a migraine attack (before the pain starts) / When the pain starts / After the pain has started and I have an idea of how severe it is
How many days per month patient takes acute Rx treatment	Outcome – Objective 5	PSC HQ4a	

8.4. Data Sources

Data will be drawn from the Adelphi Migraine DSP, fielding in the US between May and November 2022.

8.5. Study Size

Given the primary research objective is purely descriptive in nature (i.e., no *a priori* hypotheses specified), the available sample size is fixed by the DSP data collection methodology and simply impacts the precision of any estimates. Therefore, formal sample size calculations are not applicable and have not been performed. All patients who meet the eligibility criteria will be included in the study. For this study, the sample size is 528 (91 Rimegepant, 437 Triptans) for the physician-reported outcomes, and 143 (29 Rimegepant, 113 Triptans) for the patient-reported outcomes. Data Management

Pseudoanonymised data are taken from the Migraine VII DSP, which is owned and managed by ARW.

All data analysis will be conducted using Stata 17 software, version 17.0 (StataCorp, College Station, Texas) / IBM® SPSS® Data Collection Survey Reporter v7.5 or the latest available version at time of analysis. All programming code/ syntax written to conduct the required analysis will be logged for transparency and replicability.

8.6. Data Analysis

Analyses will be based on patients receiving rimegepant or triptans only as an acute treatment currently for their migraine.

Data will be stratified by time spent on rimegepant or triptans and number of migraine related headache days.

Analysis will be descriptive. 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.

The real-world nature of the DSP means many variables will contain missing data. We would expect the base of patients to vary from variable to variable due to imperfect physician knowledge, physicians not wishing to answer the question, etc. The base relevant to each analysis will be reported in any data tables provided. 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. In the derivation of PRO variables, the handling of missing data will follow the official instructions as provided by the author/owner of the PRO questionnaire.

Detailed methodology for summary and statistical analyses of data collected in this study is documented in a statistical analysis plan (SAP) below:

8.6.1. Analysis Plan for Describing Patients with Migraine Receiving Rimegepant or Triptans PRN

Variable	Data Source(s)	Analysis Plan
Patient age	PRF AQ1	Mean, Median, SD, Q1, Q3, Min, Max to be displayed
Patient biological sex	PRF AQ2	Proportion of responses to: Male, Female, Intersex
Patient BMI	PRF AQ3/4	Mean, Median, SD, Q1, Q3, Min, Max to be displayed
Patient ethnicity	PRF AQ6	Proportion of responses to: White / African American / Native American / Asian (Indian subcontinent) / South-East Asian / Asian (other) / Hispanic / Middle Eastern / Other
Employment status	PRF AQ8	Proportion of responses to: Working full time / Working part-time / Retirement / Student / Unemployed / Long-term sick / Home maker Responses of "Don't know" will be omitted from analysis.
	PRF AQ9	Proportion of responses to: Yes / No Responses of "Don't know" will be omitted from analysis.
	PRF AQ10	Number of days taken off work/studies in last 3 months due to migraine presented as Mean, Median, SD, Q1, Q3, Min, Max to be displayed. Responses of "Don't know" will be omitted from analysis.
Insurance type	PRF AQ14	Proportion of responses to: Medicaid / Medicare / Commercial / Exchange plan / Cobra / Non-medicare retired benefit /

Variable	Data Source(s)	Analysis Plan
		Tricare/veterans / Other / No insurance Responses of "Don't know" will be omitted from analysis.
Migraine diagnosis-chronic?	PRF CQ5	Proportion of responses to: Yes / No
Number of migraine related headache days in last 3 months	PRF CQ4bi	Mean, Median, SD, Q1, Q3, Min, Max to be displayed
Severity of attacks over last 3 months	PRF CQ7a	Proportion of responses to: Very mild / Mild / Moderate / Severe / Very Severe
Current migraine symptoms	PRF CQ6a	Proportion of responses to: Pain on one side of the head / Pain that moves from one side of the head to another/ Pain on both sides of the head at the same time / Pulsating/throbbing pain / Pain worsened by activity / Photophobia / Sensitivity to smell / Visual aura / Light-headedness / Speech changes / Sensory aura / Nausea / Vomiting / Allodynia / Watery/swollen/red eyes / Facial swelling / Runny nose/nasal congestion / Ear congestion / Kinesiophobia / Muscle weakness / Mood changes / Changes in appetite / Other / Unknown Responses of "Don't know" will be omitted from analysis.
Most bothersome migraine symptoms	PRF CQ6b	Proportion of responses to: Pain on one side of the head / Pain that moves from one side of the head to another/ Pain on both sides of the head at the same time / Pulsating/throbbing pain / Pain worsened by activity / Photophobia / Sensitivity to smell / Visual aura / Light-headedness / Speech changes / Sensory aura / Nausea / Vomiting / Allodynia / Watery/swollen/red eyes / Facial swelling / Runny nose/nasal congestion / Ear congestion / Kinesiophobia / Muscle weakness / Mood changes / Changes in appetite / Other / Unknown Responses of "Don't know" will be omitted from analysis.
Duration of attack without acute treatment (hours or days)	PRF CQ10	Mean, Median, SD, Q1, Q3, Min, Max to be displayed. Responses will be calculated into one unit of choice- hours or days. Responses of "Don't know" will be omitted from analysis.
Other headache conditions	PRF CQ3	Proportion of responses to: Tension type headache / Medication overuse headache / Cluster headache / SUNCT / Hemicrania continua / New daily persistent headache / Primary stabbing headache / Primary exercise headache /

Variable	Data Source(s)	Analysis Plan
		Primary thunderclap headache / Hypnic headache / Secondary headaches / Other headache conditions / None Responses of "None" will be omitted from analysis.
Current comorbidities	PRF KQ2/LQ1	Proportion of responses to: Myocardial infarction / Ischaemic stroke / Haemorrhagic stroke / TIA / Cerebrovascular disease / Hypertension / Hypotension / Ischaemic heart disease / Congestive heart failure / Atrial fibrillation / Arrhythmia / Angina / Deep vein thrombosis / Cardiomyopathy / Coronary artery disease / Peripheral vascular disease / Mitral valve disease / Reynaud's disease / Type 1 diabetes (with and without complications / Type 2 diabetes (with and without complications) / Obesity / Thyroid disease / Hyperlipidaemia / Dyslipidaemia / Mild/Moderate/Severe renal disease / Mild/Moderate/Severe liver disease / NASH/ Depression / Anxiety / Stress / Vascular dementia / Alzheimer's disease / Other dementia / Epilepsy / Parkinson's disease / Obsessive compulsive disorder / Panic disorder / Sleeping disorders / Seizures / Vertigo / Chronic pulmonary disease / Asthma / Chronic sinusitis / Connective tissue disease / Hemiplegia/Paraplegia / Rheumatologic disease / Arthritis / Neuropathic pain / Osteoporosis / Neck pain / Back pain / Fibromyalgia / Trigeminal neuralgia / Muscle weakness / Any malignancy / Metastatic solid tumour / Tumour without metastases / Gastrointestinal problems / Peptic ulcer disease / Lupus / Anorexia / Alcoholism / Menstrual disorders / IBS / Glaucoma / AIDS/HIV / Erectile dysfunction / Long term effects of COVID-19 / Other / None Responses of "None" will be omitted from analysis.
Patient receiving acute treatment(s) previously	PRF DQ10	Proportion of responses to: Triptan(s) including combinations / NSAID(s) including combinations / Anti-CGRP gepants / Opioid analgesics including combinations / Non-opioid analgesics including combinations / Ergotamines and Derivatives / Serotonin 5-HTIF agonist (ditan) / Other / No drug treatment Responses of "No treatment" will be omitted from analysis. Responses of 'Triptan' and 'Triptan combinations' will be combined.
Time spent on Rimegepant or triptans (currently	PRF DQ2a	Mean, Median, SD, Q1, Q3, Min, Max to be displayed. Responses will be calculated into one unit of choice- days,

Variable	Data Source(s)	Analysis Plan
receiving)		weeks or months. Responses of "Don't know" will be omitted from analysis.
Patient current preventive treatment(s)	PRF EQ1	Proportion of responses to: Yes / No, but this patient has received preventive prescribed treatment(s) for their migraine in the past / No, and this patient has never received prescribed preventive treatment(s) for their migraine
	PRF EQ3	Proportion of responses to: Anti-CGRP mAbs, Anticonvulsants, Beta-blockers, Anti-CGRP gepant, Antidepressant/Anxiolytics/Benzodiazepines / Calcium antagonists / Contraceptive / NSAIDs (including combinations), Opioid analgesics (including combinations) Neurotoxins / Other / No drug treatment Responses of 'No treatment' will be omitted from analysis. Responses of 'Rimegepant' will be omitted from analysis.
Patient receiving preventive treatment(s) previously	PRF EQ10	Proportion of responses to: Anti-CGRP mAbs, Anticonvulsants, Beta-blockers, Anti-CGRP gepant, Antidepressant/Anxiolytics/Benzodiazepines / Calcium antagonists / Contraceptive / NSAIDs (including combinations), Opioid analgesics (including combinations) Neurotoxins / Other / No drug treatment Responses of 'No treatment' will be omitted from analysis.

8.6.2. Analysis Plan for Objective 1

Objective 1 focuses on the reliability of effect of rimegepant or triptans over multiple attacks when taken PRN to treat migraine. This will be addressed by describing the following:

Variable	Data Source(s)	Analysis Plan
Failure to achieve pain freedom within 2 hours post dose (physician perspective)	PRF DQ18	Proportion of responses to: Yes / No Responses of "Don't know" will be omitted from analysis.
Reason for choice of current acute treatment- 'consistency of response after repeated use' (physician perspective)	PRF FQ1a	Proportion of responses to: Complete pain freedom after 2 hours / Pain relief after 2 hours / Relieves most bothersome migraine symptom / Fast onset of action / Relieves even the most severe migraine attacks / Prolonged pain relief/long duration of action / Avoids the need for a second dose or rescue treatment / Low headache recurrence (within 24 hours of attack) / Tends to work across all patients / Consistency of response after repeated use / Dual use treatment- a single drug to achieve acute and preventive treatment effects / Ability to prescribe a stronger initial dose, rather than multiple additional doses / Ability to take additional doses for non/partial response / Available as a table/capsule / Available as a melt / Available as a patch / Available via nasal administration / Available as an injection / Ability to prescribe for consecutive days (eg, for menstrual migraine and other trigger events / Allows repaid return to function / Patient can continue activities and honour commitments / Patient can enjoy recreational/leisure activities / Reduces number of days missed from school/work / Improves patient's quality of sleep / Patient can maintain relationships / Low risk of medication overuse headaches with repeated use / Lower risk of paraesthesia (abnormal sensation(s) of the skin) / Lower risk of palpitations/flushing / Lower risk of other CV side effects / Lower risk of nausea/vomiting / Lower risk of other GI side effects / Lower risk of memory/concentration problems / Lower risk of drowsiness/sedation / Lower risk of dizziness / Lower risk of fatigue / Lower risk of liver damage / Lower risk of weight problems / Lower risk of depression / Lower risk of allergic reaction / Lower risk of breathing difficulties / Lower/no risk of injection site reaction / Lower risk of addiction/abuse / Suitable for adjunctive/add-on therapy / Lack of interaction with other drugs / Safe for long term use / Efficacious in patients who have failed prior acute migraine treatments / Suitable for patients with moderate/high CV risk / Safe in patients with cardiac/circulatory disorders / Suitable for vomiting/nauseous patients / Suitable for patients with menstrual migraine / Suitable for women of child bearing age / Suitable for women of child bearing age / Suitable for physically active patients / Suitable for use in career orientated professionals / Approved for migraine / Good patient adherence / Patient convenience / Patient request/preference for therapy / Cost effective treatment / Persona; experience prescribing this

Variable	Data Source(s)	Analysis Plan
		drug / On local/national formulary / Clinical trial/publication evidence / Other selected for rimegepant or triptans
Number of migraine attacks acute treatment achieves pain freedom within 2 hours post dose (patient perspective)	PSC HQ6	Proportion of responses to: 0 out of every 5 attacks / 1 out of every 5 attacks / 2 out of every 5 attacks / 3 out of every 5 attacks / 4 out of every 5 attacks / 5 out of every 5 attacks Success will be defined as responses to '4 out of every 5 attacks' or '5 out of every 5 attacks' combined

8.6.3. Analysis for Objective 2

Objective 2 focuses on satisfaction of physicians and patients with rimegepant or triptans to treat migraine acutely. This will be addressed by describing the following:

Variable	Data Source(s)	Analysis Plan
Satisfaction with current acute treatment (physician perspective)	PRF IQ1a	Proportion of responses to: Extremely satisfied / Satisfied / Slightly Satisfied / Neither satisfied nor dissatisfied / Slightly dissatisfied / Dissatisfied / Extremely dissatisfied Satisfaction will be defined as responses to: 'Extremely satisfied' or 'Satisfied' or 'Slightly Satisfied' combined Dissatisfaction will be defined as responses to: 'Neither satisfied nor dissatisfied' or ' Slightly dissatisfied' or 'Dissatisfied' or 'Extremely dissatisfied' combined Data to be matched to PSC equivalent data (PSC HQ18a)
Drivers for lack of satisfaction with current acute treatment (physician perspective)	PRF IQ1b	Proportion of responses to: Lack of efficacy / Slow onset of action / Efficacy diminished over time / Number of side effects experienced / Severity of side effects experienced / Mode of administration / Complicated dosing regimen / The number of prescribed acute treatments / The treatment is costly for the patient / Other

Variable	Data Source(s)	Analysis Plan
Satisfaction with current acute treatment (patient perspective)	PSC HQ18a	Proportion of responses to: Extremely satisfied / Satisfied / Slightly Satisfied / Neither satisfied nor dissatisfied / Slightly dissatisfied / Dissatisfied / Extremely dissatisfied Satisfaction will be defined as responses to: **'**Extremely satisfied' or 'Satisfied' or 'Slightly Satisfied' combined Dissatisfaction will be defined as responses to: 'Neither satisfied nor dissatisfied' or ' Slightly dissatisfied' or 'Dissatisfied' or 'Extremely dissatisfied' combined Data to be matched to PRF equivalent data (PRF IQ1a)
Drivers for lack of satisfaction with current acute treatment (patient perspective)	PSC HQ18b	Proportion of responses to: It only reduces my migraine pain by half / IT reduces my migraine pain by less than half / It does not work quickly enough / It does not work as well as it used to / The number of side effects I experience / The severity of the side effects I experience / I am not happy with the way I have to take it / I find it difficult to know when to take it / I have too many different acute treatments to take / I worry about becoming dependent on it / It costs me too much money / Other

8.6.4. Analysis for Objective 3

Objective 3 focuses on willingness of patients to continue taking rimegepant or triptans to treat their migraine attacks. This will be addressed by describing the following:

Variable	Data Source(s)	Analysis Plan
Patient willingness to continue use of acute treatment (patient perspective)	PSC HQ18c	Proportion of responses to: Definitely yes / Probably yes / Do not know / Probably not / Definitely not Responses of "Don't know" will be omitted from analysis. Willingness to continue will be defined as responses to: 'Definitely yes' or 'Probably yes' combined Unwillingness to continue will be defined as responses to 'Probably not' and 'Definitely not' combined

8.6.5. Analysis for Objective 4

Objective 4 focuses on the proportion of those treating acutely with rimegepant or triptans that are optimised on their treatment. This will be addressed by describing the following:

Variable	Data Source(s)	Analysis Plan
Migraine Treatment Optimization Questionnaire (m-TOQ6)	PSC Section I- m-TOQ6	Reported by proportion of responses per time item and total score. The official m-TOQ6 scoring algorithm will be used to calculate total score.
When patient takes acute treatment	PSC HQ3	Proportion of responses to: Before any sign of a migraine attack, but in anticipation of one starting / At the first sign of a migraine attack (before the pain starts) / When the pain starts / After the pain has started and I have an idea of how severe it is
Number of days per month patient takes acute treatment	PSC HQ4a	Mean, Median, SD, Q1, Q3, Min, Max to be displayed.

8.7. Quality Control

This study will be conducted according to ARW's standard operating procedures, with the results of the analysis checked for validity and consistency.

8.8. Limitations of the Research Methods

- Physicians are asked to provide data on consecutively consulting patients who meet the eligibility criteria, thus reducing the chance of any selection bias on the consulting population by physicians. However, generalisability of the study results to the wider patient population will be impacted as follows:
    - Participants from the Migraine VII DSP (from which the study population is drawn) do not constitute a true random sample, more a pragmatic (physicians) and pseudo-random (patients) sample, and although minimal selection criteria were imposed to identify physicians for inclusion, participation is influenced by the willingness to complete the record forms.
    - The patient sample may be more severely affected by their disease and/or treatment due to their consulting nature (ie, a requirement for inclusion in the Migraine VII DSP). Furthermore, patients who consult more frequently are more likely to be included in the patient sample. However, physicians were asked to provide data for a number of consecutively consulting patients meeting the Migraine VII DSP inclusion criteria to reduce selection bias.

- No patient selection verification procedures were applied to the Migraine VII DSP, and identification of the participants included was based on physician judgement/ perception rather than formal medical coding (eg, diagnostic codes). Nevertheless, this process is representative of physicians' real-world classification of their patients.

- The cross-sectional design of the DSP does not allow for causal relationships; however, identification of associations is possible.

- Physicians and patients were requested to capture patient information retrospectively within the PRF and PSC respectively, which may introduce recall bias – a common limitation of survey data. However, physicians did have the ability to refer to the patients' medical records while completing the PRF, thus minimising the possibility of recall bias. Moreover, most questions within the PSC have a limited recall period to further minimise the risk of recall bias.

Study data are self-reported by participants (eg, physicians and patients) as no independent verification was possible due to the nature of the ARW DSP methodology.

8.9. Other Aspects

Strengths of this research methods are:

- Dataset provides the physicians' actual treatment and prescribing decisions.

- The DSP is a pseudo-random sample. The methodology used (collecting next n consulting patients) aims to reduce the likelihood of selection bias, and the sample should be representative of the consulting population.

- The dataset is an independent data source providing impartiality of data reporting with no set hypotheses at design stage.

- The DSP includes all consulting patients, covering both insured and non-insured patients. Each patient is unique and there is no double-representation.

- Amongst the variables collected, importantly, the DSP specifically includes, via the physician-completed record form, clinical characteristics, the patient's complete treatment history from diagnosis to current day and reasons for prescribing / stopping treatment.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information and Consent

This study is an analysis of secondary data from the Migraine VII DSP. Participating patients in the Migraine VII DSP were treated in accordance with usual medical practice; no additional assessments or tests were conducted in order to participate. Data were collected cross-sectionally at a single point in time and retrospectively for historical information. Patients provided their informed consent prior to completion of the PSC and did not provide any personally identifiable information.

9.2. 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.

The DSP was performed in compliance with the EphMRA Code of Conduct and ARW standard operating procedures.

The Migraine VII DSP was submitted to the Pearl IRB in the US (IRB number: 22-ADRW-143). All data were deidentified and pseudoanonymised.

All study results will be in tabular form and aggregate analyses. As this is an analysis of secondary data, additional informed consent, ethics committee or IRB approval are not required. Any publications and reports will not include subject identifiers.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a database analysis study based on secondary use of data collected for other purposes. No administration of any therapeutic or prophylactic agent was required in this protocol. No reporting of individual case safety reports (ICSRs) ie, adverse events or product quality complaints, to regulatory agencies are required for this database study, as there is no access to individual patient/subject records, it is not possible to assess the causality.

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 (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

A final study report will be prepared describing methods, results, and interpretation of results upon completion of the study (anticipated Q1 2024).

Study results are also intended to be submitted for consideration at a scientific congress and published in a peer-reviewed journal (target congress and journal to be determined). 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.[23]

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.

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

13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

Document Approval Record

Document Name:	C4951066 Adelphi DSP Consistency Study Protocol V2.0_Amendment 1 (clean) 23 April 2024
Document Title:	C4951066 Adelphi DSP Consistency Study Protocol V2.0_Amendment 1 (clean) 23 April 2024

Signed By:	Date(GMT)	Signing Capacity
PPD	02-May-2024 10:59:21	Business Line Approver
PPD	10-May-2024 14:32:44	Contributing Author