NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A network meta-analysis to compare the rates of adverse events from RCTs of CGRP-targeted therapies for the prophylaxis of episodic migraine.
Protocol number	C4951096
Protocol version identifier	1.0
Date	25 May 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000874
Active substance	N02CD01 – Erenumab N02CD02 – Galcanezumab N02CD03 – Fremanezumab N02CD05 – Eptinezumab N02CD06 – Rimegepant N02CD07 – Atogepant
Medicinal product	Erenumab (Aimovig ®) Galcanezumab (Emgality ®) Fremanezumab (Ajovy ®) Eptinezumab (Vyepti ®) Rimegepant (Nurtec ODT® /Vydura®) Atogepant (Qulipta®/Aquipta ®)
Research question and objectives	**Research question** How do the rates of adverse events from Randomized Controlled Trials (RCTs) of calcitonin gene-related peptide (CGRP)-targeted therapies for episodic migraine (EM) prophylaxis compare to each other? **Primary Objectives** 1. To compare the relative rates of adverse events from RCTs of the primary outcomes: nausea, constipation & gastrointestinal discomfort/disturbances (as grouped outcome), fatigue & somnolence (as grouped outcome), and hypersensitivity reactions (as grouped outcome) between CGRP-targeted therapies for prophylaxis in EM. 2. To compare the relative rates of adverse events from RCTs of the secondary outcomes: nasopharyngitis, dyspnea, injection site-related

	AEs (as grouped outcome), and discontinuation (all-cause and due to AEs). **Secondary Objectives** To estimate the incidence (proportion) of various AEs and treatment discontinuation (all-cause and due to AEs) from RCTs.
Country(ies) of study	United States of America
Author	[redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CGRP	Calcitonin gene-related peptides
CI	Confidence interval
CM	Chronic migraine
DSU	Decision Support Unit
EC	Ethics Committee
EM	Episodic migraine
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOD	Every other day
FDA	Food & Drug Administration
GLMM	Generalized linear mixed models
GPP	Good Pharmacoepidemiology Practices
ICHD	International classification of headache disorders
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

ITC	Indirect treatment comparison
MA	Meta-analysis
mAb	Monoclonal antibody
MAGEC	Meta-analysis of adverse drug effects with censored data
MD	Migraine Day
NCT	National clinical trial
NI	Non-interventional
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OLE	Open-label extension
OR	Odds ratio
PASS	Post Authorization Safety Study
PL-NMA	Penalized likelihood network meta-analysis
RCT	Randomized controlled trial
RWD	Real World Data
SAP	Statistical analysis plan
SAE	Serious adverse event
SLR	Systematic literature review
TRAE	Treatment-related adverse event
TR-SAE	Treatment related serious adverse event
ULN	Upper limit of normal

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title:
A network meta-analysis to compare the rates of adverse events from RCTs of CGRP-targeted therapies for the prophylaxis of episodic migraine.

Protocol version:
1.0

Date:
25 May 2026

Main author:
[redacted]

Rationale and background:
Calcitonin gene-related peptide (CGRP)-targeted therapies, including monoclonal antibodies and gepants, are widely used for the prophylaxis of episodic migraine (EM). Direct head-to-head randomized comparisons of these therapies are limited, and safety outcomes are often inconsistently reported across trials, particularly for rare adverse events. The purpose of this study is to generate comparative evidence on rates of adverse events of CGRP-targeted therapies using appropriate approaches that can circumvent issues in data synthesis for safety outcomes.

Research question and objectives:
Research questions to be addressed by this study are as follows:

How do the rates of adverse events from Randomized Controlled Trials (RCTs) of CGRP-targeted therapies for EM prophylaxis compare to each other?

Primary objectives include:

1. To compare the relative rates of adverse events from RCTs of the primary outcomes: nausea, constipation & gastrointestinal discomfort/disturbances (as grouped outcome), fatigue & somnolence (as grouped outcome), and hypersensitivity reactions (as grouped outcome) between CGRP-targeted therapies for prophylaxis in EM.

2. To compare the relative rates of adverse events from RCTs of the secondary outcomes: nasopharyngitis, dyspnea, injection site-related AEs (as grouped outcome), and discontinuation (all-cause and due to AEs).

Secondary objectives include:

To estimate the incidence (proportion) of various AEs and treatment discontinuation (all-cause and due to AEs) from RCTs.

Study design:
The study is a network meta-analysis (NMA) of randomized controlled trials.

Population:
The population for this study are adult patients (≥18 years) with EM enrolled in randomized controlled trials evaluating CGRP-targeted therapies for migraine prophylaxis.

Variables:

The exposures for the proposed NMA in this study are: Erenumab, Galcanezumab, Fremanezumab, Eptinezumab, Rimegepant, Atogepant and placebo. The outcomes are: nausea, constipation, fatigue/somnolence, hypersensitivity reactions, nasopharyngitis, dyspnea, injection site-related AEs, all-cause discontinuation and discontinuation due to AEs. Covariate adjustment may be performed as part of the analysis including but not limited to the exposure duration.

Data sources:
The data sources used are aggregated study-level data extracted from published randomized controlled trials or available clinical study reports. These data sources will be identified through a separate systematic literature review (SLR) which does not fall under the scope of this protocol.

Study size:
Sample size calculations are not applicable. The study is based on aggregated data from eligible trials identified in the literature.

Data analysis:
Comparative safety outcomes will be estimated using NMA methods, including standard frequentist approaches, penalized likelihood models, and Bayesian models, to address sparse and zero-event data. Methodological details are provided on the statistical analysis plan (SAP).

Milestones:

Milestone	Planned Date
Start of data collection	01 July 2026
End of data collection	15 July 2026

Registration in the HMA-EMA Catalogues of RWD studies	01 June 2026
Final study report	31 December 2026

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection	01 July 2026
End of data collection	15 July 2026
Registration in the HMA-EMA Catalogues of RWD studies	01 June 2026
Final study report	31 December 2026

7. RATIONALE AND BACKGROUND

Migraine is a neurological disorder characterized by recurrent attacks of moderate to severe headache, often accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia [1]. The third edition of the International Classification of Headache Disorders (ICHD-3) categories migraine as episodic migraine (EM) – individuals having <15 headache days per month, or chronic migraine (CM) – headaches on ≥15 days per month for >3 months with features of migraine on ≥8 of those days [2].

Management of migraine involves acute treatment to alleviate symptoms during an attack and prophylactic (preventive) treatment to reduce frequency and severity of future attacks [1]. Prophylactic migraine treatments are indicated for individuals experiencing frequent or debilitating migraine attacks [3]. Recent treatments targeting the calcitonin gene-related peptides (CGRP) pathway, including CGRP-monoclonal antibodies (mAbs) (erenumab [receptor antagonist, subcutaneous], fremanezumab [peptide antagonist, subcutaneous], galcanezumab [peptide antagonist, subcutaneous], and eptinezumab [peptide antagonist, intravenous]) as well as gepants (including rimegepant [receptor antagonist, oral] and atogepant [receptor antagonist, oral]) [4] have been developed for prophylaxis [5] in addition to non-migraine specific canonical oral preventive treatments (e.g., topiramate).

Pfizer Europe MA EEIG and Pfizer Inc are the market authorization holders for rimegepant in Europe and the US respectively. Rimegepant is an oral selective CGRP receptor antagonist. Treatment with a CGRP receptor antagonist is thought to relieve migraine by: 1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal); 2) halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral and central sensitization); and/or 3) inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus [6]. Rimegepant has received regulatory licenses from the Food and Drug Administration (FDA) [7], as well as approval from the European Medicines Agency (EMA) [6] for both acute treatment and prevention of migraine.

The safety and tolerability of prophylactic treatments for chronic conditions such as migraine are important considerations for effective management of the condition. However, there have been very few head-to-head randomized controlled trials performed that directly compare these novel CGRP-targeted treatments, limiting the evidence to inform clinical decision making for treatment selection in migraine prophylaxis. By incorporating the available evidence into a single analytical framework, indirect treatment comparisons (ITCs) can help address this evidence gap.

Several ITCs including network meta-analyses (NMAs) compare safety outcomes of treatments of migraine, which include adverse events (AEs) and treatment discontinuation (for any reason or due to AEs). However, the reporting of safety outcomes is generally inconsistent and often incomplete, lacking standard definition/grouping of events, inconsistent minimum thresholds for reporting in publications, limited statistical power, issues of sparsity of treatment network and rare/zero events [8–10], as well as heterogeneity between trials (e.g., different follow-up period of safety outcomes).[11]
Low/zero event rate (in one or more arms) and small sample size do not fit naturally with standard meta-analysis (MA) and ITC methods because of the invalid assumption of large-sample normal approximations [12,13], division by zero for relative effect measures (odds ratios [ORs], risk ratios and rate ratios) [12], as well as mixed consensus over conducting valid MA, ITC or NMA including studies with zero events in all arms [14–16]. Although "continuity correction" is a common practical approach to handle rare safety data using conventional NMA methods where zero-event studies are imputed arbitrarily chosen constants (e.g., 0.5) [12,14], but results may be biased [14,15]. Clinical interpretation of ratio metric could be misleading without putting relevant absolute effects (e.g., difference in baseline prevalences) into context [17]. The ratio framework assumes proportional effects, but it remains unclear such multiplicative metric can be applied to safety outcomes.
The purpose of the study is to conduct an NMA to evaluate the safety outcomes, including AEs and all cause discontinuation of treatment, of rimegepant and other CGRP-targeted therapies in EM prophylaxis, using appropriate approaches that can circumvent issues in data synthesis for safety outcomes. Details of methodological approaches to address the challenges will be provided in a separate statistical analysis plan.
This non-interventional study is designated as a PASS (Post Authorization Safety Study) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research Question

Research questions to be addressed by this study are as follows:
How do the rates of adverse events from Randomized Controlled Trials (RCTs) of CGRP-targeted therapies for EM prophylaxis compare to each other?

8.2. Study Objectives

8.2.1. Primary Objectives

1. To compare the relative rates of adverse events from RCTs of the primary outcomes: nausea, constipation & gastrointestinal discomfort/disturbances (as grouped outcome), fatigue & somnolence (as grouped outcome), and hypersensitivity reactions (as grouped outcome) between CGRP-targeted therapies for prophylaxis in EM.
2. To compare the relative rates of adverse events from RCTs of the secondary outcomes: nasopharyngitis, dyspnea, injection site-related AEs (as grouped outcome), and discontinuation (all-cause and due to AEs).

8.2.2. Secondary Objectives

To estimate the incidence (proportion) of various AEs and treatment discontinuation (all-cause and due to AEs) from RCTs.

9. RESEARCH METHODS

9.1. Study Design

RCTs are considered the gold standard of comparative evidence by payers and clinicians. When RCTs directly comparing safety outcomes between prophylactic CGRP-targeted therapies for EM are limited, estimates of relative safety and tolerability between treatments can be generated using statistical approaches such as network meta-analyses[18]. These approaches synthesize estimates across studies (using the common comparators), and so incorporate all available estimates to produce consolidated estimates. In the absence of direct comparisons from RCT evidence, these methods are recognized as an appropriate approach to estimating the relative efficacy and safety between treatments based on the gold standard RCT evidence, as seen from their acceptance by health technology assessment agencies such as the National Institute for Health and Care Excellence (NICE) in the UK. The study is designed as an NMA with the objective to compare the safety profile of rimegepant with CGRP-targeted therapies in randomized trials for prophylaxis of EM. Analyses will be performed on data extracted from published studies or if unavailable, Clinical Study Reports. These data sources will be identified through a separate systematic literature review (SLR) which does not fall under the scope of this protocol. No patients will be enrolled in the study.

9.2. Setting

9.2.1. Inclusion criteria

The inclusion criteria below will be used to identify studies to be included in the NMA.

- Adult patients (≥18 years) diagnosed with episodic migraine
- Interventions used for migraine prophylaxis:
    - Rimegepant (any dose or frequency)
    - Erenumab (any dose or frequency)
    - Galcanezumab (any dose or frequency)
    - Fremanezumab (any dose or frequency)
    - Eptinezumab (any dose or frequency)
    - Atogepant (any dose or frequency)
- Comparators:

- Placebo
- Any treatment included in list of interventions

- Safety and tolerability outcomes, including (but not limited to):
  - Nausea,
  - Constipation,
  - Gastrointestinal discomfort/disturbances,
  - Fatigue,
  - Somnolence,
  - Hypersensitivity reactions
    - Hypersensitivity reaction
    - Anaphylaxis
    - Angioedema
    - Hypersensitivity event – rash
    - Severe rash
    - Urticaria
    - Swelling
    - Oedema
  - Nasopharyngitis
  - Dyspnea
  - Injection site-related AEs
    - Injection site pain
    - Injection site erythema
    - Injection site pruritus
    - Injection site reaction

        - Injection site induration
    - Discontinuation (all cause), Discontinuation due to AEs

- TRAEs (as above for AEs)
- SAEs (as above for AEs)
- TR-SAEs (as above for AEs)
- Clinically significant laboratory abnormalities, (including but not limited to): AST or ALT >3 x ULN and total bilirubin >2 x ULN
- RCTs
- Conference abstracts published in or after 2022
- No date restrictions for full publications
- English language studies

9.2.2. Exclusion criteria

Studies meeting any of the exclusion criteria below will not be included in the NMA.

- Studies in children or adolescents (<18 years)
- Studies exclusively in chronic migraine patients
- Studies not related to prophylaxis (prevention) of migraine
- Studies that do not include specified interventions and comparators
- Publications not reporting outcomes of interest
    - Interventional non-RCTs
    - OLEs
    - Case reports/case studies
    - Economic evaluations
    - Non-systematic or narrative reviews
    - Editorials, notes or comments

- Animal/in-vitro studies

- Conference abstracts published prior to 2022

- Non-English language studies

9.3. Variables

Table 1 shows the variables and their role in the analysis. All variables are sourced from RCTs identified by the SLR and also meet the inclusion criteria for the NMA. Operational definitions of variables are determined by the individual source RCTs.

Covariate adjustment may be performed as part of the analysis including but not limited to the exposure duration. Full details will be provided in the statistical analysis plan (SAP). Owing to the availability of aggregate data, any adjustment of the covariates will be restricted at the study-level. Details of methods of pre-classification of covariates as effect modifier or prognostic factor will be provided in the SAP.

Table 1. List of variables and roles in the analysis.

Variable	Role	Data Source(s)	Operational Definition
Nausea	Primary outcome	Included RCTs (see ANNEX 2 ADDITIONAL INFORMATION)	As determined by the individual source RCTs (see ANNEX 2 ADDITIONAL INFORMATION)
Constipation & Gastrointestinal discomfort/disturbances	Primary outcome (grouped)		
Fatigue & somnolence	Primary outcome (grouped)		
Hypersensitivity reactions, including: • Hypersensitivity reaction • Anaphylaxis • Angioedema • Hypersensitivity event – rash	Primary outcome (grouped)		

• Severe rash • Urticaria			
Hypersensitivity reactions, including • Swelling • Oedema	Primary outcome (grouped)		
Nasopharyngitis	Secondary outcome		
Dyspnea	Secondary outcome		
Injection site-related AEs, including • Injection site pain • Injection site erythema • Injection site pruritus • Injection site reaction • Injection site induration	Secondary outcome (grouped)		

Discontinuation (all cause)	Secondary outcome		
Discontinuation due to AEs	Secondary outcome		
Exposure Duration	Covariate		

9.4. Data Sources

The data sources for this NMA will be identified through an SLR which does not fall under the scope of this protocol. However, methodological details are provided in this section. Note that the SLR is also used for the identification of evidence for a separate NMA on efficacy, and is therefore broader in scope than the NMA on safety described in this protocol.

Search strategy

Eligibility criteria for the SLR update are outlined in Table 2.

Table 2. Inclusion and exclusion criteria for the SLR.

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients (≥18 years) diagnosed with episodic migraine	• Studies in children or adolescents (<18 years) • Studies exclusively in chronic migraine patients
Intervention and comparators	Interventions used to prevent migraine: • Rimegepant (either 75 mg QD or 75 mg EOD regimen) • Erenumab (any dose) • Galcanezumab (any dose) • Fremanezumab (any dose) • Eptinezumab (any dose) • Atogepant (any dose) • Topiramate (any dose)	• Studies that do not include specified interventions for inclusion • Studies not investigating a relevant intervention • Studies not related to prevention of migraine • Studies not investigating any relevant comparator

Criteria	Inclusion criteria	Exclusion criteria
Outcomes	Including, but not limited to: **Clinical efficacy outcomes calculated over Weeks 1–12 and 9–12 as available, including (but not limited to):** • Frequency/reduction of headache days per month • Frequency/reduction of MDs per month • 50% response • Severity of headaches and migraines • Frequency of use of rescue medication days per month **Safety and tolerability outcomes, including (but not limited to):** AEs (individual AEs and classes, potentially including but not limited to: • Nausea, constipation, fatigue, and somnolence (individual and as a grouped outcome), injection site-related AEs, including injection site pain • Injection site erythema • Injection site pruritus • Injection site reaction • Injection site induration (individual and as a grouped outcome). Hypersensitivity reactions including: • Hypersensitivity reaction • Anaphylaxis • Angioedema; hypersensitivity event; rash • Swelling; oedema; urticaria (individual and grouped outcome) **All-cause discontinuation including**: • Discontinuation • Discontinuation due to AEs (individual and as a grouped outcome) • Nasopharyngitis • TRAEs (as above for AEs) • SAEs (as above for AEs)	Publications not reporting outcomes of interest

Criteria	Inclusion criteria	Exclusion criteria
	• TR-SAEs (as above for AEs) • Clinically significant laboratory abnormalities, (including but not limited to): AST or ALT >3 x ULN and total bilirubin >2 x ULN	
Study design	RCTs OLE to RCTs	• Interventional non-RCTs (with the exception of OLEs) • Case reports/case studies • Economic evaluations • Non-systematic or narrative reviews • Editorials, notes or comments • Animal/in-vitro studies
Publication date	Conference abstracts published in or after 2022 No date restrictions for full publications	Conference abstracts published prior to 2022
Language	English language studies	Non-English language studies

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOD, every other day; MD, migraine day; OLE, open-label extension; RCT, randomized controlled trial; SAE, serious adverse event; TRAE, treatment-related adverse event; TR-SAE; treatment related serious adverse events; ULN, upper limit of normal

Databases searched

The following electronic databases were searched via the Ovid platform (http://ovidsp.ovid.com/):

- Embase®, 1974 to present
- MEDLINE®, 1946 to present, including:
  - MEDLINE Epub Ahead of Print
  - MEDLINE In-Process & Other Non-Indexed Citations
  - MEDLINE Daily
- Evidence-Based Medicine (EBM) Reviews, incorporating:
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Cochrane Database of Systematic Reviews

Supplementary sources

Reference lists of eligible studies (primary studies and relevant reviews) included at full publication screening were searched to identify any further relevant publications that were not identified as part of the database searches.

Conference proceedings

- European Academy of Neurology (EAN)
- European Headache Federation (EHF)
- International Headache Society (IHS)
- Migraine Trust International Symposium (MTIS)
- World Congress of Neurology (WCN)

HTA Global bodies

The following HTA websites were searched to identify relevant previous HTA submissions:

- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
- Scottish Medicines Consortium (SMC): https://www.scottishmedicines.org.uk/
- Canada's Drug Agency (CDA-AMC) (formerly Canadian Agency for Drugs and Technologies in Health [CADTH]): https://www.cda-amc.ca/
- Pharmaceutical Benefits Advisory Committee (PBAC): https://www.pbs.gov.au/pbs/home
- Haute Autorité de Santé (HAS): https://www.has-sante.fr/
- Institute for Quality and Efficiency in Health Care (IQWiG): https://www.iqwig.de/
- International Network of Agencies for Health Technology Assessment (INAHTA) database website (https://database.inahta.org/)

Trial registries

The following trial registries were searched to identify ongoing/currently recruiting studies:

- US National Institutes of Health (NIH) registry and results database: https://clinicaltrials.gov
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP): http://apps.who.int/trialsearch/

Screening

Upon search completion, duplicate citations were removed and potentially relevant citations exported into an Excel® database.

Titles and abstracts of individual unique citations were then screened against the pre-defined inclusion/exclusion criteria (Table 1) by two independent reviewers. Those citations that

were excluded at this stage were assigned one of the exclusion codes (using the following hierarchy):

- Not relevant disease
- Not relevant migraine population
- Not relevant intervention
- Duplicate publication
- Not relevant study design
- Animal/*in vitro* study
- Protocol only
- Publication date pre-2022 (for conference abstracts only)
- Review/editorial
- Linked publication (e.g. a conference abstract that has been superseded by a full journal article and does not report any unique data)

Full papers were obtained for all included references. Full papers were independently examined by two reviewers to determine whether they met the inclusion criteria. All papers excluded at this second stage of the screening process were assigned one of the following exclusion codes (using the following hierarchy):

- Not relevant disease
- Not relevant migraine population
- Not relevant intervention
- Not relevant outcome
- Protocol only
- Review/editorial
- Duplicate publication
- Not relevant study design
- Animal/*in vitro* study
- Linked publication

With respect to both screening stages, any discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer. This final list was also cross-checked against the publications included in other Pfizer ITCs to confirm whether any additional publications should be considered.

Data extraction
Relevant outcome data for eligible interventions were incorporated into the summary tables from the previous NICE submission for rimegepant (TA906) in Word®.

Assessment of bias

The risk of bias of each individual study was assessed to ensure that the conclusions and findings of the review are based on the best available evidence and that any sources of bias in the data are identified. The risk of bias in the studies was assessed using the quality assessment tool developed by the University of York's CRD ([19]). Two reviewers assessed risk of bias and any discrepancies were resolved through discussion or the intervention of a third reviewer.

9.5. Study Size

In this NMA, as the data will be collected from the literature, there are no a priori hypotheses to test and sample size calculations are not applicable. The primary data source for this study will be the relevant publications identified by a separate SLR. The initial review identified six publications including rimegepant. All except one study (CHALLENGE-MiG, which included both rimegepant and galcanezumab) used placebo as comparator. For the active treatment arm(s), atogepant was included in four studies, eptinezumab in two, erenumab in eight, fremanezumab in four, and galcanezumab in six studies. The final number of included studies will be based on the results of the final SLR and may differ slightly from the results presented in this protocol. The analyses will be based on aggregate, study-level data from the literature or clinical study reports.

9.6. Data Management

All study data exist as structured data by the time of study. Analyses will be conducted using R statistical software. Versions of packages will be documented to ensure reproducibility. Data was independently extracted by at least two individuals for endpoints and study designs. Any differences in interpretation then being reconciled through discussion.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study are documented in the SAP, which will be dated, filed, and maintained. 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. As no single method can a priori clearly be stated to be ‘best’, at least two models will be used allowing for a structural sensitivity analysis, and similarity/familiarity with other estimates.[20] Although the method could differ by AE, the rationale for such an approach would be difficult to defend, and thus the use of a consistent model is preferred for all included outcomes unless there are strong reasons to vary the approach, which would be documented should it occur.
Following data extraction (previously described), data will be converted to a consistent format i.e. percentages converted to count data, and intermediate tables produced of the inputs to models, in a consistent format for all studies. These intermediate steps will then be reported, and used as inputs in analyses. An overview of the planned analyses is provided below:

1. A ‘standard’ NMA either dropping zero event studies, or using a continuity correction, i.e., for obtaining point estimates and confidence intervals (CIs) of the

relative effectiveness to illustrate the difference seen to estimates currently available in the literature.

2. The penalized likelihood NMA (PL-NMA), a frequentist approach, will be used due to its ability to handle zero events in both arms and thus provides a familiar comparison, but without the issues that can arise with zeros in the more common frameworks [21].
3. Generalized linear mixed model (GLMM), conducted within a Bayesian framework (to allow for priors) [22,23]. This would seem the most appropriate method, allowing for estimates of both the absolute and relative difference between interventions. The method is also able to handle zero-event studies but provide absolute and relative differences between treatments.

Model outputs will be reported, along with appropriate summary statistics (which differ by model), for example the I^2 statistic as a measure of heterogeneity in NMA. To handle the issue of censoring due to differential 'threshold reporting' across studies (assuming this remains following data extraction), the following analyses will be conducted:

1. Base case and sensitivity analysis. In the base case, a relationship where numbers are low (but not necessarily zero) will be assumed, and then an alternative sensitivity analysis where they are set to zero and/or the maximum possible to not trigger reporting implemented, in order to understand the difference the assumption made. The approach selected as the base case will be clearly justified and will likely depend on the number (and type) of affected variables, the key being at least two approaches be used to understand the importance of the assumption(s). Should values be assumed, these will be informed, whenever possible, by other report(s) that studied the same treatment and safety outcome(s). Otherwise, arbitrary values will be used as required (e.g., a third of the threshold value) or based on data from AEs that is reported in 'any AEs' studies, that would not have reached reporting thresholds.

2. An attempt to extend the GLMM model to include the information that is available, even though (full) count data is not. Such an approach would be in line (or potentially apply) the MAGEC (Meta-analysis of adverse drug effects with censored data) approach, and, would seem theoretically possible in a Bayesian framework to include the information that is known, which is broadly equivalent to the information in a significance marker or "p<0.01".[24] This is although the exact figure is not given, it is known the actual value is below the given threshold (albeit with different thresholds in use).

Subgroup analyses will be considered in instances where there is a strong clinical or methodological rationale with an underlying feasible mechanism of action and the availability of data allow such an analysis.

9.8. Quality Control

All analyses will be performed in the statistical software R. GitHub will be used for version control and quality assurance throughout the project lifecycle to facilitate collaboration, transparency, and traceability of code changes. All analyses will undergo an internal review process conducted by a separate member of the Petauri Evidence team. At a minimum, all study documents (protocol, report, publications) will be reviewed by the entire study team, including Pfizer statistical experts in indirect treatment comparisons. Clinical expertise is available for input into protocol and SAP development and appropriate interpretation of results. At the start of the project, a kick-off meeting will establish a regular communication plan (via e-mail and regular teleconferences); and establish internal timelines to be completed in time to allow review and quality control before submitting each deliverable. Final versions of required documentation will be stored on Pfizer's Global Document Management System, in accordance with Pfizer compliance procedures. Clinical review will be performed by an experienced clinician (M.D.) with expertise running clinical trials in the field of migraine. The statisticians performing the analysis all hold relevant postgraduate qualifications (including MPH, MSc, PhD, Cstat), with associated professional experience.

9.9. Limitations of the Research Methods

Meta-analysis and network meta-analysis (NMA) of safety outcomes face significant challenges, primarily due to rare events, inconsistent reporting, and high heterogeneity across studies. Key problems include publication bias, low statistical power for rare adverse events, and unreliable indirect comparisons in NMAs if the consistency assumption is violated [16,25,26]. Further to this, the NMA is still limited by a sparse evidence network for rare (but non-zero) events that is anchored via common placebos. This restricts the ability to estimate between-study heterogeneity or assess inconsistency. Subgroup analyses, meta-regressions, and covariate adjustments may not be feasible due to data unavailability, and small sample sizes combined with minor differences in outcome definitions introduce further uncertainty. As a result, findings should be interpreted cautiously, recognizing that the analysis provides only indirect evidence.

This analysis assumes that each study is internally consistent in providing a valid comparison against (generally) placebo, but there are differences across studies. These differences are extensive and included study duration, reported endpoints, outcome definitions, outcome measurement periods, handling of missing data, and concomitant medication allowed. [27–52]

The differences across trials include not just differences in trial design, but also differences in patient populations. For instance, development of the interventions was different with some drugs having separate studies for CM and EM patients, whilst other drugs had larger studies combining both types of patients. In addition, for some interventions separate trials were conducted for treatment naïve patients and those with failures of prior treatments, whereas other interventions had studies which enrolled patients of all experience levels. Reporting of prior failures for patients, however, was generally poor across studies, with relevant data often unavailable.

Our findings will be limited to average treatment effects due to the lack of individual patient data and we will not include combination drugs. Assumption of transitivity may be violated when both oral and injection-route treatments are included.
Analytically, it should be noted that some approaches may not work or be viable, e.g., due to model convergence issues for the Bayesian NMA, but it is believed that it is worthwhile as it would be a methodological advance in being able to include additional data points in modelling i.e. that although the exact number of events are not known, it would be under a given threshold.
As the evidence base for this analysis consists of RCTs, valid conclusions should appropriately reflect the limitations of this evidence base, including restricted patient population and follow-up time and powering for efficacy rather than safety outcomes.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

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

10.2. Patient Consent

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

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

This is a network meta-analysis based on a literature review and no IRB/EC approval is required.

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 Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE) [53], European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [54].
Where possible/applicable, all approaches to conduct NMA on evaluating safety of rimegepant in EM prophylaxis will follow international best practices for ITC, including guidance from NICE Decision Support Unit (DSU) [55], International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [56,57], and the Cochrane Handbook [58].

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 is not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

One or more abstracts may be developed and submitted to relevant scientific conference(s) and manuscript(s) will be developed and submitted to relevant peer-reviewed medical journals within 12 months of study completion. A top-line redacted report will be placed on the HMA-EMA portal according to the PASS process. Authorship will follow the guidelines proposed by the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Any potential conflicts of interest will be disclosed.
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.

13. REFERENCES

1. Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLOS ONE. 2015 Jul 14;10(7):e0130733. doi:10.1371/journal.pone.0130733

2. Olesen J. International Classification of Headache Disorders. The Lancet Neurology. 2018 May 1;17(5):396–7. doi:10.1016/S1474-4422(18)30085-1 PubMed PMID: 29550365.

3. Ha H, Gonzalez A. Migraine Headache Prophylaxis. afp. 2019 Jan 1;99(1):17–24.

4. Russo AF, Hay DL. CGRP physiology, Pharmacology, and Therapeutic Targets: Migraine and Beyond. Physiological Reviews. 2023 Apr;103(2):1565–644. doi:10.1152/physrev.00059.2021

5. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on Integrating New Migraine Treatments into Clinical Practice. Headache: The Journal of Head and Face Pain. 2021;61(7):1021–39. doi:10.1111/head.14153

6. European Medicines Agency. Vydura | European Medicines Agency (EMA) [Internet]. 2022 [cited 2025 May 19]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/vydura.

7. Scott LJ. Rimegepant: First Approval. Drugs. 2020 May 1;80(7):741–6. doi:10.1007/s40265-020-01301-3

8. Xia HA, Jiang Q. Statistical Evaluation of Drug Safety Data. Drug Inf J. 2014 Jan 1;48(1):109–20. doi:10.1177/2168479013510917

9. Chen KY, Borglund EM, Postema EC, Dunn AG, Bourgeois FT. Reporting of Clinical Trial Safety Results in ClinicalTrials.gov for FDA-approved Drugs: A Cross-sectional Analysis. Clinical Trials. 2022 Aug 1;19(4):442–51. doi:10.1177/17407745221093567

10. Council for International Organizations of Medical Sciences. Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI. Geneva: CIOMS; 2005.

11. Bennetts M, Whalen E, Ahadieh S, Cappelleri JC. An appraisal of meta-analysis guidelines: how do they relate to safety outcomes? Res Synth Methods. 2017 Mar;8(1):64–78. doi:10.1002/jrsm.1219 PubMed PMID: 27612447.

12. Efthimiou O. Practical Guide to the Meta-analysis of Rare Events. Evid Based Mental Health. 2018 May 2;21(2). doi:10.1136/eb-2018-102911 PubMed PMID: 10.1136/eb-2018-102911.

13. Xu C, Zhou X, Zorzela L, Ju K, Furuya-Kanamori L, Lin L, et al. Utilization of the Evidence from Studies With No Events in Meta-analyses of Adverse Events: An Empirical investigation. BMC Med. 2021 Jun 15;19(1):141. doi:10.1186/s12916-021-02008-2

14. J. Sweeting M, J. Sutton A, C. Lambert P. What to Add to Nothing? Use and Avoidance of Continuity Corrections in Meta-analysis of Sparse Data. Statistics in Medicine. 2004;23(9):1351–75. doi:10.1002/sim.1761

15. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much Ado About Nothing: A Comparison of the Performance of Meta-analytical Methods with Rare Events. Statistics in Medicine. 2007;26(1):53–77. doi:10.1002/sim.2528

16. Zhou Y, Zhu B, Lin L, Kwong JSW, Xu C. Protocols for meta-analysis of intervention safety seldom specified methods to deal with rare events. Journal of Clinical Epidemiology. 2020 Dec 1;128:109–17. doi:10.1016/j.jclinepi.2020.09.023

17. Tang Y, Tang Q, Yu Y, Wen S. A Bayesian Meta-analysis Method for Estimating Risk Difference of Rare Events. Journal of Biopharmaceutical Statistics. 2018 May;28(3):550–61. doi:10.1080/10543406.2017.1372767

18. Adas MA, Allen VB, Yates M, Bechman K, Clarke BD, Russell MD, et al. A systematic review and network meta-analysis of the safety of early interventional treatments in

rheumatoid arthritis. Rheumatology (Oxford). 2021 Oct 1;60(10):4450–62. doi:10.1093/rheumatology/keab429

19. Systematic Reviews: CRD's guidance for undertaking reviews in health care [Internet]. University of York CRD; 2009. Available from: https://www.york.ac.uk/media/crd/newpagesspring2025/Systematic_Reviews_CRD_guidance.pdf

20. Hong H, Wang C, Rosner GL. Meta-Analysis of Rare Adverse Events in Randomized Clinical Trials: Bayesian and Frequentist Methods. Clin Trials. 2021 Feb;18(1):3–16. doi:10.1177/1740774520969136 PubMed PMID: 33258698; PubMed Central PMCID: PMC8041270.

21. Evrenoglou T, White IR, Afach S, Mavridis D, Chaimani A. Network Meta-analysis of Rare Events using Penalized Likelihood Regression. Statistics in Medicine. 2022;41(26):5203–19. doi:10.1002/sim.9562

22. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials [Internet]. 2011 Aug. Available from: http://research-information.bristol.ac.uk/files/7215331/TSD2_General_meta_analysis.final.08.05.12.pdf.

23. Bhaumik DK, Amatya ,Anup, Normand ,Sharon-Lise T., Greenhouse ,Joel, Kaizar ,Eloise, Neelon ,Brian, et al. Meta-Analysis of Rare Binary Adverse Event Data. Journal of the American Statistical Association. 2012 Jun 1;107(498):555–67. doi:10.1080/01621459.2012.664484 PubMed PMID: 23734068.

24. Qi X, Zhou S, Peterson CB, Wang Y, Fang X, Wang ML, et al. Meta-analysis of Censored Adverse Events. N Engl J Stat Data Sci. 2024 Oct;2(3):380–92. doi:10.51387/24-nejsds62 PubMed PMID: 39991459; PubMed Central PMCID: PMC11845246.

25. Stoto MA. Drug Safety Meta-Analysis: Promises and Pitfalls. Drug Saf. 2015 Mar 1;38(3):233–43. doi:10.1007/s40264-015-0268-x

26. Huang HY, Andrews E, Jones J, Skovron ML, Tilson H. Pitfalls in meta-analyses on adverse events reported from clinical trials. Pharmacoepidemiology and Drug Safety. 2011;20(10):1014–20. doi:10.1002/pds.2208

27. Kitamura S, Matsumori Y, Yamamoto T, Ishikawa T, Hoshino Y, Yoshimatsu H, et al. Efficacy and safety of rimegepant for the preventive treatment of migraine in Japan: A double-blind, randomized controlled trial. Headache: The Journal of Head and Face Pain. 2025;65(8):1403–12. doi:10.1111/head.14995

28. Bigal ME, Dodick DW, Rapoport AM, Silberstein SD, Ma Y, Yang R, et al. Safety, tolerability, and efficacy of TEV-48125 for preventive treatment of high-frequency episodic migraine: a multicentre, randomised, double-blind, placebo-controlled, phase 2b study. Lancet Neurol. 2015 Nov;14(11):1081–90. doi:10.1016/S1474-4422(15)00249-5 PubMed PMID: 26432182.

29. Sun H, Dodick DW, Silberstein S, Goadsby PJ, Reuter U, Ashina M, et al. Safety and Efficacy of AMG 334 for Prevention of Episodic Migraine: A Randomised, Double-blind, Placebo-controlled, Phase 2 Trial. The Lancet Neurology. 2016 Apr 1;15(4):382–90. doi:10.1016/S1474-4422(16)00019-3

30. Dodick DW, Ashina M, Brandes JL, Kudrow D, Lanteri-Minet M, Osipova V, et al. ARISE: A Phase 3 Randomized Trial of Erenumab for Episodic Migraine. Cephalalgia. 2018 May 1;38(6):1026–37. doi:10.1177/0333102418759786

31. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F, et al. A Controlled Trial of Erenumab for Episodic Migraine. New England Journal of Medicine. 2017 Nov 30;377(22):2123–32. doi:10.1056/NEJMoa1705848

32. Sakai F, Ozeki A, Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. Cephalalgia Reports. 2020 Jan 1;3:2515816320932573. doi:10.1177/2515816320932573

33. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, et al. Safety, Tolerability, and Efficacy of Orally Administered Atogepant for the Prevention of Episodic Migraine in Adults: A Double-blind, Randomised Phase 2b/3 Trial. The Lancet Neurology. 2020 Sep 1;19(9):727–37. doi:10.1016/S1474-4422(20)30234-9 PubMed PMID: 32822633.

34. Sakai F, Takeshima T, Tatsuoka Y, Hirata K, Lenz R, Wang Y, et al. A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. Headache. 2019 Nov;59(10):1731–42. doi:10.1111/head.13652 PubMed PMID: 31612482; PubMed Central PMCID: PMC6900095.

35. Dodick DW, Silberstein SD, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T, et al. Effect of Fremanezumab Compared with Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018 May 15;319(19):1999–2008. doi:10.1001/jama.2018.4853

36. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and Safety of Galcanezumab for the Prevention of Episodic Migraine: Results of the EVOLVE-2 Phase 3 Randomized Controlled Clinical Trial. Cephalalgia. 2018 Jul 1;38(8):1442–54. doi:10.1177/0333102418779543

37. Ashina M, Saper J, Cady R, Schaeffler BA, Biondi DM, Hirman J, et al. Eptinezumab in Episodic Migraine: A Randomized, Double-blind, Placebo-controlled Study (PROMISE-1). Cephalalgia. 2020 Mar 1;40(3):241–54. doi:10.1177/0333102420905132

38. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurology. 2018 Sep 1;75(9):1080–8. doi:10.1001/jamaneurol.2018.1212

39. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, et al. Oral Rimegepant for Preventive Treatment of Migraine: a Phase 2/3, Randomised, Double-blind, Placebo-controlled Trial. The Lancet. 2021 Jan;397(10268):51–60. doi:10.1016/S0140-6736(20)32544-7

40. Mulleners WM, Kim BK, Láinez MJA, Lanteri-Minet M, Pozo-Rosich P, Wang S, et al. Safety and Efficacy of Galcanezumab in Patients for whom Previous Migraine Preventive Medication from Two to Four Categories Had Failed (CONQUER): A Multicentre, Randomised, Double-blind, Placebo-controlled, Phase 3b Trial. The Lancet Neurology. 2020 Oct 1;19(10):814–25. doi:10.1016/S1474-4422(20)30279-9

41. Wang SJ, RoxasJr AA, Saravia B, Kim BK, Chowdhury D, Riachi N, et al. Randomised, Controlled Trial of Erenumab for the Prevention of Episodic Migraine in Patients from Asia, the Middle East, and Latin America: The EMPOwER study. Cephalalgia. 2021 Nov 1;41(13):1285–97. doi:10.1177/03331024211024160

42. Ferrari MD, Diener HC, Ning X, Galic M, Cohen JM, Yang R, et al. Fremanezumab Versus Placebo for Migraine Prevention in Patients with Documented Failure to up to Four Migraine Preventive Medication Classes (FOCUS): A Randomised, Double-blind, Placebo-controlled, Phase 3b Trial. The Lancet. 2019 Sep 21;394(10203):1030–40. doi:10.1016/S0140-6736(19)31946-4 PubMed PMID: 31427046.

43. Sakai F, Suzuki N, Kim BK, Tatsuoka Y, Imai N, Ning X, et al. Efficacy and Safety of Fremanezumab for Episodic Migraine Prevention: Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial in Japanese and Korean Patients. Headache: The Journal of Head and Face Pain. 2021;61(7):1102–11. doi:10.1111/head.14178

44. Matsumori Y, Yamada H, Nagaseki Y, Shimizu K, Nagy K, Matsuzawa R, et al. Atogepant for the preventive treatment of episodic migraine in Japanese participants: A phase 2/3, randomized, double-blind, placebo-controlled trial with an active treatment extension (RELEASE). Cephalalgia. 2025 Sep 1;45(9):03331024251374569. doi:10.1177/03331024251374569

45. Schwedt TJ, Myers Oakes TM, Martinez JM, Vargas BB, Pandey H, Pearlman EM, et al. Comparing the Efficacy and Safety of Galcanezumab Versus Rimegepant for Prevention

of Episodic Migraine: Results from a Randomized, Controlled Clinical Trial. Neurol Ther. 2024 Feb 1;13(1):85–105. doi:10.1007/s40120-023-00562-w

46. Tassorelli C, Nagy K, Pozo-Rosich P, Lanteri-Minet M, Sacco S, Nežádal T, et al. Safety and Efficacy of Atogepant for the Preventive Treatment of Episodic Migraine in Adults for Whom Conventional Oral Preventive Treatments Have Failed (ELEVATE): A Randomised, Placebo-controlled, Phase 3b Trial. The Lancet Neurology. 2024 Apr 1;23(4):382–92. doi:10.1016/S1474-4422(24)00025-5 PubMed PMID: 38364831.

47. Hu B, Li G, Li X, Wu S, Yu T, Li X, et al. Galcanezumab in Episodic Migraine: the Phase 3, Randomized, Double-blind, Placebo-controlled PERSIST Study. J Headache Pain. 2022 Jul 28;23(1):90. doi:10.1186/s10194-022-01458-0

48. Paiva Da Silva Lima G, Rao R, Szabó G, Szklener S, Tassorelli C, Nastaj M, et al. Comprehensive assessment of erenumab efficacy in participants with high-frequency episodic migraine with at least one previously failed preventive treatment: The EMBRACE study. Headache. 2025 Oct 14;head.15071. doi:10.1111/head.15071

49. Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, et al. Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. The Lancet Neurology. 2022 Jul;21(7):597–607. doi:10.1016/S1474-4422(22)00185-5

50. Reuter U, Goadsby PJ, Lanteri-Minet M, Wen S, Hours-Zesiger P, Ferrari MD, et al. Efficacy and Tolerability of Erenumab in Patients with Episodic Migraine in Whom Two-to-four Previous Preventive Treatments Were Unsuccessful: A Randomised, Double-blind, Placebo-controlled, Phase 3b Study. The Lancet. 2018 Nov 24;392(10161):2280–7. doi:10.1016/S0140-6736(18)32534-0 PubMed PMID: 30360965.

51. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L, et al. Atogepant for the Preventive Treatment of Migraine. New England Journal of Medicine. 2021 Aug 18;385(8):695–706. doi:10.1056/NEJMoa2035908

52. Takeshima T, Sakai F, Hirata K, Imai N, Matsumori Y, Yoshida R, et al. Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study. Headache. 2021 Jun;61(6):927–35. doi:10.1111/head.14138 PubMed PMID: 34153117; PubMed Central PMCID: PMC8361926.

53. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiology Practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2–10. doi:10.1002/pds.3891 PubMed PMID: 26537534.

54. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. Methodological Guide [Internet]. 2023 [cited 2025 Sep 17]. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. Available from: https://encepp.europa.eu/encepp-toolkit/methodological-guide_en.

55. NICE DSU. Evidence Synthesis TSD Series - A series of TSDs have been produced in the area of evidence synthesis [Internet]. 2025 [cited 2025 Aug 21]. Evidence Synthesis TSD Series. Available from: https://sheffield.ac.uk/nice-dsu/tsds/evidence-synthesis.

56. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting Indirect Treatment Comparisons and Network Meta-Analysis for Health-Care Decision Making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value in Health. 2011 Jun 1;14(4):417–28. doi:10.1016/j.jval.2011.04.002 PubMed PMID: 21669366.

57. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting Indirect-Treatment-Comparison and Network-Meta-Analysis Studies: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. Value in Health. 2011 Jun 1;14(4):429–37. doi:10.1016/j.jval.2011.01.011 PubMed PMID: 21669367.

58. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions (current version) [Internet]. 2024 [cited 2025 Sep 17]. Cochrane Handbook for Systematic Reviews of Interventions (version 6.5). Available from: https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current.

14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Not applicable

ANNEX 2. ADDITIONAL INFORMATION

Table 3 presents the list of studies anticipated in the NMA and operational definitions of AEs. The final list may be subject to small changes.

Table 3. List of studies anticipated in the NMA and operational definitions of AEs.

NCT Number	Publication	Study acronym	Funder	Study drug	Study arms	Patients randomized	Population	Operational Definition of AEs	Reference
NCT04740827	Tassorelli et al. (2024)	ELEVATE	Allergan	Atogepant	2	315	mITT	SAP Section 10.2 https://cdn.clinicaltrials.gov/large-docs/27/NCT04740827/SAP_001.pdf	[46]
NCT02848326	Goadsby et al. (2020)	-	Allergan	Atogepant	6	834	mITT	SAP Section 5.1.1.4 (Safety Analyses) and Section 6.5.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/26/NCT02848326/SAP_001.pdf	[33]
NCT03777059	Ailani et al. (2021)	ADVANCE	Allergan	Atogepant	4	910	mITT	SAP Section 11 (Safety Analyses) and Section 11.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/59/NCT03777059/SAP_001.pdf	[51]
NCT05861427	Matsumori et al. (2025)	RELEASE	AbbVie	Atogepant	4	523	mITT	SAP Section 3.4 (Safety Endpoints) and Section 10.2 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/27/NCT05861427/SAP_001.pdf	[44]
NCT02559895	Ashina et al. (2020)	PROMISE-1	Alder Biopharmaceuticals	Eptinezumab	4	898	Full analysis	SAP Section 2.6 (Safety Analysis) and Section 3.6 (Analysis of Safety Endpoints) https://cdn.clinicaltrials.gov/large-docs/95/NCT02559895/SAP_001.pdf	[37]
NCT04418765	Ashina et al. (2022)	DELIVER	Lundbeck	Eptinezumab	3	892	Efficacy analysis	SAP Section 13.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-	[49]

NCT03096834	Reuter et al. (2018)	LIBERTY	Novartis	Erenumab	2	246	ITT	docs/65/NCT04418765/SAP_001.pdf SAP Section 2.7.1 (Adverse events), with term definitions in Section 2.1.2 https://cdn.clinicaltrials.gov/large-docs/34/NCT03096834/SAP_001.pdf	[50]
NCT01952574	Sun et al. (2016)	-	Amgen	Erenumab	4	483	Efficacy analysis	No protocol/SAP posted on ClinicalTrials.gov; see publication Methods (safety): Sun et al. 2016, Lancet Neurology https://doi.org/10.1016/S1474-4422(16)00019-3	[29]
NCT03812224	Takeshima et al. (2021)	-	Amgen	Erenumab	2	261	Efficacy analysis	SAP Section 5.1.3 (Safety Endpoints) and 9.6 (Safety Analyses) https://cdn.clinicaltrials.gov/large-docs/24/NCT03812224/SAP_001.pdf	[52]
NCT02630459	Sakai et al. (2019)	-	Amgen	Erenumab	4	475	Treated	SAP Section 6.1.2 (Safety Endpoints) and Section 10.6.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/59/NCT02630459/SAP_001.pdf	[34]
NCT02483585	Dodick et al. (2018)	ARISE	Amgen	Erenumab	2	577	Efficacy analysis	No protocol/SAP posted on ClinicalTrials.gov; see publication Methods (safety): Dodick et al. 2018, Cephalalgia https://doi.org/10.1177/0333102418759786	[30]
NCT02456740	Goadsby et al. (2017)	STRIVE	Amgen & Novartis	Erenumab	3	955	Efficacy analysis	No protocol/SAP posted on ClinicalTrials.gov; see publication Methods (safety): Goadsby et al. 2017, NEJM https://doi.org/10.1056/NEJMoa1705848	[31]
NCT03333109	Wang et al. (2021)	EMPOwER	Novartis	Erenumab	3	900	mITT	SAP Section 2.7.1 (Adverse events), with term definitions in Section 2.1.3	[41]

NCT04252742	Paiva da Silva Lima et al. (2025)	EMBRACE	Amgen	Erenumab	2	512	Efficacy analysis	https://cdn.clinicaltrials.gov/large-docs/09/NCT03333109/SAP_001.pdf SAP Section 5.1.4 (Safety Endpoints) and Section 9.6 (Safety Analysis) https://cdn.clinicaltrials.gov/large-docs/42/NCT04252742/SAP_001.pdf	[48]
NCT02025556	Bigal et al. (2015)	-	Teva	Fremanezumab	3	297	ITT	No protocol/SAP posted on ClinicalTrials.gov; see publication Methods (safety): Bigal et al. 2015, Lancet Neurology https://doi.org/10.1016/S1474-4422(15)00249-5	[28]
NCT03303092	Sakai et al. (2021)	-	Otsuka	Fremanezumab	3	357	Efficacy analysis	SAP Section 9.2 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/92/NCT03303092/SAP_001.pdf	[43]
NCT02629861	Dodick et al. (2018)	HALOEM	Teva	Fremanezumab	3	875	Efficacy analysis	SAP Section 2.2.4 (Safety and Tolerability Endpoints) and Section 7.3 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/61/NCT02629861/SAP_001.pdf	[35]
NCT03308968	Ferrari et al. (2019)	FOCUS	Teva	Fremanezumab	3	838	ITT	SAP Section 8.3 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/68/NCT03308968/SAP_001.pdf	[42]
NCT02959177	Sakai et al. (2020)	-	Eli Lilly	Galcanezumab	3	459	ITT	SAP Section 5.4.4 (Safety Endpoints) and Section 5.5.12.1.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/77/NCT02959177/SAP_000.pdf	[32]
NCT03559257	Mulleners et al. (2020)	CONQUER	Eli Lilly	Galcanezumab	4	463	Total	SAP Section 5.4.4 (Safety Endpoints) and Section 5.5.12.1.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/57/NCT03559257/SAP_001.pdf	[40]

NCT02614183	Stauffer et al. (2018)	EVOLVE-1	Eli Lilly	Galcanezumab	3	862	ITT	SAP Section 5.4.4 (Safety Endpoints) and Section 5.5.12.1.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/83/NCT02614183/SAP_001.pdf	[38]
NCT03963232	Hu et al. (2022)	PERSIST	Eli Lilly	Galcanezumab	2	520	Treated	SAP Section 5.4.4 (Safety Endpoints) and Section 6.14.2 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/32/NCT03963232/SAP_001.pdf	[47]
NCT02614196	Skljarevski et al. (2018)	EVOLVE-2	Eli Lilly	Galcanezumab	3	922	ITT	SAP Section 5.4.4 (Safety Endpoints) and Section 5.5.12.1.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/96/NCT02614196/SAP_001.pdf	[36]
NCT05127486	Schwedt et al. (2024)	CHALLENGE-MiG	Eli Lilly	Galcanezumab	2	580	ITT	SAP Section 20.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/86/NCT05127486/SAP_001.pdf	[45]
NCT03732638	Croop et al. (2021)	-	Pfizer	Rimegepant	2	747	Evaluable mITT	SAP Section 6.5 (Safety) and Section 6.5.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/38/NCT03732638/SAP_002.pdf	[39]
NCT05399485	Kitamura et al. (2025)	309	Pfizer	Rimegepant	2	496	DBT migraine analysis	SAP Section 6.4 (Safety), Section 6.4.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/85/NCT05399485/SAP_001.pdf	[27]
NCT05518123	0	407	Pfizer	Rimegepant	2	658	DBT migraine analysis	SAP Section 6.4 (Safety) and Section 6.4.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-docs/23/NCT05518123/SAP_001.pdf	
NCT05217927	0	404	Pfizer	Rimegepant	3	699	Migraine analysis set	SAP Section 6.4 (Safety) and Section 6.4.1 (Adverse Events) https://cdn.clinicaltrials.gov/large-	

NCT05810038	0	319	Pfizer	Rimegepant	2	787	DBT migraine analysis set	docs/27/NCT05217927/SAP_001.pdf SAP Sections 6.2.6 to 6.2.8, and SAP Section 6.6. (internal document). Public information available in secondary outcomes measures table on: https://clinicaltrials.gov/study/NCT05810038?term=NCT05810038&viewType=Card&rank=1#study-plan

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