NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS INFORMATION

Title	Post-authorisation Safety Study of Rimegepant in Patients with Migraine and History of Cardiovascular Disease in European Countries
Protocol number	C4951017 (formerly BHV3000-408)
Protocol version identifier	Version 3.0
Date	21 August 2024
EU Post Authorization Study (PAS) register number	EUPAS103990 (HMA-EMA Catalogue of RWD Studies: ID 104168)
Active substance	Rimegepant (formerly BHV-3000); ATC code N02CD06
Medicinal product	Nurtec ODT™/Vydura®
Product reference	BHV-3000 (US) EU/1/22/1645 (EU)
Procedure number	EMA/H/C/005725
Marketing authorisation holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No

Research question and objectives	Research question: does the use of rimegepant increase the risk of MACE compared with other treatments for migraine in patients with migraine and history of CVD? The study has 2 primary objectives: 1. To evaluate whether treatment initiation with rimegepant versus treatment with other preventive treatment for migraine (either continuing the current treatment or initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with preventive migraine therapies 2. To evaluate whether treatment initiation with rimegepant versus treatment with other acute treatment for migraine (either continuing the current treatment or initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with acute migraine therapies The study has 1 secondary objective: To describe the patient characteristics of rimegepant initiators with migraine and a history of CVD (including demographics, comorbidities, comedications, and health care utilisation) at the time of rimegepant initiation and to describe their patterns of rimegepant use, including acute, preventive, or both.	
Country(ies) of study	Denmark, the Netherlands, Spain, and the United Kingdom	
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MARKETING AUTHORISATION HOLDER(S)

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2. LIST OF ABBREVIATIONS

Abbreviation	Term
ACE	angiotensin-converting enzyme
ACNU	active comparator new user
AMI	acute myocardial infarction
ATC	Anatomical Therapeutic Chemical Classification System
BMI	body mass index
CGRP	calcitonin gene–related peptide
CHESS	COVID-19 Hospitalisation in England Surveillance System CHMP Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CVD	cardiovascular disease
DM+D	Dictionary of Medicines and Devices
DNHR	Danish National Health Registers
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union electronic Register of Post-authorisation Studies FDA Food and Drug Administration
GBD	Global Burden of Disease Study
GDPR	General Data Protection Regulation
GOLD	General Practitioner Online Database
GP	general practitioner
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HES	Hospital Episode Statistics
HR	hazard ratio
ICD-10	International Classification of Diseases, Tenth Revision
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICPC	International Classification of Primary Care IDIAP
IPTW	inverse probability treatment weight
Jordi Gol	Institute of Research in Primary Care [Institut Universitari D'Investigació en Atenció Primària Jordi Gol], Catalonia, Spain
HMA	Heads of Medicines Agencies
IEC	International Electrotechnical Commission
IRB	institutional review board
IHS	International Headache Society
IRB	institutional review board
ISAC	Independent Scientific Advisory Committee
ISO	International Organization for Standardization
ISPE	International Society for Pharmacoepidemiology

Abbreviation	Term
LAB_F	Register of Laboratory Results for Research
LBZ	Dutch National Basic Hospital Care Registration [Landelijke Basisregistratie Ziekenhuiszorg]
MACE	major adverse cardiovascular event
MAH	marketing authorisation holder
MHRA	Medicines and Healthcare Products Regulatory Agency
NCSP	NOMESCO Classification of Surgical Procedures
NHS	National Health Service
NIHR	National Institute for Health Research
NOMESCO	Nordic Medico-Statistical Committee
NSAID	non-steroidal anti-inflammatory drug
ODT	orally disintegrating tablet
OPCS-4	Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4
PASS	post-authorisation safety study
PHARMO	PHARMO Institute for Drug Outcomes Research
PRAC	Pharmacovigilance Risk Assessment Committee
QC	quality control
RR	risk ratio
RTI-HS	RTI Health Solutions
SAP	statistical analysis plan
SDU	Southern Denmark University
SGSS	Second Generation Surveillance System
SIDIAP	Information System for Research in Primary Care [Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària], Catalonia, Spain
SmPC	summary of product characteristics
SMRW	standardised morbidity ratio weights
SNOMED	Systematized Nomenclature of Medicine
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
UK	United Kingdom
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Post-authorisation Safety Study of Rimegepant in Patients with Migraine and History of Cardiovascular Disease in European Countries

Version 3.0, 21 August 2024

Joan Forns, MPH, PhD

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RTI Health Solutions (RTI-HS), Epidemiology

Rationale and background: Rimegepant is a calcitonin gene–related peptide (CGRP) receptor antagonist developed by Biohaven Pharmaceuticals, Inc. (Biohaven) for the treatment of acute migraine and preventive treatment of episodic migraine. It was approved by the United States (US) Food and Drug Administration (FDA) in February-2020 for the acute treatment of migraine with or without aura in adults and in May-2021 for the preventive treatment of episodic migraine in adults. The European Medicines Agency (EMA) granted approval for rimegepant in the European Union (EU) in April-2022 both for the acute treatment of migraine with or without aura in adults and for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month.

The opinion of the Committee for Medicinal Products for Human Use (CHMP) in the Day 180 review was that *"Patients with cardiovascular diseases should be included as missing information. The applicant should further elaborate on this matter, taking into account the inclusion and exclusion criteria applied in the clinical trials…setting depending on the indication, and if a (theoretical) cardiac risk for Vydura exists."*

As part of the risk management plan for rimegepant in Europe, Pfizer is committed to address the request from the EMA and the Medicines and Healthcare Products Regulatory Agency (MHRA) to conduct a post-authorisation safety study (PASS) to evaluate whether there is an increased risk of major adverse cardiovascular events (MACE) among patients with migraine and history of cardiovascular disease (CVD) initiating treatment with rimegepant compared with that among patients with migraine, with history of CVD, and being treated with other treatments for migraine, either continuing the current treatment or initiating a new one, other than rimegepant. The study will also describe the use of rimegepant in the initial years after approval in the same population.

Research question and objectives: The research question is as follows: does the use of rimegepant increase the risk of MACE compared with other treatments for migraine in patients with migraine and history of CVD?

The study has 2 primary objectives:

1. To evaluate whether treatment initiation with rimegepant versus treatment with other preventive treatment for migraine (either continuing the current treatment or initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with preventive migraine therapies

2. To evaluate whether treatment initiation with rimegepant versus treatment with other acute treatment for migraine (either continuing the current treatment or initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with acute migraine therapies

The study has 1 secondary objective: To describe the patient characteristics of rimegepant initiators with migraine and a history of CVD (including demographics, comorbidities, comedications, and health care utilisation) at the time of rimegepant initiation and to describe their patterns of rimegepant use, including acute, preventive, or both.

Study design: This is a non-interventional population-based prospective cohort study using a prevalent new-user design. The study will be conducted in multiple data sources, comparing patients with treated migraine and a history of CVD who initiate rimegepant to comparator groups of similar patients with migraine and a history of CVD from the same data source. Both the rimegepant and comparator groups will consist of patients who have been treated with other preventive or acute treatment. This study will estimate the cumulative incidence of study outcomes with corresponding 95% confidence intervals (CIs) comparing the rimegepant initiators to the appropriate comparator group (one group of continuators or initiators of a preventive migraine medication and another group of continuators or initiators of an acute migraine medication). The analysis will be conducted separately in each data source, and overall estimates of effect will be obtained using appropriate statistical techniques. Confounding will be addressed primarily by propensity score-based standardised morbidity ratio weights.

Population: The study population will comprise adults with migraine and history of CVD registered in each electronic health care data source who are on treatment with a qualifying acute or preventive migraine medication during the study period.

To be eligible for inclusion into the study populations, patients must have a prescription/ dispensing of rimegepant or a comparator treatment for migraine within the study period, be adults (aged 18 years or older) at the index date, have at least 12 months of data available before the index date, have a diagnosis of migraine any time before or on the index date, and have a CVD diagnosis any time before or on the index date. The index date in the rimegepant groups will be defined as the date in which a patient receives a first prescription/dispensing of rimegepant within the study period and meets all the eligibility criteria. Potential index dates for the comparator groups will be defined as the date on which a patient receives a prescription/dispensing of a qualifying migraine study drug within the study period and meets all the eligibility criteria. In the analysis phase, exposure sets will be created based on the time since first prescription/dispensing of migraine medication identified in the database

any time before the index date. The index date for the comparator groups will be the date of the included comparator prescriptions/dispensings within exposure sets including rimegepant index dates.

Because patients may be used as comparators for multiple rimegepant patients, a single comparator patient may have multiple comparator index dates. Furthermore, rimegepant patients may be used as comparators before their initial rimegepant prescription/ dispensing.

Three groups of rimegepant initiators will be created:

- Initiators of rimegepant among users of preventive medications for migraine (Primary Objective 1)
- Initiators of rimegepant among users of acute medications for migraine (Primary Objective 2)
- Initiators of rimegepant, including acute use, preventive use, or both, regardless of prior treatment (Secondary Objective)

Additionally, 2 comparator groups of other treatments for migraine will be created:

- Users of preventive medications for migraine other than rimegepant, either continuing the current treatment or initiating a new one (Primary Objective 1)
- Users of acute medications for migraine other than rimegepant, either continuing the current treatment or initiating a new one (Primary Objective 2)

Variables: For each of the 2 comparative objectives, different treatment strategies will be compared:

- **Primary Objective 1:** Initiators of rimegepant vs. continuators or initiators of other preventive treatments for migraine in patients on preventive treatment for migraine
  - *Rimegepant initiators:* Patients have a first prescription/dispensing for rimegepant. During follow-up, patients can switch to other preventive migraine therapies or may receive additional treatments for acute episodes of migraine when clinically indicated.
  - *Continuators or initiators of a preventive medication for migraine:* Patients continue or switch to a preventive treatment for migraine other than rimegepant. During follow-up, patients can switch to a different preventive migraine therapy or may receive additional treatments for acute episodes of migraine when clinically indicated.

- **Primary Objective 2:** Initiators of rimegepant vs. continuators or initiators of other acute treatments for migraine in patients on acute treatment for migraine

  - *Initiators of rimegepant:* Patients have a first prescription/dispensing for rimegepant. During follow-up, patients can switch to other acute migraine therapies or may receive additional preventive treatments for migraine when clinically indicated.

  - *Continuators or initiators of an acute medication for migraine:* Patients continue or switch to an acute treatment for migraine other than rimegepant. During follow-up, patients can switch to a different acute migraine therapy or may receive additional preventive treatments for migraine when clinically indicated.

The primary outcome will be MACE and will comprise the first occurrence of any of its individual components during follow-up:

- Hospitalisation for acute myocardial infarction (AMI), fatal or non-fatal
- Hospitalisation for stroke, fatal or non-fatal
- Out-of-hospital coronary heart disease death
- Out-of-hospital cerebrovascular death
- Coronary bypass surgery
- Coronary revascularisation

The secondary outcomes will be the individual components of MACE listed above.

The study will define other variables that will be used to describe the study population and to control for confounding, including demographic variables and lifestyle factors, comorbidities (including migraine), prior treatments for migraine, other comedications, and health care utilisation.

Data sources: The study will be implemented in 4 health care data sources:

- Danish National Health Registers (DNHR) (Denmark)
- PHARMO Database Network (the Netherlands)
- Information System for the Advancement of Research in Primary Care (SIDIAP) (Spain)

- Clinical Practice Research Datalink (CPRD) (United Kingdom [UK])

Study size: Considering a scenario of an IR of MACE ranging between 176.1 and 210.9 per 10,000 patients and having a cohort of patients with > 1 to 5 years after migraine diagnosis, a sample size of 2,500 patients in the rimegepant group would result in a 86% or higher probability that the upper bound of the observed RR would be below 1.8.

Data analysis: Each research partner will conduct analyses separately within each data source, and results will be pooled via meta-analytic methods, if appropriate, at the end of the study. The analysis will comprise 4 different steps: select the study population, assign exposure and define follow-up, describe the study cohorts and patterns of rimegepant use, and estimate exposure propensity scores. Propensity score-based standardised morbidity ratio weights will be used in the comparative analyses. Crude and adjusted incidence rates of MACE with their 95% CIs will be estimated using a Poisson regression model with robust estimation of variance. Cumulative incidence of MACE will be estimated using the Kaplan-Meier estimator for each of the 4 exposure groups. Finally, for each comparison, crude and adjusted RRs and risk differences at various times during follow-up (3, 6, 9, and 12 months) will be estimated using the Kaplan-Meier estimator, and 95% CIs will be derived using bootstrap methods. Adjusted hazard ratios (HRs) will be estimated with a Cox model.

Milestones: The planned milestones for submission to EMA are progress report 1 in 2024, progress report 2 in 2025, the interim report in 2027, and the final report in 2030.

[1] Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are completed.

[2] In the last study country to launch rimegepant.

5. AMENDMENTS AND UPDATES

Protocol version 2.0 was the first version approved by EMA.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V3.0	02 July 2024	Administrative	All sections	Updated to Pfizer protocol template	Study transitioned from Biohaven to Pfizer in 2023
		Substantial	Section 6 Milestones	Updated milestone dates now that rimegepant has launched in all study countries	Milestone dates in protocol V2.0 remained to be determined based on rimegepant launch dates
		Substantial	Section 9.9 Limitations of the Research Methods	Added limitation regarding medication overuse	To address PRAC comment on protocol V2.0
		Substantial	Section 9.7.4 Adjusted Analysis of MACE	Revised to align with SAP V2.0 02 July 2024	SAP V2.0 changed from inverse probability treatment weight (IPTW) to standardised morbidity ratio (SMRW) for main analysis

6. MILESTONES

The study milestones are summarised in Table 1 and Figure 1. Two progress reports will be submitted to the EMA Pharmacovigilance Risk Assessment Committee (PRAC) 1 and 2 years after rimegepant is launched in the last country participating in the study.

Progress reports will include information on the study progress and monitoring of counts of rimegepant users, as reported by the study research partners, and a discussion on the need for additional sources to reach the study size. An interim report will be submitted to the EMA PRAC 3 years after rimegepant is launched in the last country participating in the study. The interim report will include information on the study progress and monitoring of counts of rimegepant users, cohort attrition (Section 9.7.1), descriptive characteristics at baseline (Section 9.7.2), unadjusted analysis of MACE (Section 9.7.3), and drug utilisation analysis (Section 9.7.8). A final recommendation will be provided regarding the need for additional data sources to reach the study size. Additionally, a feasibility assessment of the method to be used to create the “exposure sets” will be performed (Section 9.7.1). The final study report will be submitted to the EMA PRAC

6 years after rimegepant is launched in the last country participating in the study.

Table 1. Study Milestones

Milestone	Planned Date	Comments
EMA protocol endorsement	Feb-2023	23-Feb-2023
Start of data collection[a]	Q3 2026	2.5 years after launch of rimegepant[b]
End of data collection[c]	Q3 2029	5.5 years after launch of rimegepant[b]
Progress report 1	Q4 2024	1 year after launch of rimegepant[b]
Progress report 2	Q4 2025	2 years after launch of rimegepant[b]
Interim report	Q1 2027	3 years after launch of rimegepant[b]
Registration in the EU PAS Register/ HMA-EMA Catalogue of RWD Studies	No later than 6 months after EMA protocol endorsement and before the start of data collection	Registered on EU PAS 24-Mar-2023; transferred to HMA-EMA Catalogue 15-Feb-2024
Final study report	Q1 2030	6 years after launch of rimegepant[b]

EMA = European Medicines Agency; EU PAS = European Union electronic Register of Post-authorisation Studies; SAP = statistical analysis plan.

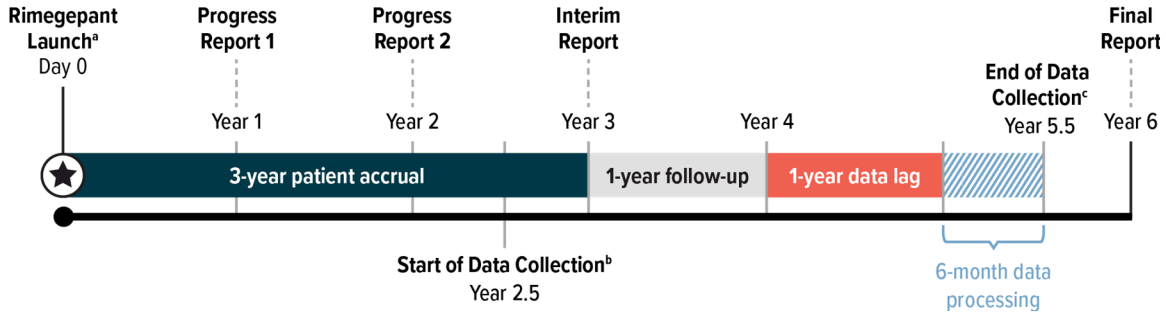
Note: Contracts between the sponsor and research organisation(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are completed.

a Start of data collection is "the date from which information on the first study patient is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" (EMA, 2017).

b In the last study country to launch rimegepant. Spain was the last study country to launch rimegepant (launched 01 January 2024).

c End of data collection is "the date from which the analytical data set is completely available" (EMA, 2017).

Figure 1. Milestones and Timelines



[a] In the last study country to launch rimegepant.

[b] Start of data collection is "the date from which information on the first study patient is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts" (EMA, 2017).

[c] End of data collection is "the date from which the analytical data set is completely available" (EMA, 2017).

7. RATIONALE AND BACKGROUND

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterised by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours (IHS, 2018). Migraine is the seventh highest specific cause of disability worldwide (Petrovski et al., 2018; Stovner et al., 2007; Vos et al., 2012). The global age-standardised prevalence of migraine in 2016 was estimated as 14.4% (95% CI, 13.8%-15.0%), with a higher prevalence among females (18.9%) than males (9.8%) (GBD 2016 Headache Collaborators, 2018). Chronic migraine is described by the International Headache Society (IHS) as a headache that occurs on 15 or more days per month for more than 3 months and that, on at least 8 days per month, has the features of migraine headache (IHS, 2018). The global prevalence of chronic migraine has been estimated to range from 1.4% to 2.2% (Natoli et al., 2010).

Patients with migraine have an increased risk of CVD, specifically coronary disease and stroke. The risk of stroke appears to be higher among patients who experience migraine with aura as well as among women, smokers, and users of oral contraceptives (Adelborg et al., 2018; Schurks et al., 2009). Population cohort studies have shown that patients with migraine also have an increased risk of myocardial infarction, haemorrhagic stroke, venous thromboembolism, and atrial fibrillation or atrial flutter (Adelborg et al., 2018; Kurth et al., 2016).

Per a consensus statement published in 2021 by the Danish Headache Society, which was endorsed by the European Headache Federation and the European Academy of Neurology, the treatments for migraine include treatment for acute migraine in addition to preventive medications. For the treatment of acute migraine episodes, first-line treatments include non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, while the second-line treatments include the triptans (Eigenbrodt et al., 2021). Third-line treatments include ditans

(lasmiditan) and CGRP (ubrogepant and atogepant). For chronic migraine, first-line preventive treatments include beta-blockers without intrinsic sympathomimetic activity (atenolol, bisoprolol, metoprolol, or propranolol), topiramate, and candesartan (Eigenbrodt et al., 2021). Second-line preventive treatments include flunarizine, sodium valproate, and amitriptyline. Third-line treatments are CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab).

Rimegepant, a CGRP receptor antagonist developed by Biohaven, was approved by the FDA in Feb-2020 for the acute treatment of migraine with or without aura in adults and in May-2021 for the preventive treatment of episodic migraine in adults (FDA, 2021; Nurtec ODT PI, 2020). The European Commission granted the marketing authorisation for rimegepant in the EU in Apr-2022 both for the acute treatment of migraine with or without aura in adults and for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month (EMA, 2022; Vydura SmPC, 2022). The opinion of the CHMP in the Day 180 review was that "*patients with cardiovascular diseases should be included as missing information. The applicant should further elaborate on this matter, taking into account the inclusion and exclusion criteria applied in the clinical trials…setting depending on the indication, and if a (theoretical) cardiac risk for Vydura exists.*"

As part of the risk management plan for rimegepant in Europe, Pfizer is committed to address the request from the EMA to conduct a PASS to evaluate whether there is an increased risk of MACE among patients with migraine and history of CVD initiating treatment with rimegepant compared with patients with migraine and history of CVD who are on other treatments for migraine, either continuing the current treatment or initiating a new one, other than rimegepant. The study will also describe the use of rimegepant in the initial years after approval in the same population.

This noninterventional study is designated as a PASS and is a commitment to EMA.

8. RESEARCH QUESTION AND OBJECTIVES

The research question is as follows: Does the use of rimegepant increase the risk of MACE compared with other treatments for migraine in patients with migraine and history of CVD who have been recently treated for migraine?

The study has 2 primary objectives:

1. To evaluate whether treatment initiation with rimegepant versus treatment with other preventive treatment for migraine (either continuing the current treatment or initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with preventive migraine therapies

2. To evaluate whether treatment initiation with rimegepant versus treatment with other acute treatment for migraine (either continuing the current treatment or

initiating a new one) increases the risk of MACE in patients with migraine, with history of CVD, and who are being treated with acute migraine therapies

The study has 1 secondary objective: To describe the patient characteristics of rimegepant initiators with migraine and a history of CVD (including demographics, comorbidities, comedications, and health care utilisation) at the time of rimegepant initiation and to describe their patterns of rimegepant use, including acute, preventive, or both.

9. RESEARCH METHODS

9.1. Study Design

This is a non-interventional population-based prospective cohort study using a prevalent new-user design. The study will be conducted in multiple health care data sources, comparing patients with treated migraine and a history of CVD who initiate rimegepant with comparator groups of similar patients with migraine and a history of CVD who continue their migraine treatment with other drugs (i.e., either continuing the current treatment or initiating a different treatment). Both the rimegepant and comparator groups will consist of patients who have been treated with other preventive or acute medications for migraine before starting treatment with rimegepant or a comparator.

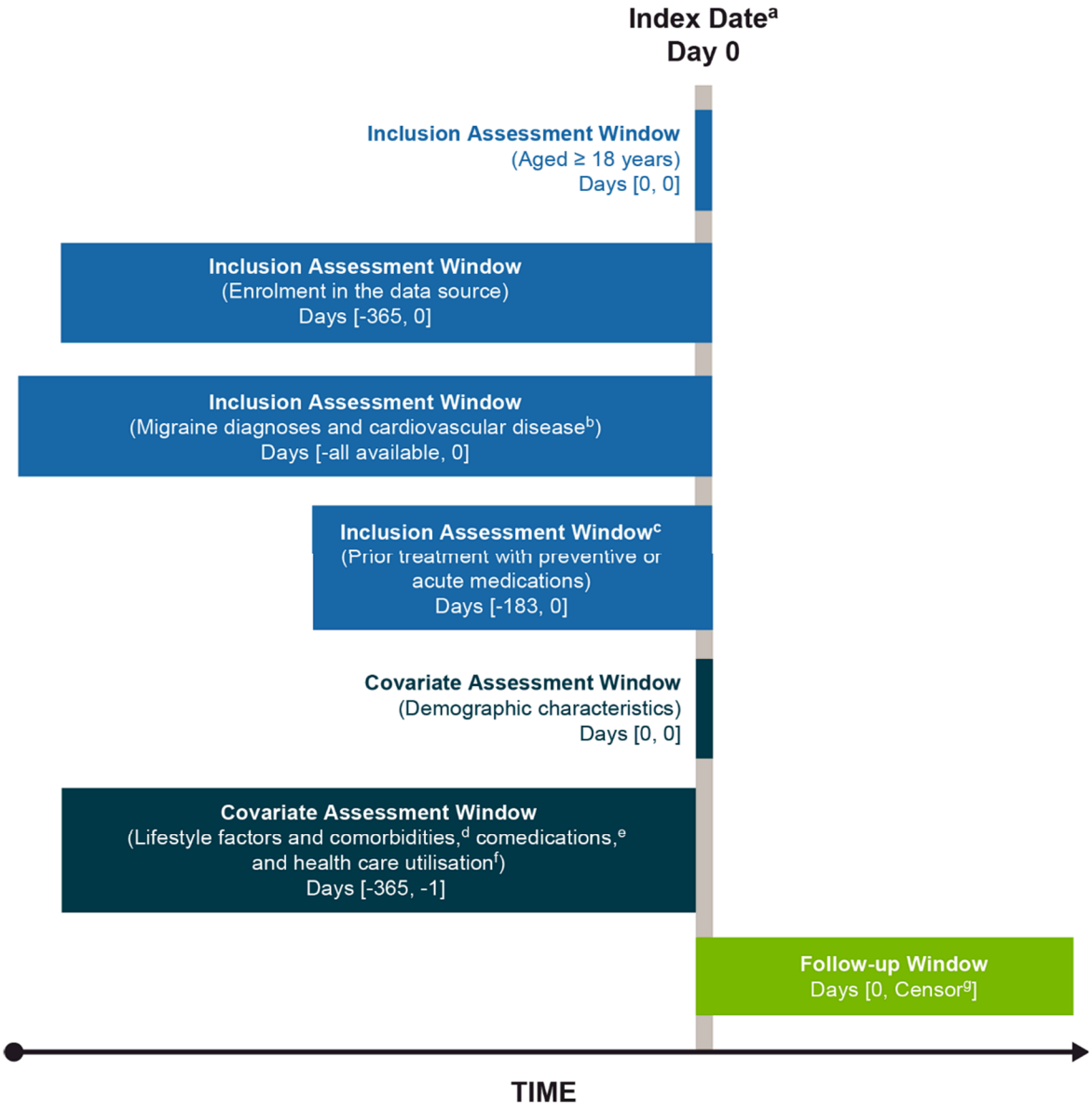
Because rimegepant can be used for both acute and preventive treatment, the primary objectives will be achieved via 2 sets of comparisons:

- A group of patients with migraine and a history of CVD who are treated with medications for the **prevention** of migraine and who initiate rimegepant will be compared with a group of similar patients with migraine and a history of CVD who are treated with other medications for **preventive** treatment of migraine, either continuing the current treatment or initiating a different preventive treatment other than rimegepant.

- A group of patients with migraine and a history of CVD who are treated with medications for the **acute** treatment of migraine and who initiate rimegepant will be compared with a group of similar patients with migraine and a history of CVD who are treated with other medications for **acute** treatment of migraine, either continuing the current treatment or initiating a different acute treatment other than rimegepant.

An overview of the study design is depicted in Figure 2.

Figure 2. Design Diagram Illustrating Cohort Eligibility and Variables Ascertainment Windows



Note: The figure is based on examples provided in Schneeweiss et al. (2019).

[a] The index date in the rimegepant groups will be defined as the date on which a patient receives a first prescription/dispensing of rimegepant within the study period and meets all the eligibility criteria. The index date in the comparator groups will be identified in the analysis phase as the date of the comparator therapy prescription/dispensing that meets all eligibility criteria and corresponds to the rimegepant prescription/ dispensing of the exposure set. Patients in the comparator group may have more than 1 index date if they have more than 1 eligible prescription/dispensing used in different exposure sets.

[b] History of transient cerebral ischaemic attack, stroke, myocardial infarction, acute coronary syndrome, unstable angina, percutaneous coronary intervention, or cardiac bypass surgery at any time before the index date.

[c] Inclusion assessment window applied to Primary Objectives 1 and 2 (Section 8).

[d] Chronic cardiovascular disease, hypertension, diabetes mellitus (severity and complications), hyperlipidaemia, lifestyle cardiovascular disease risk factors (smoking, obesity), stage of chronic kidney disease, other kidney disorders, liver disease, chronic obstructive pulmonary disease, and Charlson Comorbidity Index score.

[e] Cardiovascular medications (antihypertensives, cholesterol-lowering medications, anticoagulants, aspirin and other antiplatelets [e.g., clopidogrel, ticlopidine, prasugrel], digoxin, and nitrates), anti-inflammatory drugs, antibiotics, and other medications (paracetamol, anticonvulsants, antifungals, antituberculars, and chemotherapeutic agents).

[f] General practitioner visits, hospital visits, hospitalisations, specialist visits, and emergency department visits.

[g] Censored at the earliest of death, disenrolment, occurrence of the individual components of the MACE outcome, loss to follow-up, 365 days after initiating rimegepant or comparator, or end of the study period. In addition, patients in the comparator group will be censored if they initiate rimegepant during follow-up. Note that patients in the comparator groups can be in more than 1 group at any given time based on the index medication start date. Patients in the rimegepant groups will not be eligible to enter any other exposure group.

9.1.1. Rationale for Choice of Study Design

Persistence with migraine preventive therapy seems to be low, and switching medications or restarting after treatment discontinuation is common among patients with migraine (Eigenbrodt et al., 2021; Hepp et al., 2017). The use of acute treatments while on preventive treatment is often applied concomitantly for breakthrough migraines (Woolley et al., 2017). Rimegepant represents a new and unique therapeutic option that may be used for the acute or preventive treatment of migraine, or both (Vydura SmPC, 2022). As a new marketed drug for the treatment of migraine, it is anticipated that individuals initiating rimegepant will have previously used other migraine medications and that this drug will primarily be targeted to patients whose migraines are poorly controlled by other regimes. To address the research question of interest in the present study (i.e., Does the use of rimegepant increase the risk of MACE compared with other treatments for migraine in patients with migraine and history of CVD who have been recently treated for migraine?), a prevalent new-user design is considered more suitable than a more traditional active comparator new user (ACNU) design. The ACNU design addresses a different research question than that articulated in the present study: “Does the use of rimegepant increase the risk of MACE in patients initiating rimegepant vs. comparators among patients with migraine and history of CVD not previously treated with other drugs for migraine?”. Moreover, an ACNU design would require new users (i.e., individuals with no previous use of rimegepant or its comparator), thus potentially excluding a large number of patients who receive rimegepant in clinical practice by applying a washout period of no use. Additionally, the use of an ACNU design would potentially include a selected group of patients with mild migraine and a short history of recent treatments, thus reducing the generalizability of study results.

The prevalent new-user design addresses the present study research question and will allow for the inclusion of the large majority of rimegepant users by including patients with prior migraine treatment.

Exposure Sets

To control for the possible confounding by indication and healthy-user bias caused by including patients in both groups with prior history of migraine treatments, initiators of the

treatment of interest (i.e., rimegepant) will be matched to comparators on time since initiating migraine treatment, thereby forming exposure sets. Accordingly, exposure sets control for time since the first prescription/dispensing of migraine medications (proxy for disease duration) and past treatment history (i.e., confounding by indication). To reduce the risk of healthy-user bias, additional propensity score standardized morbidity ratio (SMR) weighting techniques will be used to control for confounders. Overall, the use of exposure sets within the prevalent- new user design has been considered a valid method to conduct a cohort study and to control for confounding (Suissa et al., 2017; Webster-Clark et al., 2021).

An alternative method to create the exposure sets would be to match initiators of rimegepant to comparators on the total number of prescriptions/dispensings of prior migraine treatments. A feasibility assessment to determine the most suitable method (either matching patients on time since the first prescription/dispensing of migraine medications or the total number of prior prescriptions/dispensings of migraine medications) will be conducted during the interim analysis and presented in the interim report. The selected method will be applied in the final study analyses (see Section 6).

9.2. Setting

The study population will include adults with migraine (Section 9.3.3.1) and history of CVD (Section 9.3.3.2) registered in each electronic health care data source who are on treatment with a qualifying acute or preventive migraine medication (Table 3) during the study period.

The **index date in the rimegepant groups** will be defined as the date on which a patient receives a first prescription/dispensing of rimegepant within the study period and meets all of the eligibility criteria.

The **index date in the comparator groups** will be the date on which an individual patient receives a prescription/dispensing of a qualifying comparator migraine study drug (Table 3) within the study period in which all eligibility criteria are met. This date is also the date on which an individual is identified with a rimegepant index date with the same time since first prescription/dispensing of migraine medication (Figure 3 and Table 2).

These sets of rimegepant and comparator patients will comprise the exposure sets (further details are provided in Section 9.7.1).

Per the prevalent new-user design (Webster-Clark et al., 2022), patients in the comparator groups may contribute multiple **comparator index dates.** An individual comparator patient may have multiple qualifying index dates, thereby serving as comparators for multiple individual rimegepant patients. Furthermore, individual rimegepant patients may serve as comparators before their initial rimegepant prescription/dispensing (Figure 3).

Figure 3 provides an overview graphic of the creation of exposure sets. This overview graphic is based on Table 2, which provides fictionalised simple examples to illustrate how index dates and exposure sets are formed. In this hypothetical example, a simple database with 5 patients is created:

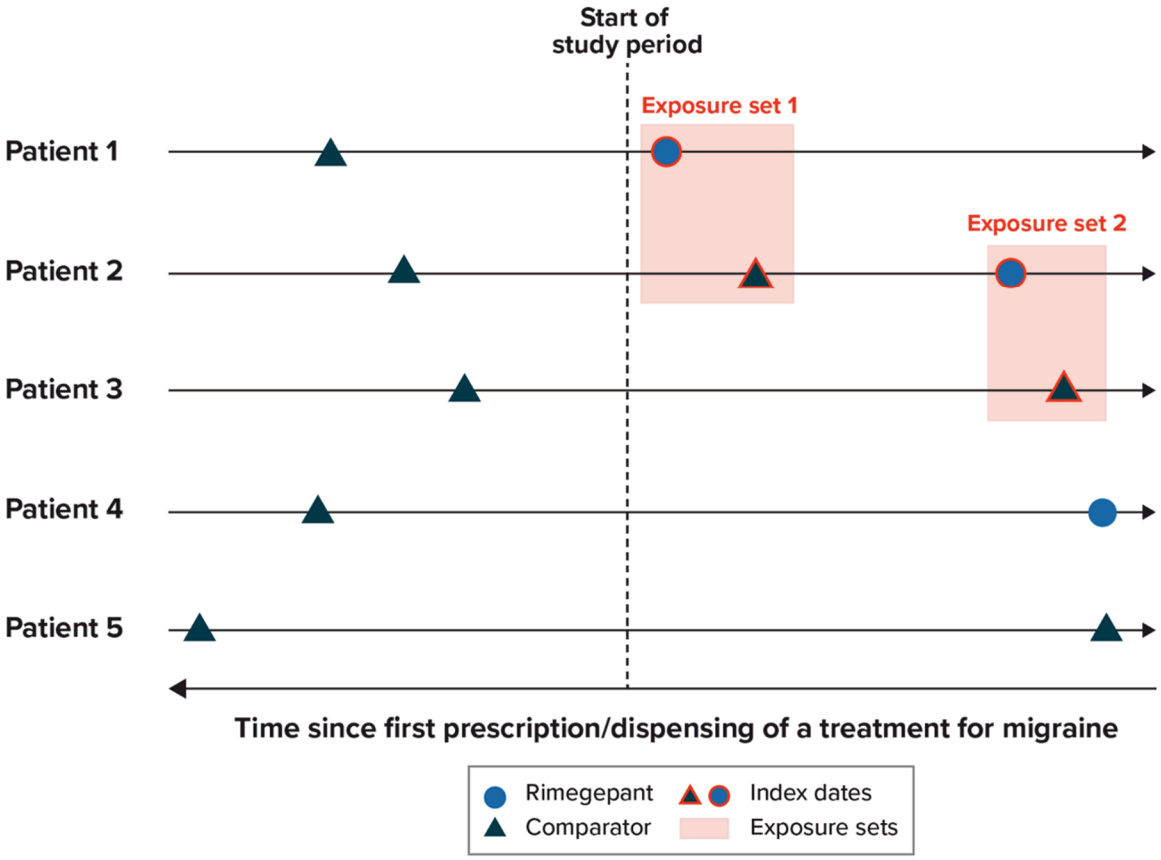
- Patient 1 initiates rimegepant within the study period after 2 years since first prescription/dispensing of migraine treatment and meets the eligibility criteria. This patient will be in the same exposure set as any comparator or rimegepant user who has 2 years since the first prescription/dispensing of migraine treatment in the database. In this example, patient 2 will be in the same exposure set as patient 1 because they initiate a comparator treatment within the study period 2 years since the first prescription/dispensing of a migraine treatment and meet all eligibility criteria.

- Patient 2 has a subsequent prescription for rimegepant 1 year after the prescription for a comparator drug that allowed entry into the exposure set 1. This subsequent rimegepant prescription occurred 3 years after the first prescription/dispensing of migraine treatment in the database. Therefore, this subsequent prescription will be in the same exposure set as any comparator or rimegepant after 3 years since the first prescription/dispensing of migraine treatment. In this case, patient 3 will be in the same exposure set. Patient 3 has a comparator prescription within the study period and 3 years since the first prescription/dispensing of migraine treatment. Note that patient 2 has entered the study twice: first as a comparator in exposure set 1 and later as a rimegepant user in exposure set 2.

- For patients 4 (rimegepant) and 5 (comparator), there are no other patients with the same time since migraine treatment start; thus, these patients would not be included in the analyses.

Further details about how the exposure sets will be created and defined in the SAP.

Figure 3. Example Patient Index Dates and Exposure Sets Creation



Note: The figure assumes that the eligibility criteria described in Sections 9.2.1 and 9.2.2 have been met and that all patients in each exposure set had the same time since the first prescription/dispensing of migraine medication identified in the database any time before the index date. The method used to define the exact time since first prescription/dispensing medication to create the exposure sets will be further described in the study SAP. Additionally, an alternative method to create the exposure sets (total number of prior prescriptions/dispensings of treatments for migraine) will be evaluated in the interim report. The results of this feasibility assessment will determine the final method to be used to create the exposure sets for the final analysis.

Table 2. Example Patient Index Dates and Exposure Sets Creation Based on the Example Provided in Figure 3

Patient ID	Potential Index Dates	Drug	Date of the First Treatment for Migraine in the Data Source	Time in Years Since Migraine Treatment Start	Exposure Set
1	1 February 22	Rimegepant	1 February 20	2	1
2	1 April 22	Comparator	1 April 20	2	1
2	1 April 23	Rimegepant	1 April 20	3	2
3	1 May 23	Comparator	1 May 20	3	2

Table 2. Example Patient Index Dates and Exposure Sets Creation Based on the Example Provided in Figure 3

Patient ID	Potential Index Dates	Drug	Date of the First Treatment for Migraine in the Data Source	Time in Years Since Migraine Treatment Start	Exposure Set
4	1 June 23	Rimegepant	1 June 19	4	None
5	1 June 23	Comparator	1 June 19	5	None

ID = identifier.

Note: Assuming that the eligibility criteria are fulfilled and the study start was on 01-Jan-2022. The method used to define the exact time since first prescription/dispensing of migraine medication to create the exposure sets will be further described in the study SAP. Additionally, an alternative method to create the exposure sets (total number of prior prescriptions/dispensings of treatments for migraine) will be evaluated in the interim report. The results of this feasibility assessment will determine the final method to be used to create the exposure sets for the final analysis.

9.2.1. Inclusion Criteria

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

- Receive a prescription/dispensing of a qualifying migraine study drug (Table 3) within the study period
- Are aged 18 years or older at the index date
- Have a minimum of 12 months of continuous enrolment in the database before the index date
- Have a diagnosis of migraine that meets the criteria in Section 9.3.3.1 and is recorded any time before or on the index date
- Have a diagnosis of CVD that meets the criteria in Section 9.3.3.2 and is recorded any time before or on the index date

Table 3. Qualifying Migraine Study Drugs

Medication Groups and Categories	Medication (ATC Code)[a]	Type of Migraine Treatment
Rimegepant group		
CGRP antagonist	▪ Rimegepant (N02CD06)	Acute and preventive treatment
Comparator groups		
Acute treatments for migraine		
Triptans	▪ Almotriptan (N02CC05)	Acute treatment
	▪ Eletriptan (N02CC06)	
	▪ Frovatriptan (N02CC07)	
	▪ Naratriptan (N02CC02)	
	▪ Rizatriptan (N02CC04)	
	▪ Sumatriptan (N02CC01)	
	▪ Zolmitriptan (N02CC03)	
Ditans	▪ Lasmiditan (N02CC08)	Acute treatment
Ergots	▪ Dihydroergotamine (N02CA01)	Acute treatment
	▪ Ergotamine (N02CA02)	
Preventive treatments for migraine		
Beta-blockers	▪ Atenolol (C07AB03)	Preventive treatment
	▪ Bisoprolol (C07AB07)	
	▪ Metoprolol (C07AB02)	
	▪ Nadolol (C07AA12)	
	▪ Propranolol (C07AA05)	
Angiotensin II–receptor blocker	▪ Candesartan (C09CA06)	Preventive treatment
or ACE inhibitors	▪ Lisinopril (C09AA03)	
Anticonvulsant	▪ Topiramate (N03AX11)	Preventive treatment
	▪ Sodium valproate (N03AG01)	
Tricyclic antidepressant	▪ Amitriptyline (N06AA09)	Preventive treatment
Calcium antagonist	▪ Flunarizine (N07CA03)	Preventive treatment
Botulinum toxin	▪ Onabotulinumtoxin A (M03AX01)	Preventive treatment

ACE = angiotensin-converting enzyme; ATC = Anatomical Therapeutic Chemical Classification System; CGRP = calcitonin gene–related peptide.

a Includes fixed-dose combinations of available medications. The medication list will be updated during the study as appropriate.

The following additional medications approved for the treatment of migraine will not be included in the comparator group:

- NSAIDs and paracetamol will not be included in the comparator group because they are over-the-counter medications, and information on over-the-counter medication use is not captured in the selected data sources. Additionally, these medications are considered first-line treatments for acute migraine treatment; thus, the patient profiles may be different for patients receiving these medications (i.e., milder severity) than for those initiating rimegepant, which is recommended as second-line or third-line treatment. Finally, these medications are commonly used for conditions other than migraine.

- Other CGRP antagonists (e.g., ubrogepant, atogepant) are not included among the qualifying study medications because they belong to the same class as rimegepant and may have a similar safety profile. However, they will be considered as part of a patient's prior history of use of acute migraine medications.

- The CGRP monoclonal antibodies will not be included among the qualifying migraine study medications for the comparator group because they are injectable medications with longer half-lives than rimegepant. Because these are third-line injectable treatments for the preventive treatment of migraine, the profiles of patients receiving these medications may be different (i.e., greater migraine severity) from those of patients initiating rimegepant. Additionally, these medications likely share a similar safety profile with rimegepant. However, they will be considered as part of a patient's prior history of use of preventive migraine medications.

9.2.2. Exclusion Criteria

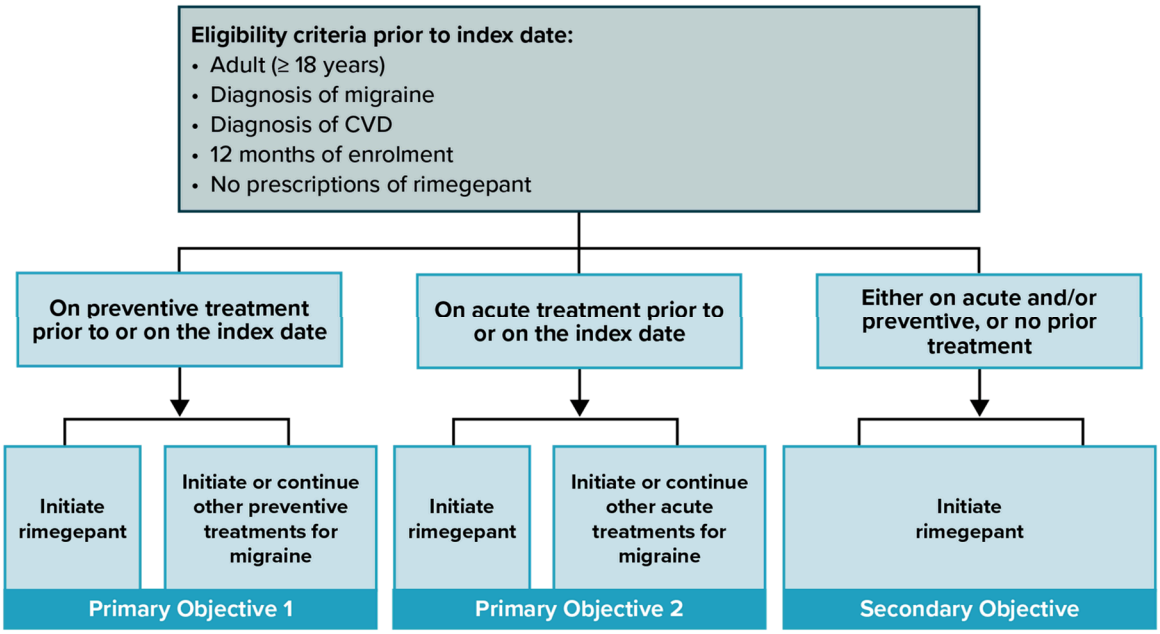
Patients meeting any of the following criteria will not be included in the study:

- Prescriptions/dispensings of rimegepant recorded before the index date.

9.2.3. Assignment of Patients in the Different Comparisons Populations

After the eligibility criteria are fulfilled, patients will contribute to different populations as described in the following subsections (Figure 4).

Figure 4. Study Groups



CVD = cardiovascular disease.

Preventive Treatment Comparison

This population will be used for primary objective 1. After the eligibility criteria are met, patients will be classified in the rimegepant or preventive comparator group as follows:

- Rimegepant group: Patients receiving a first prescription/dispensing of rimegepant within the study period having received treatment with a preventive medication for migraine other than rimegepant (Table 3) within the last 6 months before or on the index date. Additionally, patients may be included who have received treatment with CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, or eptinezumab) within the last 6 months before the index date.

- Preventive Comparator Group: Patients with a prescription/dispensing for a preventive treatment for migraine within the study period who have received treatment with a preventive medication for migraine, other than rimegepant (Table 3) within the last 6 months before or on the index date. Patients may be included who have received treatment with CGRP monoclonal antibodies within the last 6 months before the index date.

Acute Treatment Comparison

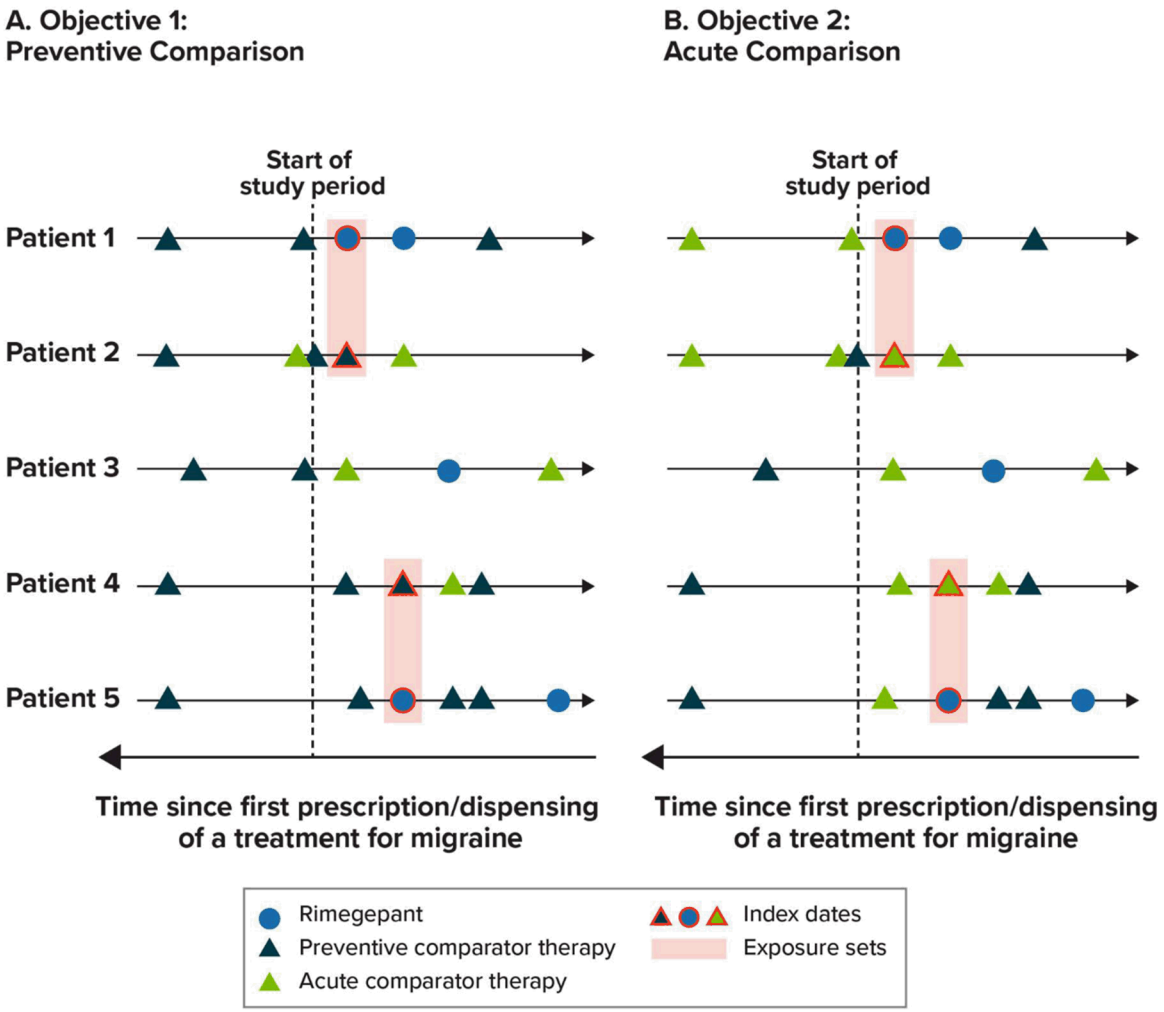
This population will be used for primary objective 2. After the eligibility criteria are met, patients will be classified in the rimegepant or acute comparator group as follows:

- Rimegepant group: Patients receiving a first prescription/dispensing of rimegepant within the study period having received treatment with an acute medication for migraine other than rimegepant (Table 3) within the last 6 months before or on the index date. Additionally, patients may be included who have received treatment with other CGRP antagonists (ubrogepant or atogepant) within the last 6 months before the index date.

- Acute Comparator Group: Patients with a prescription/dispensing for a preventive migraine treatment within the study period who have received treatment with a preventive medication for migraine other than rimegepant (Table 3) within the last 6 months before or on the index date. Additionally, patients may be included who have received treatment with other CGRP antagonists (ubrogepant or atogepant) within the last 6 months before or on the index date.

Figure 5 provides an overview graphic of the assignment of patients to the different populations.

Figure 5. Graphic Overview of the Assignment of Patients to the Preventive and Acute Migraine Comparisons Populations



Note: The figure assumes that the eligibility criteria described in Sections 9.2.1 and 9.2.2 have been met and that all patients in each exposure set had the same time since first prescription/dispensing of migraine medication identified in the database any time before the index date. The method used to define the exact time since first prescription/dispensing medication to create the exposure sets will be further described in the study SAP. Additionally, an alternative method to create the exposure sets (total number of prior prescriptions/dispensings of migraine treatments) will be evaluated in the interim report. The results of this feasibility assessment will determine the final method used to create the exposure sets

Because patients may be treated for migraine for long periods, they may be eligible as participants more than once during the study period as follows:

- Patients starting treatment with rimegepant will not be able to enter the comparator groups after the rimegepant prescription/dispensing.

  - However, patients receiving rimegepant may be used as comparators before their initial rimegepant prescription/dispensing.

- Patients in the comparator groups will be allowed to switch to the rimegepant groups if they start treatment with rimegepant. They may therefore be assigned to different exposure groups (addressing primary objective 1 and/or objective 2) with different corresponding index dates, provided that the eligibility criteria continue to be met.

  - The study groups for each study objective will not be mutually exclusive. For example, patients in the rimegepant group for primary objective 2 may include patients who are in the comparator group for primary objective 1.

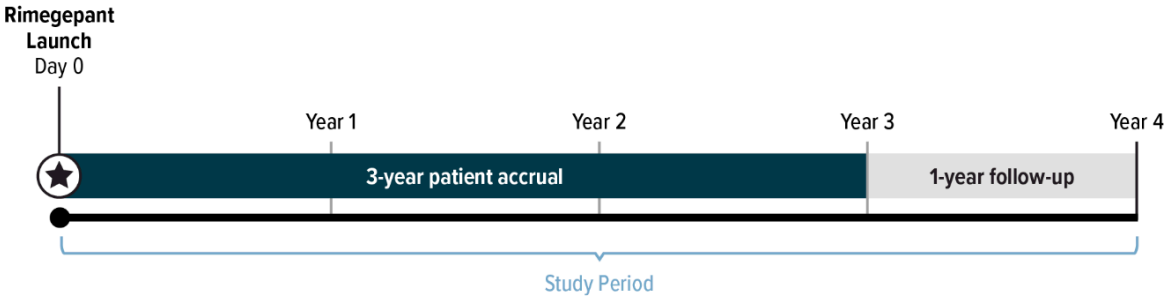
Drug Utilisation Study

All patients starting treatment with rimegepant, regardless of prior migraine treatments, will be included. This population will be used for the secondary objective, including acute use, preventive use, or both.

9.2.4. Study Period

The study period start is defined in each data source as the time of rimegepant launch in each country. Patient accrual is planned to extend for 36 months (3 years) from the launch date of rimegepant in each country, followed by a minimum of 1 year of additional follow-up (Figure 6).

Figure 6. Study Period



Due to differences in the frequency with which data are updated at each data source and lag times for data availability, the exact study period end date may differ across data sources at the time of data extraction.

9.2.5. Follow-up

Patient follow-up time starts the day after the index date and ends at the diagnosis of the first event of interest or when 1 of the following censoring events occurs:

- End of the study period
- Disenrolment from the database or migration
- Death
- 365 days[1] after the index date with rimegepant or comparator
- Lost to follow-up (after index date, 6 months without a recorded visit to the general practitioner [GP] or hospital specialist or prescription/dispensing for any other drug)
- Initiation of treatment with rimegepant (only applicable to the comparator groups)

9.3. Variables

9.3.1. Exposures

For primary objectives 1 and 2, the following treatment strategies will be compared:

[1] The rationale for the specific length of follow-up (365 days) is built on several considerations. First, no treatment episodes will be estimated due to the lack of rimegepant use indication (i.e., no information on whether rimegepant is used for acute or preventive migraine treatment). Second, in the absence of treatment episodes, follow-up will be considered as time at risk. In other words, a patient will be considered exposed from the day on which they start treatment with rimegepant and up to the end of follow-up (365 days) in the absence of a censoring event. Any MACE event occurring during follow-up will be considered as occurring during treatment. Third, the 365-day length of follow-up after index date was based on the duration of the long-term safety open-label extension studies conducted for rimegepant (Vydura SmPC, 2022). This follow-up duration should be sufficient to capture possible acute and delayed CVD effects associated with rimegepant exposure. The analytical strategy proposed will evaluate whether any CVD risk associated with rimegepant varies over time by estimating relative and absolute risks at 3, 6, 9, and 12 months. Additionally, a sensitivity analysis has been included to evaluate the effect of increasing the follow- up to all available time and thus looking for a possible delayed CVD risk associated with rimegepant exposure (Section 9.7.6). A second sensitivity analysis has been included that reduces the follow-up period to 6 months, thus avoiding classification of events as associated with rimegepant when occurring several months after possible treatment discontinuation (Section 9.7.6). This sensitivity analysis will also confirm the consistency of the primary study analysis.

- **Primary Objective 1:** Initiators of rimegepant vs. continuators or initiators of other **preventive** treatments for migraine in patients on preventive treatment for migraine

  - *Rimegepant initiators:* Patients have a first prescription/dispensing for rimegepant. During follow-up, patients can switch to other preventive migraine therapies or may receive additional treatments for acute episodes of migraine when clinically indicated.

  - *Continuators or initiators of a preventive medication for migraine:* Patients continue or switch to a preventive treatment for migraine other than rimegepant (Table 3). During follow-up, patients can switch to a different preventive migraine therapy or may receive additional treatments for acute episodes of migraine when clinically indicated, with the exception of rimegepant.

- **Primary Objective 2:** Initiators of rimegepant vs. continuators or initiators of other **acute** treatments for migraine in patients on acute treatment for migraine

  - *Initiators of rimegepant:* Patients have a first prescription/dispensing for rimegepant. During follow-up, patients can switch to other acute migraine therapies or may receive additional preventive treatments for migraine when clinically indicated.

  - *Continuators or initiators of an acute medication for migraine:* Patients continue or switch to an acute treatment for migraine other than rimegepant (Table 3). During follow-up, patients can switch to a different acute migraine therapy or may receive additional preventive treatments for migraine when clinically indicated, with the exception of rimegepant.

The exposure to rimegepant and other treatments for migraine will be identified by prescription/dispensing information as recorded in each data source (see Table 5 in Section 9.4).

Time at risk will start after the index date and will be up to 1 year (Section 9.2.5).

9.3.1.1. Patterns of Rimegepant Use During Follow-up

To achieve the Secondary Objective, the following outcomes will be evaluated:

- Total number of rimegepant prescriptions/dispensings per patient during the study period and average per year.
- Total number of rimegepant days' supply.
- Duration of continuous treatment: defined as the number of days with continuous use of rimegepant (with prescription/dispensing gaps of less than 30 days).
- Discontinuation of treatment: defined as 30 days after the end of the rimegepant treatment episode.
- Discontinuation of rimegepant with switching to other medications for migraine: defined as the start of a different treatment for migraine anytime between a rimegepant prescription/dispensing date and 30 days after the end of the rimegepant treatment episode. Migraine medications considered are included in Table 3, and other CGRP antagonists (ubrogepant and atogepant) and monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) will be included.
- Concomitant use of other medications for migraine: defined as the use of other treatments for migraine included in Table 3 during the rimegepant treatment episode. In addition, prescribed/dispensed other CGRP antagonists (ubrogepant and atogepant) and monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) will be included.

The duration of episodes of treatment with rimegepant (or comparator medications to define concomitant use of other medications and switching) will be estimated based on days' supply as recorded in all prescriptions/dispensings in each data source. When days'supply is not directly provided, this information will be estimated from other information, such as the amount prescribed/dispensed and the defined daily dose (not yet defined by the World Health Organization [WHO]) or numeric daily dose (dosing instructions), the number of individual product packs prescribed, and the pack type or size.

Estimation of the treatment episodes will be performed with the sole purpose of characterising the rimegepant patterns of use based on uncertainties regarding the actual indication and intake (see Section 9.9).

The population used to address the secondary objective will include acute or preventive use of rimegepant, or both.

9.3.2. Outcomes

9.3.2.1. Major Adverse Cardiovascular Events

Major adverse cardiovascular events are the primary outcome and will be defined as the first occurrence of any of its individual components during follow-up:

- Hospitalisation for AMI, fatal or non-fatal
- Hospitalisation for stroke, fatal or non-fatal
- Out-of-hospital coronary heart disease death
- Out-of-hospital cerebrovascular death
- Coronary bypass surgery
- Coronary revascularisation

The secondary outcomes will be the individual components of MACE listed above.

The composition of the MACE events was selected based on previous studies showing that ischaemic heart disease and cerebrovascular disease are potential risks associated with migraine (Adelborg et al., 2018; Kurth et al., 2007; Kurth et al., 2006; Kurth et al., 2010; Kurth et al., 2016; Rambarat et al., 2017; Schurks et al., 2009). Ischaemic coronary and stroke events were also included in the MACE outcome analysed as a primary outcome in the meta-analysis by Mahmoud et al. (2018), which investigated the association of migraine with the risk of cardiovascular and cerebrovascular events. In that meta-analysis, all-cause mortality was added as outcome (Mahmoud et al., 2018). In the present study, out-of-hospital coronary heart disease and cerebrovascular deaths have been added in the MACE outcome definition. This approach has proven feasible and was validated in previous studies conducted in CPRD (Arana et al., 2021). In the MACE outcome definition, several methodological considerations relevant to the definition of combined outcomes are considered: 1) the components of the composite outcome must be of similar clinical importance to patients; 2) the frequency of the occurrence of the components over the same time period must be similar; and 3) the effect of the treatment must be similar for each component of the composite (Palileo-Villanueva and Dans, 2020).

Case Identification

To identify events of interest during follow-up, each data source will be searched for electronic codes that indicate potential occurrences of outcomes. Events will be identified through hospital discharge diagnoses, procedural codes, primary care diagnoses, and cause-of-death records from the cause-of-death registries. A case-finding algorithm in which cases are identified based on a combination of relevant codes for diagnoses and procedures will be developed and adapted to each data source. This algorithm will be based on published and validated case-finding algorithms to maximise sensitivity of case ascertainment while selecting those with a high positive predictive value (Andrade et al., 2012; Arana et al., 2021;

Lo Re et al., 2017; McCormick et al., 2014). A preliminary list of *International Classification of Diseases, Tenth Revision* (ICD-10) codes to be included in the algorithms to identify each of the components of MACE is displayed in Table 4.

Hospitalisation for AMI or stroke will be identified based on the presence of a hospitalisation with a primary or secondary hospital discharge code for AMI or stroke, as appropriate. These events will be considered fatal if the patient died within 30 days after the admission or event date, irrespective of the cause and place of death.

Out-of-hospital coronary heart disease death (including sudden cardiac death) and out-of-hospital cerebrovascular death include death events from a cardiovascular or cerebrovascular cause before reaching the hospital. These events will be identified through any out-of-hospital death record with an underlying cause of death recorded on the death certificate, in the absence of a code for a terminal illness or end- of-life care in the death certificate. The out-of-hospital death outcome will also include death events that occur outside a hospital setting but within 30 days after a hospitalisation for a cardiovascular or cerebrovascular event and that will be identified through a record of out-of-hospital death occurring outside a hospital setting within 30 days after a hospitalisation (admission or event date) for AMI or stroke, irrespective of the cause of death. A fatal event is defined as such if it occurs within 30 days of the hospitalisation event. This definition has been included in previous studies conducted in CPRD and other data sources, and the algorithms have been validated (Arana et al., 2021; Ruigómez et al., 2021).

Coronary bypass surgery or coronary revascularisation will be identified based on the presence of procedural codes identifying the event, as appropriate in each data source. Other studies have also shown high positive predictive values for revascularisation codes in claims data and electronic health records (Derington et al., 2020; Lee et al., 2013).

Table 4. Case-finding Codes for Each Outcome Included in the MACE Outcome

MACE Component	ICD-10 Codes	References
Hospitalisation for AMI	I21	Joensen et al. (2009); Pajunen et al. (2005)
Hospitalisation for stroke	I60, I61, I63, I64, H34.1	Krarup et al. (2007); Kokotailo and Hill (2005);
		Kirkman et al. (2009); Flynn et al. (2010); Andrade et al. (2012)
Out-of-hospital coronary heart disease death	I10, I11.9, I20-I25, I42.8- I42.9, I46, I47.0, I47.2, I49.0, I49.8-I49.9, I51.6, I51.9, I70.9, R96.1, R98	Chung et al. (2010)

Out-of-hospital cerebrovascular death	I60-I69, R96.0, R96.1, R98	Muller-Nordhorn et al. (2008); Inghammar et al. (2016); Svanström et al. (2013)
Coronary bypass surgery	Z95.1	Heiskanen et al. (2016)
Coronary revascularisation	Z95.5	Heiskanen et al. (2016)

AMI = acute myocardial infarction; ICD-10 = *International Classification of Diseases, Tenth Revision*; MACE = major adverse cardiovascular event.

Note: All nested codes will be included in the corresponding definition (e.g., I21.1 and I21.2 will be used for identifying hospitalisation for AMI). All codes presented in this table will be mapped to other coding systems used in the study data sources before the start of data analysis.

Validation of the MACE outcome via medical record review is not feasible in PHARMO or SIDIAP; stringent ethics requirements in Denmark make it challenging although validation efforts have been performed in the past years (Schmidt et al., 2015). In CPRD, validation via GP questionnaires could be implemented, but response rates are very low at present. Therefore, validation of MACE is not planned. However, the positive predictive value of the codes or the algorithms for each of the components of MACE is high in Spain, Denmark, the UK, and the Netherlands (Arana et al., 2021; Davidson et al., 2020).

9.3.3. Covariates

In addition to well-known risk factors for CVDs, the list of covariates comprises a set of comorbidities, medications, and health care resource utilisation that have been shown to be prevalent among patients with migraine, more often in patients with chronic migraine than in those with episodic migraine (Amiri et al., 2021; Burch et al., 2019; Minen et al., 2019; Payne et al., 2011) as well as well-known risk factors for CVDs. These variables will be used to characterise patients included in the study. In addition, these variables will be used for adjustment in the comparative analysis through propensity score estimation and SMR weighting.

9.3.3.1. Ascertainment and Definition of Migraine

For this study, patients meeting 1 or more of the following criteria will be considered as having migraine:

- At least 1 inpatient/outpatient hospital clinic/emergency department diagnosis code for migraine, including all the time before or at the index date
- 2 or more primary care/GP diagnosis codes for migraine at least 7 days apart, including all the time before or at the index date
- 2 or more prescriptions/dispensings for migraine-specific treatments, either preventive or acute, at least 7 days apart, including all the time before or at the index date

To identify patients, ICD-10-CM G43.xx (any code nested in G43) will be considered and each data source will map the codes to their specific coding system. The migraine- specific treatments will include the following:

- Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan)
- Ergots (dihydroergotamine and ergotamine)
- Gepants (rimegepant, ubrogepant, and atogepant)
- Ditans (lasmiditan)
- CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab)

The proposed algorithm is a variation of previously published algorithms (Hoffman et al., 2019; Yusuf et al., 2018). Due to the type of data sources included in the current study (i.e., hospital data sources, GP linked to hospital data sources) and the selected population included (i.e., patients with history of CVD), the algorithm used in the current study relaxed the requirements of previously published studies (specifically, only 1 inpatient/outpatient hospital clinic/emergency department code will be required).

9.3.3.2. History of Cardiovascular Disease

To be eligible to enter in the study, a patient must have 1 or more of the following recorded diagnoses (inpatient setting) or revascularisation procedures at any time before or at the index date:

- Acute myocardial infarction
- Acute coronary syndrome
- Unstable angina
- Percutaneous coronary intervention
- Cardiac bypass surgery
- Ischaemic or haemorrhagic stroke
- Transient ischaemic attack

This list of CVD components has been slightly modified from the list included in the protocol synopsis submitted to the EMA (15-Dec-2021). Specifically, the following conditions are not included:

- Uncontrolled, unstable, or recently diagnosed CVD
- Ischaemic heart disease
- Coronary artery vasospasm
- Uncontrolled hypertension
- Uncontrolled diabetes
- History or current evidence of any significant and/or unstable medical conditions (e.g., history of congenital heart disease or arrhythmia)
- Long QT syndrome
- Left anterior fascicular block
- Paroxysmal tachycardia

The rationale for removing the above-mentioned conditions from the list is to keep individual CVD components instead of overarching conditions. Additionally, some of these conditions are not identifiable through diagnosis or procedural codes in the selected data sources or are identified with low precision.

9.3.3.3. Demographics and Lifestyle Factors

The following variables will be ascertained at the index date:

- Age (years)
- Sex
- Smoking status, as available in each data source
- Body mass index (BMI), as available in each data source

9.3.3.4. Migraine History

Information about migraine any time before the index date will be described:

- Duration of migraine (i.e., time since first migraine diagnosis [Section 9.3.3.1] in the data source)
- Migraine type (with aura, without aura, chronic, other), as available in each data source

9.3.3.5. Comorbidities

The following comorbidities will be evaluated within the 12 months before the index date:

- Depression
- Bipolar disorder
- Anxiety and panic disorders
- Schizophrenia
- Epilepsy and seizures
- Substance abuse
- Malignancy
- Thyroid disease
- Respiratory disease
- Liver disease
- Chronic kidney disease
- Hypertension
- Hyperlipidaemia
- Diabetes
- Obesity
- Alcohol abuse and alcohol abuse–related conditions

9.3.3.6. Comedications

Prior treatments for migraine will be evaluated within the 12 months before the index date:

- Acute migraine drugs
  - Analgesics (e.g., opioids, prescribed/dispensed NSAIDs or paracetamol)
  - Triptans
  - Ditans

  - Ergots
  - Other CGRP receptor antagonists
- Preventive migraine drugs
  - Beta-blockers (atenolol, bisoprolol, metoprolol, nadolol, propranolol)
  - Candesartan
  - Lisinopril
  - Topiramate
  - Amitriptyline
  - Flunarizine
  - Sodium valproate
  - Onabotulinumtoxin A
  - Anti-CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab)

Other comedications will be evaluated within the 12 months before the index date:

- Antidepressants (other than amitriptyline)
- Anti-epileptic medications (other than topiramate and valproate)
- Antipsychotics
- Anxiolytics/sedatives/hypnotics
- Cholesterol-lowering medications
- Antihypertensive medications (other than beta-blockers and candesartan)
- Antiplatelet agents
- Anticoagulants
- Antibiotics
- Antifungals
- Antituberculars

- Chronic obstructive pulmonary disease (COPD) medications
- Chemotherapeutic agents

9.3.3.7. Health Care Utilisation

The following health care utilisation indicators will be evaluated within the 12 months before the index date:

- Number of hospitalisations
- Number of emergency department visits
- Number of outpatient clinic visits

9.4. Data Sources

The main features of the selected data sources are included in Table 5. Specific details are provided in the following subsections.

Table 5. Main Features of the Preselected European Data Sources for the Rimegepant PASS

Feature	DNHR, Denmark	PHARMO, Netherlands	SIDIAP, Spain	CPRD, United Kingdom
Country population[a]	5,840,045	17,475,415	Catalonia, 7.739.758[b]	67,081,000[c]
Database population	5.8 million	> 7 million active persons	5.8 million Catalonian residents (75%)	13.4 million (Aurum)
Database type	National health record databases capable of linkage with other databases through a unique personal ID number	Data network linking pharmacy, hospital, and primary care data	Primary health care electronic medical record database plus partial linkage to other data	Primary health care electronic medical record database plus partial linkage to HES and other data
Drug dictionary codes/therapeutic classification	ATC	ATC	ATC	DM+D and Gemscript
Disease and procedure coding system(s)	▪ ICD-10 ▪ Procedure codes: NCSP	▪ ICPC (GP database) ▪ ICD-10 (hospital database) ▪ Dutch procedure codes (hospital database)	▪ ICD-10 for primary care diagnoses ▪ ICD-10-CM for hospital discharge diagnoses since 2018	▪ ICD-10 for hospital discharge diagnoses ▪ OPCS-4 procedural codes in HES ▪ SNOMED CT and local EMIS codes
Frequency of updates of data source	Annually	Annually	Biannually (January and July)	Monthly (Aurum) and 2 per year (linkages)
Lag time in months	3-6	9-21	3	Less than 1 month (Aurum) and 6 months (linkages)

ATC = Anatomical Therapeutic Chemical Classification System; CPRD = Clinical Practice Research Datalink; DM+D = Dictionary of Medicines and Devices; DNHR = Danish National Health Registers; EMIS = Egton Medical Information Systems; Gemscript = integrated dictionary of medicines and devices used in the United Kingdom; GP = general practitioner; HES = Hospital Episode Statistics; ICD-10 = *International Classification of Diseases, Tenth Revision*; ICD-10-CM = *International Classification of Diseases, Tenth Revision, Clinical Modification*; ICPC = International Classification of Primary Care; NCSP = NOMESCO Classification of Surgical Procedures; NOMESCO = Nordic Medico-Statistical Committee; OPCS-4 = Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4; PASS = post-authorisation safety study; PHARMO = PHARMO Database Network of the PHARMO Institute for Drug Outcomes Research (the Netherlands); SIDIAP = Information System for the Advancement of Research in Primary Care; SNOMED CT = Systematized Nomenclature of Medicine Clinical Terms.

a Population data from Eurostat (2021) except for the Catalan region of Spain and the UK.

b Population data (2021) from the Catalan regional government. https://www.idescat.cat/pub/?id=ep&n=9122&lang=en. Accessed 9 May 2022.

c Population data (2021) from UK statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates. Accessed 9 May 2022.

9.4.1. DNHR (Denmark)

Denmark has a tax-funded health care system that ensures easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers (Pottegård et al., 2017). Health care coverage includes visits to GPs and specialists, hospital admissions, and outpatient visits. The costs of most medicines used outside the hospital setting are partially reimbursed by the Danish health system. The civil registration system in Denmark allows the personal identification of each person in the entire Danish population through a 10-digit personal identifier ("central pharmaceutical reference number") assigned to all Danish residents in Denmark, which enables linkage between all Danish registers, such as the Danish National Patient Register, the Danish National Prescription Registry, the Danish Cancer Registry, and the Danish Register of Causes of Death (Schmidt et al., 2014). Data collected in these registers are available for research purposes. The research process requires collaboration with a local university or an investigator affiliated with a research institute to access the data, in addition to ethics committee notification or approval to handle the data from Danish Data Protection Agency (Danish Data Protection Agency, 2021; Danish Health Authority, 2021). All applications must be submitted in Danish.

The Danish National Patient Register includes data on all hospital admissions since 1977 and on hospital outpatient clinic visits, visits to specialists, and emergency department visits since 1995 (Lynge et al., 2011). Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths, and some selected drugs are recorded (e.g., chemotherapy, biologics) (Schmidt et al., 2015). Beginning in Jan-1994, hospital discharge diagnoses are coded using the ICD-10. Diagnoses for conditions that do not require hospitalisation are captured only as secondary diagnoses when patients are hospitalised for another condition or as visits to a hospital outpatient clinic; thus, GP visits are not captured (Lynge et al., 2011). The Danish National Prescription Registry provides patient-level data on all drug prescriptions filled by pharmacies since 1995 (Pottegård et al., 2017). The National Health Board records all procedures in public hospitals through procedure codes used in Demark. Results of laboratory tests are available in Denmark for both outpatient and inpatient settings through the Register of Laboratory Results for Research (LAB_F) database, which covers 4 of 5 Danish regions (the North, South, Zeeland, and Capital regions) (Arendt et al., 2020).

Although the Danish National Prescription Registry contains data on all drugs sold in primary care or purchased for use in Danish hospitals, the drugs used during hospital admissions and drugs supplied directly by hospitals or treatment centres (e.g., chemotherapeutic agents) are not captured (Pottegård et al., 2017). However, from 2020 onwards, information on those drugs will be available via a new hospital prescription register.

In the DNHR, information on oral medications dispensed from hospital (hospitalised and non-hospitalised patients) and ambulatory pharmacies is available, including Anatomical

Therapeutic Chemical Classification System (ATC) code, product name, strength, date of dispensing, and amount dispensed.

Access to the DNHR will be provided by Southern Denmark University (SDU).

9.4.2. PHARMO (Netherlands)

The PHARMO Database Network, which is maintained by the PHARMO Institute for Drug Outcomes Research, is a population-based network of electronic health record databases that combines anonymous data from different primary and secondary health care settings in the Netherlands. These different data banks—including data from general practices, inpatient and outpatient pharmacies, clinical laboratories, hospitals, the cancer register, the pathology register, and the perinatal register—are linked on the patient level through validated algorithms. To ensure data privacy in the PHARMO Database Network, the collection, processing, linkage, and anonymisation of the data are performed by STIZON, which is an independent, ISO/IEC 27001–certified foundation that acts as a trusted third party between the databases in the network and the PHARMO Institute.

The longitudinal nature of the PHARMO Database Network system enables follow-up of more than 10 million persons of a well-defined population in the Netherlands for an average of 12 years. Currently, the PHARMO Database Network covers over 7 million active persons of the 17 million inhabitants of the Netherlands. Data collection period, catchment area, and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the specific databases included. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Other available information depends on the database. The linkage of data in the PHARMO Database Network is updated yearly, in the fourth quarter of each calendar year. A detailed description of the different databases is given below (Kuiper et al., 2020; Willame et al., 2021).

- The **Hospital Database** comprises data sets containing data on hospital admissions, ambulatory consultations, and high budget-impact medication. The Hospital Database is collected and maintained by the Dutch Hospital Data Foundation and comprises records from nearly all hospitals in the Netherlands. The hospital admissions data set includes discharge dates, discharge diagnoses, and procedures for hospitalisations longer than 24 hours (or shorter if the patient required a bed, i.e., inpatient records). Hospital discharge diagnoses are available from the Dutch National Basic Hospital Care Registration (Landelijke Basisregistratie Ziekenhuiszorg [LBZ]) and are recorded using ICD-10 codes. Procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures. Currently, PHARMO has access to data from 1998 onwards and from over 80% of general and academic hospitals.

  - The Ambulatory Consultations Data Set includes information on each outpatient contact, including date, diagnoses, and procedures. This

information does not include emergency department visits. Diagnoses are recorded using ICD-10 codes, and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures. Currently, PHARMO has access to data from 2014 onwards and from over 50% of the hospitals.

- The **General Practitioner Database** comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists, and health care product/drug prescriptions. Primary care data are available for a portion of the population of approximately 3.2 million inhabitants (approximately 20% of the Dutch population). Information on lifestyle variables (e.g., BMI, smoking, alcohol consumption) is available in the General Practitioner Database if recorded by GPs in the electronic medical records.

- The **Outpatient Pharmacy Database** comprises GP-prescribed or specialist-prescribed health care products dispensed by the outpatient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty, and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) classification system. Outpatient pharmacy data cover a catchment area representing 4.2 million residents (approximately 25% of the Dutch population).

9.4.3. SIDIAP (Spain)

The Information System for Research in Primary Care (SIDIAP) in Catalonia, Spain, is a primary care database set up by the Institute of Research in Primary Care (IDIAP Jordi Gol) and the Catalan Institute of Health (Institut Català de la Salut). The database collects information from 278 primary health care centres and includes more than 5.8 million patients covered by the public Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population (Recalde et al., 2022; Willame et al., 2021).

The SIDIAP data comprise the clinical and referral events registered by primary care health professionals (i.e., GPs, paediatricians, and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results. The SIDIAP data can also be linked to other databases, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using ICD-10 codes, ATC codes, and structured forms designed for the collection of variables relevant to primary care clinical management, such as country of origin, sex, age, height, weight, BMI, tobacco and alcohol

use, blood pressure measurements, and blood urine test results. In relation to vaccines, information on all routine childhood and adult immunisations is included in addition to the antigen and the number of administered doses.

The SIDIAP data source is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database (https://www.encepp.eu/encepp/viewResource.htm?id=4646).

9.4.4. CPRD (United Kingdom)

The CPRD collates the computerised medical records of a network of GPs in the UK who act as the gatekeepers of health care and maintain patients' lifelong electronic health records. The data are sourced from over 2,000 primary care practices and include 62 million patients, of whom 16.5 million are currently registered and active (MHRA and NIHR, 2021). General practitioners act as the first point of contact for any non- emergency health-related issue, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to GPs about their patients, including key diagnoses. The data in CPRD are updated monthly and include demographic information, prescription details, clinical events, preventive care, specialist referrals, hospital admissions, and major outcomes, including death (Herrett et al., 2015; Wolf et al., 2019). Most of the data are coded using Read or SNOMED codes.

Depending on the type of electronic medical software used by the general practice, data are collected into either the CPRD General Practitioner Online Database (GOLD) or the CPRD Aurum database. Data include demographics, all GP/health care professional consultations, diagnoses and symptoms, results from laboratory tests, information about treatments (including prescriptions), data on referrals to other care providers, hospital discharge summaries (date and Read/SNOMED codes), hospital clinic summaries, preventive treatment and immunisations, and death (date and cause). Lag time for CPRD Aurum is 1 month. Information about vaccinations from mass vaccination campaigns during the COVID-19 pandemic is expected to transfer to GPs and into the patient's medical records (via National Health Service [NHS] systems rather than patients informing the GP); however, the lag time for this transfer is not yet clear.

Linkage of CPRD primary care data with other patient-level data sets is available for English practices that have consented to participate in the linkage scheme. In more than 80% of CPRD panel practices, the GPs have agreed to permit CPRD to link at the patient level to these patient-level data sets. The Hospital Episode Statistics (HES) database contains details of all admissions to NHS hospitals in England (accident and emergency, admitted subject care, and outpatient); approximately 46.8 million individuals in CPRD are linked to the HES database. Not all patients in CPRD have linked data (e.g., if they live outside England, if their GP has not agreed that their data may be used in this way). As with standard CPRD patients, HES data are limited to patients with research-standard data. The CPRD records are linked to the HES using a combination of the patient's NHS number, sex, and date of birth (Williams et al., 2012). Additional CPRD-linked data sets include death registration data from the

Office for National Statistics, which includes information on the official date and causes of death (using ICD codes).

Linked data sets are usually updated every 6 months, and the lag time between data recording and data availability varies by data set. The latest linkage set (set 21) contains an update of priority linkages to support COVID-19 research, along with the CPRD-linked Second Generation Surveillance System (SGSS) COVID 19–positive virology test data and COVID-19 Hospitalisation in England Surveillance System (CHESS) hospitalisation and intensive care unit/high dependency unit data through the end of Sep-2020.

The present study will include active CPRD Aurum practices. These practices include an estimated 13.4 million current patients. The CPRD is listed under the ENCePP resources database, and access is provided by RTI-HS.

9.5. Study Size

Given the uncertainty regarding the size of the exposed population, the precision of potential study results for various study sizes ranging from 500 to 5,000 patients of rimegepant exposure was estimated by summing data from the 4 selected data sources. Table 6 shows the probability that the upper bound of the 95% CI around the observed RR will be below 1.5, 1.8, 2.0, and 2.5 for various study sizes. These calculations assume a 1-to-1 ratio between exposed and comparator patients and that the true RR between those exposed and comparators is 1.0. Several scenarios of cumulative incidence for individual MACE components were considered in a cohort of patients with migraine and at least 1 CVD risk factor (Adelborg et al., 2018). In this population, the cumulative incidence per 10,000 patients for AMI ranged from 33.4 (0-1 year since migraine diagnosis) to 176.1 (> 1 to 5 years since migraine diagnosis). The cumulative incidence per 10,000 patients for ischaemic stroke ranged from 102.0 (0-1 year since migraine diagnosis) to 210.9 (> 1 to 5 years since migraine diagnosis).

Table 6. Probability That the Upper 95% Confidence Limit of the Observed Risk Ratio Will Be Below 1.5, 1.8, 2.0, and 2.5 for Various Study Sizes of Exposed Patients, Assuming That the True Risk Ratio Is 1 and the Ratio of Exposed to Comparator Patients Is 1 to 1

Cumulative Incidence per 10,000 Patients	Patients Exposed	Upper Confidence Limit of RR			
		1.5	1.8	2.0	2.5
Patients with 1 CVD risk factor and 0-1 year since migraine diagnosis					
33.4 (for AMI)	500	0.056	0.078	0.092	0.131
	1,000	0.076	0.115	0.144	0.220
	2,500	0.129	0.225	0.294	0.466
	5,000	0.216	0.398	0.518	0.756
102.0 (for stroke)	500	0.095	0.155	0.198	0.312
	1,000	0.149	0.266	0.350	0.548

Table 6. Probability That the Upper 95% Confidence Limit of the Observed Risk Ratio Will Be Below 1.5, 1.8, 2.0, and 2.5 for Various Study Sizes of Exposed Patients, Assuming That the True Risk Ratio Is 1 and the Ratio of Exposed to Comparator Patients Is 1 to 1

Cumulative Incidence per 10,000 Patients	Patients Exposed	Upper Confidence Limit of RR			
		1.5	1.8	2.0	2.5
	2,500	0.307	0.559	0.701	0.908
	5,000	0.539	0.847	0.940	0.996
Patients with 1 CVD risk factor and > 1 to 5 years since migraine diagnosis					
176.1 (for AMI)	500	0.135	0.237	0.311	0.492
	1,000	0.228	0.421	0.546	0.783
	2,500	0.484	0.795	0.907	0.991
	5,000	0.775	0.976	0.996	1.000
210.9 (for stroke)	500	0.154	0.276	0.363	0.566
	1,000	0.265	0.488	0.624	0.853
	2,500	0.557	0.862	0.949	0.997
	5,000	0.845	0.991	0.999	1.000

AMI = acute myocardial infarction; CVD = cardiovascular disease; RR = risk ratio.

Note: Background rates were obtained from Adelborg et al. (2018).

For the scenario including patients with 1 CVD risk factor and > 1 to 5 years after migraine diagnosis, a cumulative incidence for AMI was 176.1 per 10,000 patients or higher. Under this assumed cumulative incidence, the inclusion of 2,500 patients in the rimegepant group would result in a 90% or higher probability that the upper bound of the observed RR is below 2. The inclusion of 1,000 patients in the rimegepant group would result in a 90% or higher probability that the upper bound of the observed RR is below 3.

Under the assumption of a cumulative incidence of stroke of 210.9 per 10,000 patients, the inclusion of 2,500 patients in the rimegepant group would result in a 95% or higher probability that the upper bound of the observed RR is below 2. The inclusion of 1,000 patients in the rimegepant group would result in a 95% or higher probability that the upper bound of the observed RR is below 3.

In summary, considering a scenario of an IR of MACE ranging between 176.1 and 210.9 per 10,000 patients, and having a cohort of patients with > 1 to 5 years after migraine diagnosis, a sample size of 2,500 patients in the rimegepant group would result in a 86% or higher probability that the upper bound of the observed RR would be below 1.8.

9.6. Data Management

DNHR (Denmark)

Data will be provided on a secure site offered by the DNHR (Sundhedsdatastyrelsen). After access is granted, the data will be validated in terms of completeness and consistency with the prespecified structure.

The standard protocol of the DNHR will be followed, which specifies that data will be pseudonymised to preserve confidentiality and that data will never leave the DNHR's server, only aggregate data or table output from the analyses conducted at the DNHR though a remote desktop. No table cells with count lower that 5 will be downloaded to SDU. Only personnel with a legitimate need for analysing data will be given access through the remote desktop.

The analysis will conform to SDU's protocol for quality assurance, specifying that analytical code will be reviewed by a senior programmer. To avoid manual transcript error, all results will be transferred to table output through programming.

With respect to physical data integrity and security, the protocols of the DNHR will be followed.

PHARMO (the Netherlands)

Data proportional to the needs of the study will be extracted from the pseudonymised PHARMO Database Network. The study data can be accessed by authorised personnel only through a remote desktop for analysis.

At PHARMO, data management and statistical analysis and reporting will be performed using the utility SAS Enterprise Guide version 7.1, an environment for SAS version 9.4. (SAS Institute Inc.; Cary, North Carolina) enabling the storage of syntaxes or codes belonging to a single study in 1 project file.

Standard operating procedures will be applied, ensuring all programming will be reviewed by a senior programmer. Only aggregated data will be shared, for samples of at least 5 persons.

SIDIAP (Spain)

The SIDIAP database contains pseudonymised data emerged from the primary care electronic health records (I) from approximately 300 primary care practices around Catalonia. All these practices use the same I software, and all primary care health professionals receive similar training on the correct use of the software for optimal coding regarding clinical management of their patients.

For each study, the local research team and SIDIAP data managers develop a data specification and extraction protocol based on the approved protocol. Specific data quality checks are performed on a study-per-study basis. Patients are regarded eligible to be included in a study if they are registered and can be followed in the database.

Study data are processed using SQL and Python by the data management team and analysed by the research team.

CPRD (UK)

RTI-HS will be the responsible centre for the analysis of CPRD data and, if feasible, the meta-analysis. Data management will be conducted in accordance with RTI-HS standard operating procedures. Routine procedures include checking electronic files, maintaining security and data confidentiality, following the statistical epidemiological analysis plan, and performing quality-control (QC) checks of all programmes.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Analyses will be conducted separately by each data source, and results will be pooled via meta- analytic methods, if appropriate, at the end of the study. The following subsections describe in a sequential way the different steps of the statistical analysis.

In accordance with the recommendations of the American Statistical Association, the International Committee of Medical Journal Editors (ICMJE, 2022), and expert opinion on the misuse of significance testing (Greenland et al., 2016; *Nature* editorial, 2019; Rothman and Lash, 2021), we avoid relying on statistical significance to interpret study results. Instead of a dichotomous interpretation based on p-values and significance testing, we rely on a quantitative interpretation that considers the magnitude, precision, and possible bias in the estimates that we derive and report. We believe that this is a more appropriate approach than one that ascribes to chance any result that does not meet conventional criteria for statistical significance.

9.7.1. Creation of the Cohort and Treatment Groups

All patients meeting the eligibility criteria (Sections 9.2.1 and 9.2.2) and with a rimegepant prescription/dispensing during the study period will be included in the rimegepant study groups, per the criteria described in Sections 9.2.2 and 9.3.1.

As discussed in Section9.2, the **index date for the Rimegepant groups** will be the first date of a rimegepant prescription/dispensing during the study period. The **index date for the comparator groups** will be the date of the comparator prescription/dispensing and also the date on which an individual is identified with a rimegepant index date with the same time since first prescription/dispensing of migraine medication (i.e., within the same exposure set) and meeting all eligibility criteria.

Patients in the rimegepant cohort will be matched to comparators on time since initiating treatment for migraine, thereby forming exposure sets. The method used to define the exact time since first prescription/dispensing medication to create the exposure sets (i.e., the number of months may be different depending on the data available at each data source) will be further described in the study SAP, which will be updated upon the endorsement of the

study protocol. In addition, it is possible that the data available in any of the data sources (i.e., the available lock-back period) may not allow the creation of exposure sets with sufficient granularity. To address this possible situation, an alternative method to create the exposure sets will be considered by matching patients in the rimegepant group to comparators by the total number of prior prescriptions/dispensings of migraine treatments. The final decision regarding the method used will be evaluated during the interim analysis to be submitted to the EMA by the end of the 3rd year after rimegepant launch (see Section 6). The results of this **feasibility assessment** will determine the final method to be used to create the exposure sets in the final analysis.

Because patients may be used as comparators for multiple rimegepant patients, a single patient may have multiple index dates. Furthermore, patients included in the rimegepant group may also contribute index date(s) and follow-up data to the comparator group before their first rimegepant exposure. The variance of the effect estimates will be calculated with methods that account for such clustering of the information, such as the sandwich variance estimator or bootstrapping.

Two rimegepant initiator groups with different comparison groups and 1 rimegepant initiator group for the drug utilisation study will be created according to the study objectives (Section 9.2).

The interim report will include an assessment of the cohort attrition at the end of the 3rd year of the study period. The final study report will include the final cohort attrition.

9.7.2. Description of Included Patients

The attrition of patients (and within patients, each potential comparator index date within exposure sets) because of failing to meet study eligibility criteria will be reported, and the number of eligible patients (and within patients, each potential comparator index date within exposure sets) included in each of the study groups (Section 9.2) will be reported. The number of patients and potential comparator index dates within exposure sets that were excluded for not meeting the inclusion criteria will be reported along with the reasons for exclusion.

The characteristics of those included in the study will be described, and baseline differences between the treatment groups will be evaluated.

The distributions of all baseline covariates described in Section 9.3.3 will be calculated and reported for each of the 4 groups (initiators of rimegepant on preventive treatment, initiators or continuators of other preventive treatment among patients on preventive treatment, initiators of rimegepant who are receiving acute treatment, and initiators or continuators of other acute treatments among patients receiving acute treatment). The distribution of characteristics will be calculated and displayed as counts and percentages for binary or categorical variables and as means and standard deviations for continuous variables. The distribution of characteristics will be accompanied by relevant statistical plots, such as bar charts and histograms.

Standardised mean differences between exposure groups will be calculated to assess baseline balance.

The interim report will include the distribution of all baseline covariates. The final study report will include the distribution of all baseline covariates and the standardised mean differences between groups.

9.7.3. Unadjusted Analysis of MACE

Crude incidence rates of MACE with their 95% CIs will be estimated using a Poisson regression model with robust estimation of the variance (to take into account any repeated patients) (Zou, 2004). The cumulative incidence of MACE will be estimated using the Kaplan-Meier estimator.

Unadjusted risk differences and RRs between the 2 exposure groups in the 2 sets of comparisons at 3, 6, 9, and 12 months of follow-up will be estimated using data from the Kaplan-Meier estimator, and 95% CIs will be estimated using a non-parametric bootstrap estimation (Efron and Tibshirani, 1993). The unadjusted HR at 1 year of follow-up will be estimated using a Cox regression model and with robust variances to account for any repeated patients in the estimation of 95% CIs (Lin and Wei, 1989).

The interim report and the final study report will include unadjusted analyses of MACE, but only the final report will present fully adjusted analyses.

9.7.4. Adjusted Analysis of MACE

To adjust for potential baseline confounding, standardised morbidity ratio weights (SMRW) at baseline will be used. These weights will be calculated and applied as follows. This analysis will be conducted only for the final study report.

9.7.4.1. Standardised Morbidity Ratio Weights

SMRW (Sato and Matsuyama, 2003) are defined as:

$$SMRW = 1, \text{ for the initiators of rimegepant}$$

$$SMRW = \frac{PS}{1-PS} \text{ for the continuators of comparator drugs}$$

Where PS is the propensity score.

Propensity scores are the predicted probability of receiving the treatment of interest, given a set of measured covariates. Individuals in different treatment groups with the same propensity score are assumed to have the same probability of receiving the treatment and are considered exchangeable (Brookhart et al., 2013).

Propensity scores will be estimated with logistic regression models separately within the acute and preventive groups and by exposure set (i.e., time since start of the comparator

migraine medications that the patient has been taking before the index date) (Webster-Clark et al., 2022; Webster-Clark et al., 2021). The a priori–identified list of baseline covariates (Section 9.3.3) will be the base from which to select the variables to be included in the propensity score baseline model. Baseline variables will be selected based on their association with the outcome (incidence rate ratio > 1.25 or < 0.80) using a univariate Poisson regression model. Some variables might be forced into the model based on prior knowledge or clinical reasons.

Covariate balance will be reassessed using standardised mean differences and will be displayed graphically. If balance cannot be achieved for all important covariates, it is proposed that the model be refitted to include interactions or higher-order terms to improve balance.

9.7.4.2. Weighted Outcome Model

Adjusted incidence rates will be obtained by adding the standardised morbidity ratio weights in the Poisson models. The adjusted Kaplan-Meier estimator will be obtained by incorporating the weights in the calculation of the cumulative incidence of MACE (Xie and Liu, 2005), and risk differences and RRs will be derived from this adjusted Kaplan-Meier estimator.

Adjusted HRs will be estimated incorporating the weights in the Cox model. For all effect estimates described above, the 95% CIs will be calculated using a non-parametric bootstrap estimation.

9.7.5. Subgroup Analyses

Subgroup analyses will be conducted as follows:

- Age categories: age groups to be determined
- Sex: male, female
- Type of migraine: acute, chronic, undetermined
- CVD risk profile: low and high
- Cumulative dose: categories to be determined during follow-up
- Drug classes in the comparator groups:
  - Acute comparison: triptans, ditans, and ergots
  - Preventive comparison: beta-blockers, angiotensin II–receptor blocker or ACE inhibitors, anticonvulsant, tricyclic antidepressant, calcium antagonist, and botulinum toxin

- This analysis will be conducted only for the final study report.

9.7.6. Sensitivity Analysis

The following analyses will be conducted for the final study report.

Evaluating the Effect of Initiation Rimegepant and Initiation Comparators

A sensitivity analysis will be conducted including only patients who initiate new treatments in the comparator groups. Patients continuing the same medication will not be included. These analyses will be conducted separately by preventive and acute treatments.

Restricting the Comparison Between Rimegepant and Acute Migraine Treatments to Patients Without Prior Prescriptions/Dispensings of Preventive Treatments

A sensitivity analysis will be conducted restricted to patients without prior prescriptions/ dispensings of preventive migraine treatments when comparing initiators of rimegepant versus continuators or initiators of acute migraine treatments.

Evaluating the Impact of Duration of Follow-up

A sensitivity analysis will be conducted restricting the follow-up up to 183 days. In addition, another sensitivity analysis will be conducted without censoring patients after the index date in the absence of other censoring events, thus including all available follow-up time.

New-User Design

An additional sensitivity analysis will be conducted using a washout period before the index date to identify treatment-naive rimegepant initiators and comparators. An additional eligibility criterion will be applied to the criteria described in Section 9.2.1: patients will be required to have a period of 2 months without prescription/dispensing of preventive (for Objective 1) and acute (for Objective 2) migraine treatments. By applying a short washout period (i.e., 2 months), the objective of a “clean period” before the new treatment would be fulfilled and, simultaneously, the target population of those receiving rimegepant would be identified. If a longer washout period were applied, the included population would have a very small sample size and the patients included would likely be characterised as having mild migraine severity.

Unmeasured Confounding

The potential effect of unmeasured confounding will be evaluated using quantitative bias analysis methods described by VanderWeele and Ding (2017). This analysis will evaluate how strong unmeasured confounding would have to be to explain away the association reported in the analysis of the risk of MACE. The analysis will use a bias factor to obtain the maximum degree to which a given set of unmeasured confounders could alter the observed RR in the main analysis.

The reported study results will include the e-value, which represents the minimum strength of association on the RR scale that an unmeasured confounder would need to have with both the

treatment (probability of receiving rimegepant) and the outcome (probability of experiencing a MACE) to fully explain away the specific treatment- outcome association reported as the main result of the study, conditional on the measured covariates.

Adjustment for Potential Selection Bias

A sensitivity analysis using weights for the artificial censoring of patients in the comparator group that switch to rimegepant will be conducted to evaluate potential selection bias by informative censoring. To adjust for the potential selection bias introduced by the artificial censoring (Hernán et al., 2004), each individual's contribution to the outcome model will be inverse-probability weighted (Robins and Hernán, 2009), with weights depending on baseline and time-varying adjustment variables defined a priori.

9.7.7. Meta-analysis

The main estimates of association from the participating data sources will be pooled using fixed-effects or random-effects meta-analytic methods. Pooled crude and/or adjusted HRs along with 95% CIs will be estimated. The heterogeneity across data sources will be assessed, and a forest plot will be produced showing the data source– specific and pooled estimates.

This analysis will be conducted for the final study report.

9.7.8. Drug Utilisation Analysis

Descriptions of all rimegepant initiators will be described in tables and figures. Summary statistics on the following variables will be included:

- Total number of prescriptions/dispensings per patient of rimegepant during the study period and average per year
- Total number of rimegepant days' supply
- Duration of continuous treatment
- Discontinuation of treatment
- Concomitant use of other medications for migraine
- Discontinuation of rimegepant with switching to other medications for migraine

Patterns of use of rimegepant will be graphically represented with Sankey diagrams (Thomas et al., 2017). Alternative methods to describe rimegepant use (e.g., Lorenz curve, waiting-time distribution) will be considered and described in the SAP (Hallas and Støvring, 2006).

This analysis will be conducted for the interim report and the final study report.

9.7.9. Missing Data

Because the underlying data represent attended medical care, it is generally assumed that the absence of information of clinical events or prescriptions/dispensings indicates an absence of the condition or the treatment. Therefore, no missing data are expected on the critical variables for the study, including diagnoses and medications. Missing values are expected only for some lifestyle or biometric data, such as smoking status or BMI in primary care electronic medical records. In the other data sources, these variables are not captured and will be defined based on proxies that do not have missing data (i.e., use of smoking cessation drugs or diagnosis of obesity).

In the descriptive analyses, variables with missing values will be reported as a separate category. If more than 10% of patients have missing values, the use of inverse- probability weighting to account for the missing values will be considered (Toh et al., 2012).

9.8. Quality Control

Rigorous QC will be applied to all deliverables. Data transformation will be conducted by each research partner in its associated data source, with processes as described in the following corresponding sections. Standard operating procedures or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; QC procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff. A quality assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

SIDIAP (Spain)

Data quality processes will be implemented at each phase of the data flow cycle. Quality-control checks will be performed at the extraction and uploading steps. To assess data completeness, the elements present will be described by geographical areas, registering physician, time, and the distribution function of values. Correctness will be assessed by validity checks on outliers, out-of-range values, formatting errors, and logical date incompatibilities. Completeness and correctness measures will be used to inform decisions on the required transformations to improve data quality (e.g., harmonisation, normalisation, clean-up) and data fitness for the purpose of specific research projects.

PHARMO (Netherlands)

PHARMO is ISO 9001:2015 certified for its quality management system. At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work frame of the PHARMO quality management system.

The PHARMO Database Network combines data from different sources (e.g., pharmacy, hospital, laboratory). These different sources are probabilistically linked through validated algorithms to ensure that patient privacy is maintained. Before databases are linked, those

patients for whom linkage-critical information (e.g., date of birth, sex, GP) is missing are removed. All data are handled in a way that meets the full requirements for managing and storing sensitive patient data. Involved researchers have signed a confidentiality agreement. The anonymised data are stored on an internal network drive. Relevant extractions will be stored in a project folder. Specific checks on the linked data are performed, depending on which data sources are used. The study data folder, including all extracted and derived data tables, will be archived after study closure.

All programming is developed in accordance with standard operating procedures, prepared by the lead analyst, and reviewed/quality controlled by an experienced analyst at PHARMO. Additionally, all results and reports are audited by the QC department, using a standardised check list.

The use of the PHARMO data is controlled by the independent Compliance Committee STIZON/PHARMO Institute. The Compliance Committee STIZON/PHARMO Institute consists of representatives of the participating data suppliers and a privacy expert (chairman of this committee). Each study requires permission from this committee, according to the applicable legislation in the Netherlands (e.g., the Personal Data Protection Act and the Medical Treatment Contract Act). Within this legal framework, the Code of Conduct "Use of Data in Health Research" is an important document for the interpretation of the use of this kind of data for scientific research in the Netherlands and is approved by the Dutch Data Protection Authority (www.dutchdpa.nl).

DNHR (Denmark)

The Danish study data are stored at the Danish Health Data Authority, which is a public enterprise under the Danish Ministry of Health. Data will be accessed through a secure gateway only by selected study staff of Clinical Pharmacology and Pharmacy, SDU. All data that could potentially lead to patient identification are encrypted, and transmission of output follows strict rules according to Danish legislation (the Personal Data Law). Key programming modules are written by a study analyst and independently reviewed by a different analyst, with oversight by a senior epidemiologist.

CPRD (United Kingdom)

Because RTI-HS will be the responsible centre for the analysis for CPRD, QC procedures for CPRD data will be conducted in accordance with RTI-HS policies. At RTI-HS, all key study documents will undergo QC review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate patient matter area will provide advice on the design of research study approaches and the conduct of the study and will review results, reports, and other key study documents.

Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) (ISPE, 2015).

9.9. Limitations of the Research Methods

The effect estimates will rely on assumptions common to other observational studies:

- That there will not be unmeasured confounding
- That the models are not misspecified
- That there is no measurement error in the study

variables Violations to these assumptions may yield biased estimates.

Confounding by indication is always a concern in pharmacoepidemiology studies and even more with newly approved drugs (Gagne et al., 2013). Currently, rimegepant is the only drug approved both for the acute treatment and for the prevention of migraine.

Although rimegepant initiators will be compared separately with preventive treatment groups and acute treatment groups, it might be challenging to differentiate whether rimegepant is prescribed for the treatment of acute or preventive migraine needs in the electronic health data sources proposed. Differences in clinical characteristics between patients taking rimegepant for preventive or acute treatments may result in potential bias. The use of propensity scores is intended to minimise the likelihood of this bias.

The proposed migraine algorithm in the current study is a variation of previously published algorithms (Hoffman et al., 2019; Yusuf et al., 2018). Although the algorithm will not be validated in the current study, the prevalence of migraine cases obtained will be compared with those in previous studies (Hoffman et al., 2019; Wood et al., 2021; Yusuf et al., 2018). However, it is expected that the possible misclassification of migraine will not be different between patients in the rimegepant or the comparator groups.

Misclassification bias can occur when exposure or outcome status are ascertained with error. Although prescribing and dispensing records will be used, misclassification of exposure is still possible and may vary between data sources based on the structure (i.e., pharmacy dispensing vs. physician prescribing). Prescription data may not reflect actual exposure. A prescription issued or a prescription dispensed reflect the intent to use a drug, not actual patient use. In the current study, it is assumed that a patient is exposed at the time of the dispensing of the medication prescription/dispensing. This approach might represent an overestimation of the true exposure, particularly for those treated in the acute treatment regimen. Even for those treated with a preventive regimen, misclassification of exposure is possible (eg, if a patient temporarily stops taking the medication due to medication overuse headaches). In addition, identifying medication overuse in this study is challenging given the nature of the data sources. A patient with acute migraine may overuse the medication used to treat acute episodic migraine (e.g., increasing the dose of the medication or taking multiple medications), and this overuse will be only captured if there is a change in the prescription/dispensing patterns. Also, if the patient is taking multiple medications, including over-the-counter medications, this information is only partially captured in the data sources used in this study because only information on prescribed/dispensed medications is collected.

Because rimegepant may be prescribed for either acute, preventive, or both treatments for migraine, the actual indication will be uncertain. Medications indicated for the acute treatment of migraine are used on demand (e.g., only during an episode of migraine). For example, rimegepant to treat acute episodes is to be used at a maximum dose of 75 mg (1 tablet) in a 24-hour period (Vydura SmPC, 2022). For rimegepant, each dispensing constitutes 1 pack of 8 oral lyophilisate tablets, and the estimated number of days for use is 30 days for acute treatment. For preventive treatment, given the recommended dose, it is anticipated that 2 packs will be used in a 30-day period. In the selected data sources, as well as in most of European health care data sources, data on indication for treatment is not available. Therefore, the actual use of rimegepant can only be estimated using proxies. This is acknowledged as a potential limitation of the present study. Prior prescriptions/dispensings identified within 6 months before the index date will be used to classify patients either in the comparison for acute treatments, in the comparisons for preventive treatments or in both comparisons. However, the use of preventive medication such as beta-blockers or ACE inhibitors may also be indicated for cardiovascular diagnoses, which makes this classification prone to misinterpretation.

Moreover, 2 subgroup analysis will be conducted stratifying results by type of migraine (to the extent possible in each data source) and by dose. Additionally, a sensitivity analysis will be conducted restricting the comparison between rimegepant and acute migraine treatments to patients without prior prescriptions/dispensings of preventive treatments.

The risk of misclassification bias in the outcome is expected to be low. Because of the serious nature and clinical guidelines for the management of MACE, hospitalisation is expected for most of the non-fatal events under study. The selected data sources for this study (CPRD, DNHR, SIDIAP, PHARMO) have been shown to reliably capture and classify hospitalisations, and these data sources are also capable of capturing conditions and deaths that occur in a hospital. Date of death is available in all data sources. On the other hand, cause of out-of-hospital death cannot be captured in all data sources.

Information on some relevant confounders (e.g., indication) may be limited. To estimate the potential effect of unmeasured confounding and other type of biases (e.g., misclassification bias) on study results, quantitative bias analyses methods will be used (VanderWeele and Ding, 2017).

A limited uptake of rimegepant in patients with migraine and a history of CVD would yield a small study size in the initiator group and, thus, would limit the capacity to adjust for a comprehensive number of potential confounders and affect the precision of the estimates. In that scenario and in consultation with regulators, strategies will be considered to address target study size needs. These may include extending the study and/or adding data sources.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The proposed study is a non-interventional study reusing health care data. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each data access provider will apply for an independent ethics committee review according to local regulations, and the local data protection impact assessment should be informed. Data protection and privacy regulations (GDPR) should be respected in collecting, forwarding, processing, and storing data from study participants.

Each research partner will apply for an independent ethics committee review according to local regulations; in addition, RTI-HS as the coordinating centre will obtain approval or exemption from the RTI International institutional review board (IRB) (RTI-HS is a unit of the not-for-profit research organisation RTI International).

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)/Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

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 the following documents:

- Guide on Methodological Standards in Pharmacoepidemiology issued by ENCePP
- Module VIII of the EMA's Guideline on good pharmacovigilance practices (GVP) – Post-authorisation safety studies
- Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)
- International Ethical Guidelines for Health-related Research Involving Humans issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO (CIOMS)

10.5. RTI International

RTI International holds a Federal-wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organisation to review and approve human patient protocols through its IRB committees.

RTI International currently has 3 IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has 2 members who are medical doctors. These IRBs have been audited by the US FDA and are fully compliant with applicable regulatory requirements. RTI-HS will obtain approval for the study from the RTI International IRB.

10.6. CPRD (United Kingdom)

Research at CPRD requires approval from the CPRD Independent Scientific Advisory Committee (ISAC). RTI-HS will prepare the required documentation and submit to ISAC for approval.

10.7. DNHR (Denmark)

This being an observational study, the dominant concern regarding protection of human subjects is about data privacy. The measures to protect data privacy include the following:

- The DNHR strictly adheres to GDPR's "need to know" principle.
- Access to DNHR data sources is guarded by several layers of data protection, including use of real-time updated passwords.
- Data are pseudonymised, and person identifiers are not visible at any time in the data handling.
- Data do not physically leave the DNHR's servers, only analytical output such as tables.
- A limited number of scientists have access to the servers.

Access to data requires approval from the Danish Data Protection Agency, as delegated to an internal review board at SDU.

10.8. PHARMO (Netherlands)

This being an observational study, the dominant concern regarding protection of human subjects is about data privacy. The PHARMO Database Network contains de-identified data using pseudonymised patient identifiers, and birth dates have been converted to birth years. Access to the data is limited to only authorised personnel who have signed a confidentiality agreement regarding data privacy. Only aggregated data will be shared. Aggregated data from fewer than 5 persons will not be shown to avoid recognition of patient profiles that might compromise data privacy.

10.9. SIDIAP (Spain)

Depending on the nature of the data and in accordance with the provisions of Organic Law 3/2018, of 5-Dec, on the Protection of Personal Data, the appropriate level of security will be established.

The data included in the SIDIAP database come from the electronic health records, which include personal data. SIDIAP data are pseudonymised and identified with an internal code that makes it impossible to identify the subjects included in the study. The owner of these data is the Catalan Institute of Health. The procedure foreseen for access to these data consists of the generation of the study database by SIDIAP staff and its secure transfer to the research team. The data will be stored in the local servers of IDIAP Jordi Gol, where they will be stored for 8 years after extraction. They will be accessible to the research team for the duration of the study.

The study protocol, protocol amendments, and other relevant documents will be evaluated for approval by the IRB (CEIm for its acronym in Spanish) of the IDIAP Jordi Gol.

10.10. Other Good Research Practice

This study will adhere to the Guidelines for GPP and has been designed in line with the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (ENCePP, 2021). The ENCePP Checklist for Study Protocols (ENCePP, 2018) was completed (see Annex 1).

The study is a post-authorisation study of rimegepant safety and will comply with the definition of the non-interventional (observational) study referred to in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004) and provided in the EMA Guidelines on Good Pharmacovigilance Practices (GVP) Module VIII: Post-authorisation Safety Studies (EMA, 2017), and with the 2012 EU pharmacovigilance legislation, adopted on 19-Jun-2012 (European Commission, 2012). The study will comply with the study reporting requirements specified in Module VIII Section VIII.B.6.3.1, “Progress Reports” and VIII.B.6.3.2, “Final Study Report” of the Guidelines of GVP (EMA, 2017).

The study will be registered in the EU PAS Register (ENCePP, 2022) before the study implementation commences.

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 (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, periodic benefit-risk evaluation report, and other regulatory milestones and requirements. Study reports will be prepared using a template following the GVP Module VIII Section B.6.3 (EMA, 2017).

The progress report will include status updates (i.e., progress against milestones, number of rimegepant users) and will report and address any challenges in the progress of the project.

In its GPP, the ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015), e.g., results pertaining to the safety of a marketed medication. Study results will be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2022). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology Checklist will be followed (von Elm et al., 2008). The Consolidated Standards of Reporting Trials statement (Schulz et al., 2010) refers to randomised studies but also provides useful guidance applicable to non-randomised studies.

Communication via appropriate scientific venues (e.g., ISPE) will be considered. The marketing authorisation holder and the investigators will agree upon a publication policy: the principal and coinvestigators will coauthor scientific manuscript(s) of the results to be published, irrespective of data ownership. In line with EMA GVP Module VIII, the research team will have independent publication rights. The marketing authorisation holder will be entitled to view the results and interpretations included in the manuscript(s) and provide comments before submission of the manuscript(s) for publication (EMA, 2017); however, final decisions rest with the research team.

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

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Post-authorisation Safety Study of Rimegepant in Patients with Migraine and History of Cardiovascular Disease in European Countries

EU PAS Register® number: not yet registered
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6, 9.7
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Monitoring of rimegepant users will be done annually starting in 2022.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

2.1.4 and 2.1.5: Rather than formal hypothesis testing, we will describe the effect measure and confidence interval, adjusting for potential confounders.

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

[2] Date from which the analytical data set is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g., cohort, case- control, cross-sectional, other design)	☒	☐	☐	9.1, 9.2
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2, 9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g., relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm [NNH])	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☐	☒	☐	

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.4
	4.2.2 Age and sex	☒	☐	☐	9.3.3
	4.2.3 Country of origin	☐	☒	☐	
	4.2.4 Disease/indication	☒	☐	☐	9.3.3.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.7.5, 9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) an appropriate comparator(s) identified?	☒	☐	☐	9.1, 9.2

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQOL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	9.7.4, 9.7.6
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.7.6
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time- related bias)	☒	☐	☐	9.7.6

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to- face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1, 9.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2, 9.4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.3.3, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.9
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9

12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Joan Forns, MPH, PhD Date: 02-July-2024

Signature:

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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