DRUG:	Rimegepant (BHV-3000) (PF-07899801)
STUDY NUMBER(S):	BHV3000-407 (C4951012)
PROTOCOL TITLE:	A Phase 4, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Tolerability of Rimegepant for the Prevention of Migraine in Adults with a History of Inadequate Response to Oral Preventive Medications
US IND NUMBER:	109886
EU CT NUMBER: (if applicable)	2024-513270-21-00
ClinicalTrials.gov ID:	NCT05518123
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	15-Jul-2022
VERSION NUMBER:	Version 7.0
VERSION DATE:	31 Aug 2024

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter.

SUMMARY OF CHANGES

Amendment Version 7.0

Overall Rationale for the Amendment: Alignment with the Clinical Trials Regulation EU No 536/2014 (CTR). Amendment also includes protocol administrative change letters (dated 11 Sept 2023, 02 Nov 2023, 01 Feb 2024, 07 Mar 2024 and 16 Apr 2024) and edits to align with the SAP and Pfizer protocol template.

Description of change	Brief Rationale	Section # and Name
Non-Substantial Modification(s)		
EudraCT number replaced by EU CT number	Alignment with EU CTR requirement	Cover page and Synopsis
Clarified procedures relative to collection of data regarding withdrawn subjects	Alignment with EU CTR requirement	6.6 Subject Early Discontinuation Criteria
Reference to European directive 2001/20/EC replaced by reference to EU CTR No 536/2014	Alignment with EU CTR requirement	8.1.2 Collection and Reporting Serious Adverse Events
Handling of SAP deviations from protocol-specified analyses added	Alignment with EU CTR requirements	9 Statistics
Handling of missing, unused, and spurious data added	Alignment with EU CTR requirements	9.3 Statistical Methods
Clarification of procedures relative to Urgent Safety Measures and Serious Breaches	Alignment with EU CTR requirement	10.1 Good Clinical Practice
Clarification regarding timelines for clinical trial results publication on CTIS	Alignment with EU CTR requirement	10.7 Dissemination of Clinical Study Data
Addition of various sponsor reporting requirements per EU CTR	Alignment with EU CTR requirements	16.7.2 European Union
Primary and Secondary Endpoints tabulated in the Synopsis	To align with Pfizer's protocol template	Synopsis
Main exclusion criteria added	To align with Pfizer's protocol template	Synopsis
Statistical paragraph removed	To align with Pfizer's protocol template	Synopsis
Ethical considerations regarding placebo use rationale; treatment duration	To align with Pfizer's protocol template	Synopsis

Description of change	Brief Rationale	Section # and Name
and burden for subjects clarified		
Study intervention table added	To align with Pfizer's protocol template	7.1.1 Investigational Product
Section header renamed to 'Statistical hypotheses' and text added to describe the null hypothesis for primary and secondary endpoints	Alignment with Statistical Analysis Plan	9.3.1.3 Statistical Hypotheses
AEs by relationship to study drug replaced with AEs related to study drug	Alignment with Statistical Analysis Plan	9.3.2 Safety Analyses
FDA laboratory test toxicity grading scale added	Alignment with Statistical Analysis Plan and FDA request	9.3.2 Safety Analyses
Clarification added to the stratification criteria	Clarification regarding the timeline for the assessment of the number of preventative medications with previous inadequate response	Synopsis 1.3.1 Study Design Rationale 4.3.2.1 Baseline (randomization) Visit 7.2.1 Method of Assigning Subject Identification 7.3 Blinding and Unblinding
Updated the number of subjects involved in Rimegepant clinical studies/received Rimegepant dose	IB update alignment	1.1.2 Product Development Background
Exclusion of subjects with "ALT and AST > 2 x ULN" replaced by "ALT or AST >2 x ULN"	Alignment with rimegepant program-level exclusion criteria	5.3 Exclusion criteria
"Rescue" is replaced by "acute migraine attack treatment"	To maintain the consistency of the definition for the same event across the protocol	5.8 Permitted Acute Migraine Treatment
Addition of FSH post menopausal range (>35 mIU/mL)	Reinstatement of FSH menopausal range deleted by mistake in prior amendment	16.6.2 Women of childbearing Potential
List of references updated	Ensuring alignment with protocol updates	17 References
List of Abbreviations updated	Ensuring alignment with protocol updates	List of abbreviations
SoA table updated for concomitant medication and	Incorporation of nonsubstantial changes	SoA table updated for concomitant medication and

Description of change	Brief Rationale	Section # and Name
study drug medication compliance review	described in previous PACL dated 11 Sept 2023	study drug medication compliance review
Clarification on reporting of Medication Errors	Incorporation of nonsubstantial changes described in previous PACL dated 02 Nov 2023	8.7 Medication Errors
To clarify that the PSSA tool is the primary source for SAE reporting	Incorporation of non-substantial changes described in previous PACL dated 02 Nov 2023	8.1.2 Collection and Reporting Serious Adverse Events
Update on the age of postmenopausal female subjects for FSH testing	Incorporation of non-substantial changes described in previous PACL dated 01 Feb 2024	6.3.4.1 Safety Laboratory Testing
Change to the process for contacting a medically qualified individual from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List. Emergency Contact Card replaced by a study information card	Incorporation of non-substantial changes described in previous PACL dated 07 Mar 2024	10.8 Sponsor's Medically Qualified Individual
Clarification and administrative updates regarding the +3 day window around the 28-day Observation Phase.	Incorporation of non-substantial changes described in previous PACL dated 16 Apr 2024.	Synopsis 4.1 Study Design and Duration 4.3 Schedule of Assessments 4.3.1 Observation Phase 4.3.1.2 Pre-randomization Evaluation Visit 4.3.2.1 Baseline (Randomization) Visit 5.1 Number of Subjects 5.2 Inclusion Criteria (e) 5.3 Exclusion Criteria (c, d) 5.3 Exclusion Criteria 7a Other Exclusion Criteria 6.6 Subject Early Discontinuation Criteria 7.2.1 Method of Assigning Subject Identification 7.3 Blinding and Unblinding

STUDY SUMMARY (SYNOPSIS)

PROTOCOL SUMMARY

Synopsis

Protocol Title: A Phase 4, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Tolerability of Rimegepant for the Prevention of Migraine in Adults with a History of Inadequate Response to Oral Preventive Medications

Brief Title: A Phase 4 Study Evaluating Efficacy and Tolerability of Rimegepant for Prevention of Migraine in Adults with Inadequate Response to Oral Medications

Regulatory Agency Identification Number(s):

US IND Number:	109886
EU CT Number:	2024-513270-21-00
ClinicalTrials.gov ID:	NCT05518123
Pediatric Investigational Plan Number:	N/A
Protocol Number:	C4951012
Phase:	4

Rationale:

Rimegepant is the first and only dually-approved medication for the treatment of acute migraine and prevention of episodic migraine. Effectiveness for the acute treatment of migraine was initially demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia.

Efficacy was confirmed for the acute treatment of migraine in three pivotal single attack Phase 3 trials using the registrational co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2 hours post dose. Effectiveness for the preventive treatment of migraine was demonstrated in a Phase 2/3 double-blind, randomized, placebo-controlled study of rimegepant 75 mg dosed every other day (EOD). EOD dosing was also well tolerated with no signals of Medication-overuse headache, abuse potential, cardiovascular events, or hepatotoxicity.

A variety of orally-administered medications have been re-purposed for the preventive treatment of migraine. However, these medications often lack the requisite efficacy and/or tolerability profile that migraineurs are seeking. Consequently, there is a sizable sub-population of adults living with episodic migraine whose treatment needs are not being adequately addressed with currently available therapies. This study is being conducted to evaluate the efficacy and tolerability of rimegepant for prophylaxis in adults with a history of inadequate response, within 10 years of the Screening Visit, to agents across 2-4 categories of recognized, orally-administered migraine-preventive medications where at least one

example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication).

Objectives	Endpoints
Primary:	**Primary:**
To compare the efficacy of rimegepant to placebo as an EOD dosing regimen for prophylaxis in adults with a history of inadequate response to agents across 2-4 categories of recognized, orally-administered migraine preventive medications as measured by the mean reduction from the Observation Phase in the number of migraine days per month (28 days) over the entire DBT Phase.	Mean change from the Observation Phase in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).
Key Secondary:	**Key Secondary:**
To compare the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12) between rimegepant and placebo.	Proportion of subjects with ≥50% reduction from the Observation Phase in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12).
To compare the mean reduction from the Observation Phase in the number of migraine days per month in the first 4 weeks of the DBT Phase between rimegepant and placebo.	Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase.
To compare the mean reduction from the Observation Phase in the number of migraine days per month in the last 4 weeks of the DBT Phase between rimegepant and placebo.	Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.
To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase.
To compare the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MIBS score at Week 12 of the DBT Phase.
Other Secondary:	**Other Secondary:**
To evaluate the frequencies of adverse events by intensity, serious adverse events, adverse events leading to study drug discontinuation, and grade	Number and percentage of subjects with AEs by intensity, SAEs, AEs leading to study drug discontinuation, and Grade 3 to 4 laboratory test

3 to 4 laboratory test abnormalities during the DBT and OLE Phases.	abnormalities on treatment during the DBT and OLE Phases.
To evaluate the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days (regardless of headache pain intensity) per month over the entire DBT Phase (Weeks 1 to 12) in rimegepant and placebo.	Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days (regardless of headache pain intensity) per month over the entire DBT Phase (Weeks 1 to 12).
To evaluate the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase in rimegepant and placebo.	Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase (Weeks 1 to 12).
To evaluate the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score over time in the DBT Phase in rimegepant and placebo	Mean change from baseline in MIBS scores at Weeks 4, 8, and 12 in the DBT Phase.
To evaluate the mean change from baseline in MSQ domains scores (restrictive role function domain, preventive role function domain and emotional function domain) over time in the DBT Phase in rimegepant and placebo.	Mean change from baseline in the MSQ domain scores (restrictive role function domain, preventive role function domain, and emotional function domain) at Weeks 4, 8, and 12 in the DBT Phase.
To evaluate the mean change from baseline in the Migraine Functional Impact Questionnaire (MFIQ) scores (Physical Function, Usual Activities, Social Function, Overall Impact on Usual Activities, and Emotional Function) over time in the DBT Phase in rimegepant and placebo.	Mean change from baseline in the MFIQ scores (Physical Function, Usual Activities, Overall impact on Usual Activities, Social Function, and Emotional Function) in each month of the DBT Phase.
To evaluate the mean change from baseline in the Work Productivity and Activity Impairment (WPAI) – Migraine scores (absenteeism, presenteeism, work productivity loss and activity impairment) over time in the DBT Phase in rimegepant and placebo.	Mean change from baseline in the WPAI − Migraine scores (absenteeism, presenteeism, work productivity loss and activity impairment) at Weeks 4, 8, and 12 in the DBT Phase.
To evaluate the mean change from baseline in the Patient Global Assessment (PGA) - Migraine score over time in the DBT Phase in rimegepant and placebo.	Mean change from baseline in the PGA score in each month of the DBT Phase.

Overall Design:

This is a multicenter, Phase 4, randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of rimegepant for migraine prophylaxis in adults with inadequate

response to previous treatment with multiple different, orally-administered preventive medications.

The total study duration for each subject will be up to ~30 weeks with 4 phases:

- The 28-day Observation Phase
- The 12-week DBT Phase
- The 12-Week OLE Phase
- The 2-week Follow-up Phase

Eligible subjects must report 4-14 **migraine days** per month, on average, across the 3-months prior to the Screening Visit, and during the first 28-days of the Observation Phase. In addition, eligible candidates must report less than 15 **headache days** (migraine or non-migraine) per month in each of the 3-months prior to the Screening Visit and during the first 28-days of the Observation Phase. A month is defined as 28 days for the purpose of this protocol.

After completing the 28-day Observation Phase, eligible subjects will begin the 12-week DBT Phase. Throughout the DBT Phase, subjects will be instructed that they must take one tablet of study drug (blinded rimegepant 75 mg ODT or matching placebo) every other calendar day (EOD, regardless of whether they have a migraine on that calendar day or not. **Throughout the DBT Phase, study drug is NOT to be used for the treatment of acute migraine attacks.** Permitted acute migraine medication may be used, as needed, and in accordance with the standard of care, to manage acute migraine attacks, regardless of any attack that occurs on a study drug dosing day or non-dosing day. Subjects are to continue to record each migraine occurrence, related pain features, and other associated symptoms on each day in the eDiary, throughout the DBT Phase.

Upon successful completion of the 12-week DBT Phase, eligible subjects will be given the opportunity to enroll into a 12-week OLE Phase. Throughout the OLE Phase, all subjects will be instructed that they must take one tablet of study drug (open-label rimegepant 75 mg) every other calendar day (EOD), regardless if they experience an acute migraine on that calendar day or not. **Throughout the OLE Phase, study drug is NOT to be used for the treatment of acute migraine attacks.** Permitted acute migraine medication may be used, as needed, and in accordance with the standard of care, to manage acute migraine attacks, regardless if the attack occurs on a study drug dosing day or non-dosing day.

At select visits throughout the study (DBT and OLE Phases), subjects are to complete self-assessment questionnaires including: the Migraine-Specific, Quality-of-Life Questionnaire v 2.1 (MSQ v 2.1), Migraine Interictal Burden Scale (MIBS), Headache Impact Test (HIT-6), Work Productivity and Activity Impairment (WPAI) – Migraine Questionnaire, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Subjects who begin but do not complete a treatment phase (i.e., DBT or OLE Phase) must complete the corresponding End-of-Treatment (EOT) Visit (DBT EOT or OLE EOT) and the

(post-treatment) Follow-up Week 2 Visit, except in the case of withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.

The end of the study occurs when the last study visit is completed by the last participating subject or the subject is otherwise discontinued from the study (e.g., as in the case of lost to follow-up).

Number of Subjects:

Approximately 600 subjects will be randomized in a 1:1 ratio to rimegepant or matching placebo across 2 treatment groups in the Double-blind Treatment (DBT) Phase: blinded rimegepant (75 mg ODT) (n = 300) or matching placebo (n = 300), dosed EOD. Randomization will be stratified by 1) the number of migraine days reported to have occurred during the first 28-days of the Observation Phase (4-7 or 8-14); and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories).

Upon successful completion of the DBT Phase, eligible subjects will be given the opportunity to enroll into a 12-week Open-label Extension (OLE) Phase. It is estimated that approximately 480 subjects will enter the OLE Phase of the study.

Study Population:

The study will recruit subjects, ≥18 years of age with a minimum 1 year documented history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition.

Per self-report, with confirmation from Investigator/supporting medical record, subjects must have:

1. Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age

2. Migraine attacks, on average, lasting about 4 - 72 hours, if untreated.

3. 4 to 14 **migraine days** per month, on average, across the 3 months prior to the Screening Visit (month is defined as 28-days for the purpose of this protocol).

4. 4 to 14 migraine days during the first 28-days of the Observation Phase

5. Less than 15 **headache days** (migraine or non-migraine) per month in each of the 3-months prior to the Screening Visit and during the first 28-days of the Observation Phase.

6. Subjects must be able to distinguish migraine attacks from tension/cluster headaches.

7. Prior inadequate response, within 10 years of the Screening Visit, to agents across 2-4 categories of recognized, orally-administered, migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication).

Subjects must not have:

8. History of cluster headaches, basilar migraine (migraine with brainstem aura), or hemiplegic migraine

9. Current medication overuse headaches

10. 7 or more non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit or during the first 28-days of the Observation Phase

Ethical Considerations:

Rimegepant is being developed for the treatment of migraine. Effectiveness for the acute treatment of migraine was initially demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia.1 Efficacy was confirmed for the acute treatment of migraine in three pivotal Phase 3 trials using the current registrational co-primary endpoints of Pain Freedom and Freedom from Most Bothersome Symptom at 2 hours after dosing. Effectiveness for the preventive treatment of episodic migraine was demonstrated in a Phase 2/3 double-blind, randomized, placebo-controlled study of rimegepant 75 mg dosed every other day (EOD).2 Every other day dosing was also well tolerated with no signals of hypersensitivity, cardiovascular events, or hepatotoxicity. Every other day scheduled dosing with as needed dosing was shown to be well tolerated with a favorable safety profile.

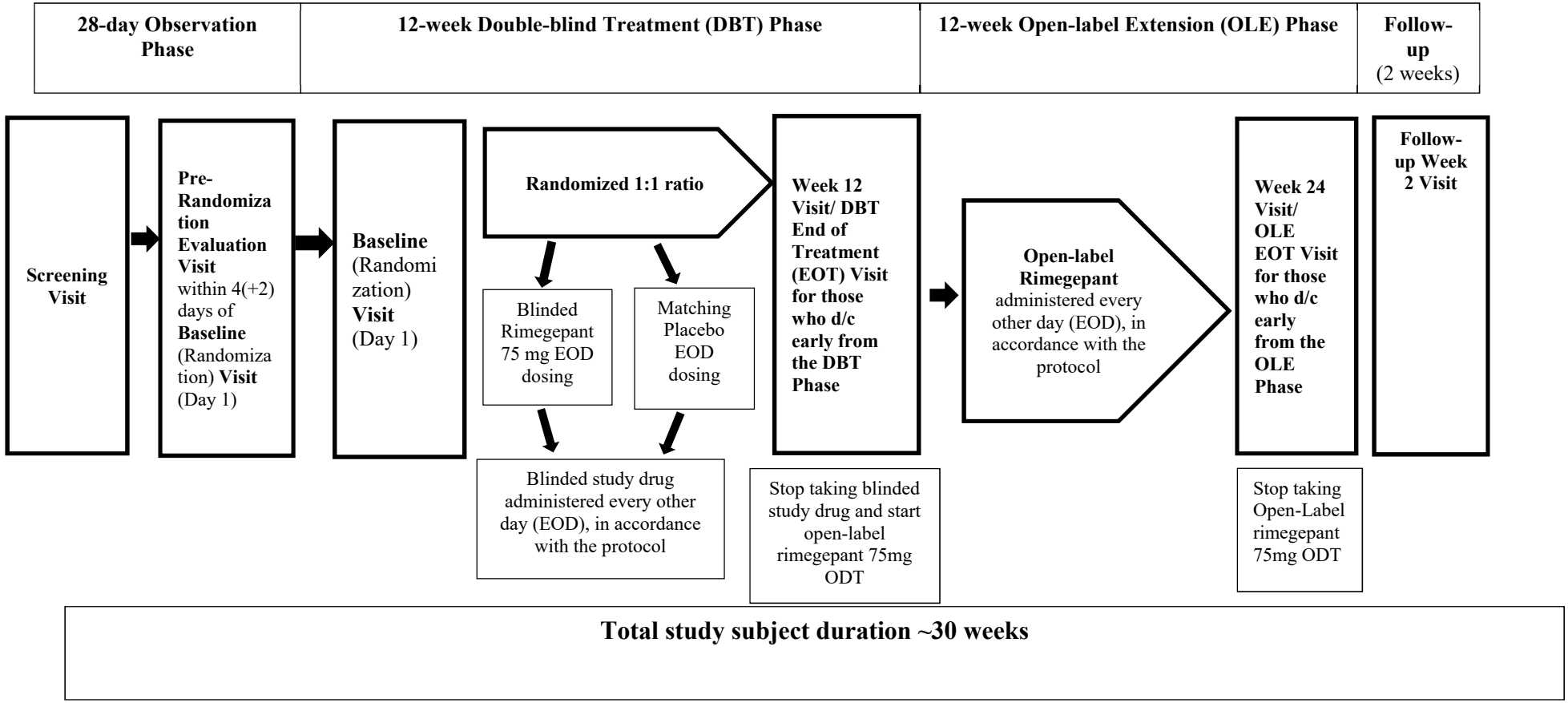
The randomized, double-blind, placebo-controlled study design takes into consideration all potential influences such as the placebo effect and variability in pain intensity, whilst minimizing bias. Placebo-controlled design of the study is in accordance with the most current International Headache Society (IHS) guidelines on the conduct of controlled trials in the preventive treatment of migraine attacks in adults, which stipulates that the conduct of migraine prevention studies must use an appropriate control, placebo. Additionally, during the study, subjects may use their permitted acute migraine medication (prescribed or OTC agents) for the management of acute attacks, as needed, and in accordance with the standard of care.

Subjects randomized to placebo may not obtain any specific benefit beyond close monitoring of their medical condition and safety. Those randomized to rimegepant may benefit from the pharmacological effects of the active drug in regard to, prophylactic treatment of migraine. All subjects who remain eligible will receive open-label rimegepant for 12 weeks, regardless of whether they are randomized to placebo or Rimegepant in DBT phase.

Moreover, review of all data available, including post-marketing information, nonclinical, clinical, and scientific literature data, demonstrates a favorable benefit-risk profile for the use of rimegepant in this study.

During the study, subjects will undergo ECG, blood and urine sampling and will be asked to complete electronic and paper diaries and to attend visits.The results of previous studies of rimegepant support the investigation of rimegepant in acute migraine prevention with multiple dosing regimens, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to subjects, the potential risks associated with rimegepant are justified by the anticipated benefits that may be afforded to subjects with acute migraine.

STUDY SCHEMATIC



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LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACS	Acute Coronary Syndrome
AD	Anxiety Disorder
ADHD	Attention-deficit/hyperactivity disorder
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
AST	Aspartate aminotransferase
AxMP	Auxiliary Medicinal Product
BHV	Biohaven
BUN	Blood urea nitrogen
CI	Confidence interval
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene-Related Peptide
C_{max}	Maximum plasma concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant medication
CRF	Case report form
CRS	Chronic Rhinosinusitis
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
CYP	Cytochrome P450
CV	Cardiovascular
DAIDS	Division of Aids
DBT	Double-blind Treatment Phase

DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DSMC	Data and Safety Monitoring Committee
DSU	Drug Safety Unit
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	electronic Clinical Outcomes Assessment
eCRF	Electronic Case Report Form
EDP	Exposure during Pregnancy
EDB	Exposure During Breastfeeding
EDC	Electronic Data Capture
eDiary	Electronic Diary
EOD	Every Other Day
EFD	Embryo-fetal development
EOT	End of Treatment
EQ-5D	European Quality of Life Five Dimension
eTMF	Electronic Trial Master File
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HIT-6	Headache Impact Test
HR	Heart rate
ICF	Informed consent form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
IHS	International Headache Society
IMP	Investigational Medicinal Product
IP	Investigational Product
iv	Intravenous
kg	Kilogram
L	Liters
LBBB	Left Bundle Branch Block
LFT	Liver Function Test
LSLV	Last subject last visit
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFIQ	Migraine Functional Impact Questionnaire
mg	Milligram
MIBS	Migraine Interictal Burden Scale
min	Minute
mmHg	Millimeters mercury
MQI	Medically Qualified Individual
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NIMP	Non-Interventional Medicinal Product
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
NSAID	Non-steroidal anti-inflammatory drug
PACL	Protocol Administrative Clarification Letter
PCD	Primary completion date
PGA	Patient Global Assessment
po	By mouth, orally
PRN	Pro re nata, as needed
PSSA	Pfizer SAE Submission Assistant

qd	Once daily
ODT	Orally Disintegrating Tablet
OLE	Open-label Extension
OTC	Over- The -Counter
QTcF	QTc corrected using Fridericia's formula
QTL	Quality Tolerance Limit
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SE	Standard error
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
T Bili	Total bilirubin
TMF	Trial Master File
ULN	Upper limit of normal
VAS	Visual analogue scale
WOCBP	Woman/Women of Child-Bearing Potential
WPAI	Work Productivity and Activity Impairment

1. INTRODUCTION AND RATIONALE

1.1. Background

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. People living with migraines often experience recurrent attacks of unilateral, pulsating, headaches of moderate-to-severe pain intensity that can last for 4 to 72 hours, if left untreated. Commonly, migraine headaches are aggravated by routine physical activity and can be associated with nausea, photophobia and/or phonophobia.[1]

BHV3000 (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist that has been developed and approved for the acute and preventive treatment of migraine in adults. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology. Research and clinical studies have shown: Serum levels of CGRP are elevated during migraine attacks; infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers; and treatment with anti-migraine drugs normalize CGRP levels. Additionally, multiple clinical studies have demonstrated that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors (such as rimegepant), are effective in aborting migraine attacks. Treatment with a CGRP receptor antagonist is believed to relieve migraine headaches and related symptoms through the following possible mechanisms: 1) blocking neurogenic inflammation; 2) decreasing artery dilation; and 3) inhibiting pain transmission. There is widespread agreement that this new approach avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists (e.g., sumatriptan [Imitrex™])).

1.1.1. Clinical Experience

Rimegepant (Nurtec® ODT, Vydura BHV-3000) is an oral, small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist approved by the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and UK Medicines and Healthcare Products Regulatory Agency (MHRA) for the acute and preventive treatment of migraine in adults.[2,3]Rimegepant has also been approved for the acute treatment of migraine in adults in Israel, the United Arab Emirates (UAE), and Kuwait. The efficacy, safety, and tolerability of rimegepant for the acute and preventive treatment of migraine in the pediatric population is currently being evaluated. Rimegepant is currently in development for the acute and preventive treatment of migraine in pediatric subjects, as well as for the treatment of refractory trigeminal neuralgia, the acute treatment of chronic rhinosinusitis (CRS), and temporomandibular disorders (TMD). Collectively, the data demonstrate a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine.

Please refer to the most up to date Investigator's Brochure for additional information.

1.1.2. Product Development Background

Details of the clinical and preclinical studies are provided in the most current Investigator Brochure.[4] A summary of the relevant data to the study are presented below.

Rimegepant is approved for the acute treatment and prevention of episodic migraine in the United States (US), United Kingdom (UK), and European Union (EU) and is well tolerated in humans when given as a single oral dose of 75 mg for the acute treatment of migraine and at a dose of 75 mg every other day (EOD) for the prevention of episodic migraine. The efficacy, safety, and tolerability of rimegepant for the acute and preventive treatment of migraine in the pediatric population is currently being evaluated.

As of 26 February 2024, it is estimated that 12,135 participants have been involved in Rimegepant clinical development studies and approximately 6630 participants have received Rimegepant at any dose. Collectively, the current data demonstrates a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine.

1.2. Benefit/Risk Assessment

Rimegepant represents an advancement in migraine therapeutics, providing the first CGRP antagonist to demonstrate benefit for both the acute treatment and prophylaxis of migraine.

Rimegepant appears to be generally safe and well tolerated in humans when given as single oral doses from 75 mg up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days.

Broad and sustained efficacy of rimegepant 75 mg was demonstrated in 3 previously completed Phase 3 studies (BHV3000-301, BHV3000-302, and BHV3000-303). Statistically significant efficacy was demonstrated on the co-primary endpoints of freedom from pain, and freedom from most bothersome symptom at 2 hours post-dose. Similar results were demonstrated in the BHV3000-310 study recently completed in China and Korea. In the Phase 2/3 placebo-controlled study (BHV3000-305) for the preventive treatment of migraine, rimegepant at a dose of 75 mg every other day (EOD) demonstrated statistically significant superiority to placebo on the primary endpoint of change from the observation period in the mean number of migraine days per month on treatment in the last month of the double-blind treatment phase.

A multicenter open-label, long-term study (BHV3000-201) was conducted to evaluate the safety and tolerability of rimegepant 75 mg tablet taken as needed (up to one tablet per day upon onset of a migraine of mild, moderate, or severe intensity) for the acute treatment of migraine for up to 52 weeks. This multiple-dose, long-term study of rimegepant 75 mg administered for up to 52 weeks confirmed the favorable safety profile across a variety of safety endpoints, including AE assessments, clinical laboratory testing including liver function tests (LFTs), vital signs and electrocardiograms (ECGs). Safety data from the double-blind treatment and the open-label extension phases of the pivotal Phase 2/3, randomized, double-blind, placebo-controlled preventive treatment of migraine study (BHV3000-305) support a favorable safety profile of rimegepant 75 mg administered EOD for the preventive treatment of migraine. Rimegepant 75 mg administered EOD + PRN (as needed) for up to 52 weeks in the open-label phase is well tolerated, with no new safety signals observed in the open-label-extension phase.

Across rimegepant clinical development program, low frequency of events of hypersensitivity (including urticaria, angioedema, anaphylactic reaction and rash) were observed. No AEs representing serious cutaneous manifestation of hypersensitivity (e.g, Stevens-Johnson syndrome) were observed.

Across the rimegepant clinical development program, no cases of Hy's Law were identified, and there was no signal of DILI due to rimegepant when administered up to once daily PRN for up to 52 weeks of treatment.

There are no adequate data on the developmental risk associated with the use of rimegepant in pregnant women. Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of embryo-fetal development (EFD) nonclinical toxicity studies with rimegepant. Contraception method is required, and measures will be taken to limit the risk of pregnancy in the female population of childbearing potential enrolled (See Section 5.9, Appendix 6). The potential risk of exposure to rimegepant in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male subjects is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[5]

Subjects undergo regular pregnancy testing throughout the duration of the study. Although no safety issues in clinical trials of rimegepant were observed, cardiovascular events, cerebrovascular events, hypertensive events, and serious gastrointestinal events associated with constipation are reviewed in each aggregate report per FDA request. None of these reviews have detected any safety signal associated with these events. Subjects are excluded if there is uncontrolled, unstable, or recently diagnosed cardiovascular disease or hypertension. Subjects are monitored through multiple safety endpoints, including AE assessments, clinical laboratory testing, vital signs and ECGs.

Review of all data available, including post-marketing information, nonclinical, clinical, and scientific literature data, demonstrates a favorable benefit-risk profile for the use of rimegepant in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rimegepant may be found in the Investigator Brochure, which is the SRSD for this study.

Investigators are to monitor changes in hematology, chemistry, and other laboratory measures (see Section 8.4. In addition, Investigators are required to monitor all reported AEs, changes on physical examination, ECG, and emergent lab abnormalities, etc. (see Table 1).

1.3. Study Rationale

A variety of orally-administered medications have been re-purposed for the preventive treatment of migraine. The most commonly prescribed, orally-administered, migraine preventive medication classes are antiepileptics (e.g., topiramate), beta blockers (e.g.,

propranolol), and tricyclic antidepressants (e.g., amitriptyline), none of which were specifically developed for the preventive treatment of migraine.[6] The large majority of adults who are placed on oral migraine preventive therapy discontinue these treatments within 6-months of initiation due to a combination of factors including poor tolerability and a lack of efficacy.[7] Consequently, there is a sizable sub-population of adults living with episodic migraine whose treatment needs are not being adequately addressed with currently available oral therapies. This study is being conducted to evaluate the efficacy and tolerability of rimegepant for prophylaxis in adults with a history of inadequate response, within 10 years of Screening Visit, to agents across 2-4 categories of recognized, orally-administrated migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication) (see Section 16.2 , Appendix 2).

Rimegepant is the first and only dually-approved medication for the treatment of acute migraine and prevention of episodic migraine. Effectiveness for the acute treatment of migraine was initially demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia.[1]

Efficacy was confirmed for the acute treatment of migraine in three pivotal Phase 3 trials using the registrational co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2-hours post-dose. Effectiveness for the preventive treatment of migraine was demonstrated in a Phase 2/3 double-blind, randomized, placebo-controlled study of rimegepant 75 mg dosed every other day (BHV3000-305).[8] In this study, EOD dosing was well tolerated with no signals of hypersensitivity, cardiovascular events, or hepatotoxicity.

Previous subgroup analysis within the galcanezumab development program have consistently demonstrated significant efficacy improvements among adults with multiple prior preventive failures who received the galcanezumab, relative to placebo. Notably, reduction in mean monthly migraine days were routinely greater among those in the placebo-arm with no prior failure on preventive therapy.[6,9,10] Rimegepant represents an important alternative treatment option for adults with episodic migraine who are not well served by existing standard of care preventive therapies. Rimegepant is the first orally-administered, migraine-specific agent approved for the preventive treatment of migraine. It has a convenient every-other-day dosing regimen (75 mg PO EOD). The primary aim of the current study is to evaluate the efficacy, safety, and tolerability of rimegepant for migraine prophylaxis in adults with a history of inadequate response (due to lack of efficacy, prior intolerance, or contraindication) to multiple oral preventive medications (see Section 16.2, Appendix 2).

1.3.1. Study Design Rationale

This is a multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of rimegepant (75 mg ODT taken every other day) for prophylaxis in adults with a history of inadequate response to a variety of available oral migraine-preventive medications from different mechanistic classes. The double-blind, placebo-controlled, parallel group design to assess the efficacy, safety and tolerability of rimegepant as preventative treatment is in accordance with international guidelines .[11] Up to approximately

600 eligible subjects will be randomized in a 1:1 ratio to blinded rimegepant (75 mg) or matching placebo and stratified by: 1) the number of migraine days reported to have occurred during the 28-day Observation Phase (4-7 or 8-14); and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories).

During the 12-week DBT Phase, subjects will be instructed that they must take one tablet of blinded study drug every other calendar day (EOD). If subjects have a migraine during the DBT Phase, permitted acute migraine medication (see Section 16.4, Appendix 4) may be used, as needed, and in accordance with the standard of care, to manage acute attacks regardless if the migraine occurs on a study drug dosing day or non-dosing day. **Blinded study drug is NOT to be used for the treatment of acute migraine attacks during the DBT Phase.**

Upon successful completion of the DBT Phase, eligible subjects will be given the opportunity to enroll into a 12-week OLE Phase. It is estimated that approximately 480 subjects will enter the OLE Phase of the study.

The inclusion of an OLE Phase allows all study subjects, including those originally randomized to blinded placebo during the DBT Phase, the potential benefits of receiving active study drug (rimegepant) for the preventive treatment of episodic migraine attacks. During the OLE Phase, subjects will be required to take one tablet of open-label rimegepant (75 mg) EOD, regardless if they experience an acute migraine on that calendar day or not, consistent with dosing in the DBT Phase. **Throughout the OLE Phase, study drug is NOT to be used for the treatment of acute migraine attacks.** Permitted acute migraine medication may be used, as needed, and in accordance with the standard of care, to manage acute migraine attacks, regardless if the attack occurs on a study drug dosing day or non-dosing day.

Throughout the study (including the DBT and OLE Phases), subjects are required to take one tablet of study medication every-other-day (EOD and are not permitted to take more than one tablet of study medication on any single calendar day.

The study design, including placebo-control, described herein, represents a gold-standard approach for assessing the efficacy and safety of an investigational therapy for the management of migraine prophylaxis, particularly in the context of use in a population with history of failure on existing oral standard of care preventive therapies. The primary and secondary endpoints are well established to demonstrate the overall therapeutic benefits of rimegepant. The study design is similar to previously completed or ongoing trials of migraine prophylaxis in this population (Per clinicaltrials.gov; ELEVATE NCT04740827 and LIBERTY NCT03096834).

1.3.2. Dose Selection Rationale

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine. The three Phase 3 studies

BHV3000-301, BHV3000-302, and BHV3000-303 confirmed this efficacy using the current registrational endpoints for acute treatment of migraine. The pivotal Phase 3 Study BHV3000-305 demonstrated that rimegepant 75 mg EOD is effective and has a favorable safety profile for the prevention of migraine headache. The current study will evaluate the efficacy and tolerability of rimegepant for prophylaxis in adults with a history of inadequate response, within 10 years of the Screening Visit, to agents across 2-4 categories of recognized, orally-administered migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication) (see Section 16.2 , Appendix 2).

1.3.3. Research Hypothesis

Rimegepant has a favorable benefit risk profile in the prevention of migraine in adults who have previously experienced inadequate response, within 10 years of the Screening Visit, to recognized, orally-administered, migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication) (see Section 16.2, Appendix 2).

2. STUDY OBJECTIVES

2.1. Primary Objective

To compare the efficacy of rimegepant to placebo as an EOD dosing regimen for prophylaxis in adults with a history of inadequate response to agents across 2-4 categories of recognized, orally-administered migraine preventive medications as measured by the mean reduction from the Observation Phase in the number of migraine days per month (28 days) over the entire DBT Phase.

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

1. To compare the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12) between rimegepant and placebo.

2. To compare the mean reduction from the Observation Phase in the number of migraine days per month in the first 4 weeks of the DBT Phase between rimegepant and placebo.

3. To compare the mean reduction from the Observation Phase in the number of migraine days per month in the last 4 weeks of the DBT Phase between rimegepant and placebo.

4. To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the DBT Phase between rimegepant and placebo.

5. To compare the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score at Week 12 of the DBT Phase between rimegepant and placebo.

2.2.2. Other Secondary Objectives

1. To evaluate the frequencies of adverse events by intensity, serious adverse events, adverse events leading to study drug discontinuation, and Grade 3 to 4 laboratory test abnormalities during the DBT and OLE Phases.

2. To evaluate the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days (regardless of headache pain intensity) per month over the entire DBT Phase (Weeks 1 to 12) in rimegepant and placebo.

3. To evaluate the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase in rimegepant and placebo.

4. To evaluate the mean change from baseline in Migraine Interictal Burden Scale (MIBS) score over time in the DBT Phase in rimegepant and placebo.

5. To evaluate the mean change from baseline in MSQ domains scores (restrictive role function domain, preventive role function domain and emotional function domain) over time in the DBT Phase in rimegepant and placebo.

6. To evaluate the mean change from baseline in the Migraine Functional Impact Questionnaire (MFIQ) scores (Physical Function, Usual Activities, Social Function, Overall Impact on Usual Activities, and Emotional Function) over time in the DBT Phase in rimegepant and placebo.

7. To evaluate the mean change from baseline in the Work Productivity and Activity Impairment (WPAI) – Migraine scores (absenteeism, presenteeism, work productivity loss and activity impairment) over time in the DBT Phase in rimegepant and placebo.
8. To evaluate the mean change from baseline in the Patient Global Assessment (PGA)-Migraine score over time in the DBT Phase in rimegepant and placebo.

2.3. Exploratory Objectives

1. To evaluate the mean reductions from the Observation Phase in the number of migraine days per month and headache days per month by headache pain intensity (total; moderate or severe) in each month and over the entire DBT Phase in rimegepant and placebo.

2. To evaluate the proportions of subjects with ≥ 30% reduction, ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by headache pain intensity (total; moderate or severe) in each month and over the entire DBT Phase in rimegepant and placebo.

3. To evaluate the mean reductions from the Observation Phase in the number of migraine days per week and number of headache days per week by headache pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase in rimegepant and placebo.

4. To evaluate the proportions of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days per week and number of headache days per week by headache pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase in rimegepant and placebo.

5. To evaluate the proportions of subjects with a migraine day and headache day by headache pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase in rimegepant and placebo.

6. To evaluate the median time to ≥ 30% reduction and ≥ 50% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by headache pain intensity (total; moderate or severe) in the DBT Phase in rimegepant and placebo.

7. To evaluate the mean number of acute migraine medication days per month in each month and over the entire DBT Phase in rimegepant and placebo.

8. To evaluate the mean change from baseline in the Headache Impact Test (HIT-6) score over time in the DBT Phase in rimegepant and placebo.

9. To evaluate the proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score over time in the DBT Phase in rimegepant and placebo.

10. To evaluate the mean changes from baseline in the MSQ domain, MIBS, WPAI – Migraine, HIT-6 and PGA scores over time in the OLE Phase.

11. To evaluate the proportion of subjects with ≥ 5-point reduction from baseline in the HIT-6 score over time in the OLE Phase.

12. To evaluate the frequencies of hepatic-related adverse events and hepatic-related adverse events leading to study drug discontinuation during the DBT and OLE Phases.

13. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or total bilirubin) based on fold changes above ULN during the DBT and OLE Phases.

14. To evaluate the Columbia-Suicide Severity Rating Scale (C-SSRS) during the DBT and OLE Phases.

3. STUDY ENDPOINTS

Migraine days per month, acute migraine-specific medication days per month, MFIQ scores, and PGA scores are derived from eDiary data.

AEs are determined from CRFs.

Endpoints based on other rating scale and questionnaires (i.e., C-SSRS, HIT-6, MIBS, MSQ, WPAI) are derived from their respective CRFs.

Grade 3 to 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria. Laboratory tests are identified from CRFs and central laboratory data.

3.1. Primary Endpoint

Mean change from the Observation Phase in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).

3.2. Secondary Endpoints

3.2.1. Key Secondary Endpoints

1. Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12).

2. Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase.

3. Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.

4. Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase.

5. Mean change from baseline in the MIBS score at Week 12 of the DBT Phase.

3.2.2. Other Secondary Endpoints

1. Number and percentage of subjects with AEs by intensity, SAEs, AEs leading to study drug discontinuation, and Grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases.

2. Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days (regardless of headache pain intensity) per month over the entire DBT Phase (Weeks 1 to 12).

3. Mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase (Weeks 1 to 12).

4. Mean change from baseline in MIBS scores at Weeks 4, 8, and 12 in the DBT Phase.

5. Mean change from baseline in the MSQ domain scores (restrictive role function domain, preventive role function domain, and emotional function domain) at Weeks 4, 8, and 12 in the DBT Phase.

6. Mean change from baseline in the MFIQ scores (Physical Function, Usual Activities, Overall impact on Usual Activities, Social Function, and Emotional Function) in each month of the DBT Phase.

7. Mean change from baseline in the WPAI – Migraine scores (absenteeism, presenteeism, work productivity loss and activity impairment) at Weeks 4, 8, and 12 in the DBT Phase.

8. Mean change from baseline in the PGA score in each month of the DBT Phase.

4. STUDY PLAN

4.1. Study Design and Duration

This is a multicenter, Phase 4, randomized, double-blind, placebo-controlled study to assess the efficacy and tolerability of rimegepant for migraine prophylaxis in adults with inadequate response to previous treatment with multiple different, orally-administered preventive medications. Eligible subjects who complete the 12-week DBT Phase may continue to the 12-week OLE Phase.
The total study duration for each subject will be up to ~30 weeks with 4 phases:

- The 28-day Observation Phase
- The 12-week DBT Phase
- The 12-week OLE Phase
- The 2-week Follow-up Phase.

The 28-day Observation Phase will have 2 scheduled visits, Screening and Pre-randomization Evaluation, which should be completed in person. Eligible subjects must report **4-14 migraine days** per month, on average, across the 3-months prior to the Screening Visit, and during the first 28-days of the Observation Phase. In addition, eligible candidates must report **less than 15 headache days** (migraine or non-migraine) per month **and fewer than 7 non-migraine headaches** per month in each of the 3-months prior to the Screening Visit and during the first 28-days of the Observation Phase. A month is defined as 28 days for the purpose of this protocol.

Upon completion of the Screening Visit, for use throughout the DBT Phase, subjects will be provided an electronic diary (eDiary) to record each migraine occurrence, related migraine pain features and other associated symptoms (e.g., nausea, vomiting, photophobia, and phonophobia), and the use of acute migraine medication on each day of the Observation Phase.

The Pre-randomization Evaluation Visit is to occur toward the end of the Observation Phase and within 4 days of the Baseline (Randomization) Visit for the 12-week DBT Phase. In the event of scheduling challenges, site staff may use an additional +2-day window for completing the Pre-randomization Evaluation (e.g., within as many as 6-days of randomization). During the Pre-randomization Evaluation, confirmatory laboratory testing is completed with results available prior to the Baseline (Randomization) Visit.

After completing the 28-day Observation Phase, subjects are to return to the clinic with their eDiary as part of the DBT Baseline Visit. During this visit, eligibility for participation in the double-blind treatment phase of the study will be assessed prior to randomization and before study drug is initially dispensed.

The 12-week DBT Phase will have scheduled visits at Baseline, Week 2, Week 4, Week 8, and Week 12 /End of Treatment (EOT). Throughout the 12-week DBT Phase, subjects will be instructed that they must take one tablet of study drug (blinded rimegepant 75 mg ODT or matching placebo) every other calendar day (EOD), regardless of whether they have a migraine on that day or not. **Study drug is NOT to be used for the treatment of acute migraine attacks.** Permitted acute migraine medication (see Section 16.4, Appendix 4) may be used, as needed, and in accordance with the standard of care, to manage acute migraine attacks, regardless if an attack occurs on a study drug dosing day or non-dosing day. Subjects are to continue to record each migraine occurrence, related pain features, and other associated symptoms on each day in the eDiary, throughout the DBT Phase.

Subjects will record all concomitant medications, including standard of care acute migraine medications (both prescribed and OTC), taken throughout the entire study (Screening Visit to Follow-up Week 2 Visit), in the Concomitant Medication paper diary.

At select study visits throughout the study (DBT and OLE Phase), subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ v 2.1), the Migraine Interictal Burden Scale (MIBS), Headache Impact Test (HIT-6), Work Productivity and Activity Impairment (WPAI) – Migraine Questionnaire, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Please reference Section 4.3, Table 1 and Table 2.

Additional assessments and visit schedule during the DBT Phase are outlined in the procedural table in Section 4.3. Procedures include study personnel review of the eDiary and paper diaries with the subject, assessment of medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). After the DBT Phase, subjects should enter the OLE or Follow-up Phase. Subjects who successfully complete the Week 12 DBT Visit can be considered for entry into the OLE Phase. Subjects who discontinue early from the DBT Phase or are otherwise not eligible for the OLE Phase, per the discretion of the Investigator, in consultation with the Medical Monitor, should enter the Follow-up Phase.

Subjects randomized to rimegepant 75 mg EOD or matching placebo in the DBT Phase will receive open-label rimegepant 75 mg EOD in the OLE Phase. Subjects will continue dosing EOD based on the dosing schedule established during the DBT Phase.

Subjects who discontinue early from the DBT Phase or have already entered the Follow-up Phase are not eligible to enter the OLE Phase.

During the OLE Phase, study visits will occur at Week 14 (2 weeks into the OLE Phase) and Week 24 (12 weeks into the OLE Phase). See Table 2 for schedule of procedures during the OLE Phase. Throughout the OLE Phase, subjects will be instructed that they must take one tablet of study medication (open-label rimegepant 75 mg) every other calendar day (EOD). **Throughout the OLE Phase, study drug is NOT to be used for the treatment of acute migraine attacks**. Permitted acute migraine medication may be used, as needed, and in accordance with the standard of care, to manage acute migraine attacks, regardless if the attack occurs on a study drug dosing day or non-dosing day.

The Follow-up Phase will have one scheduled visit at Follow-up Week 2 for targeted safety assessment, and end-of-study procedures (see Table 1 and Table 2 for the schedules of assessments).

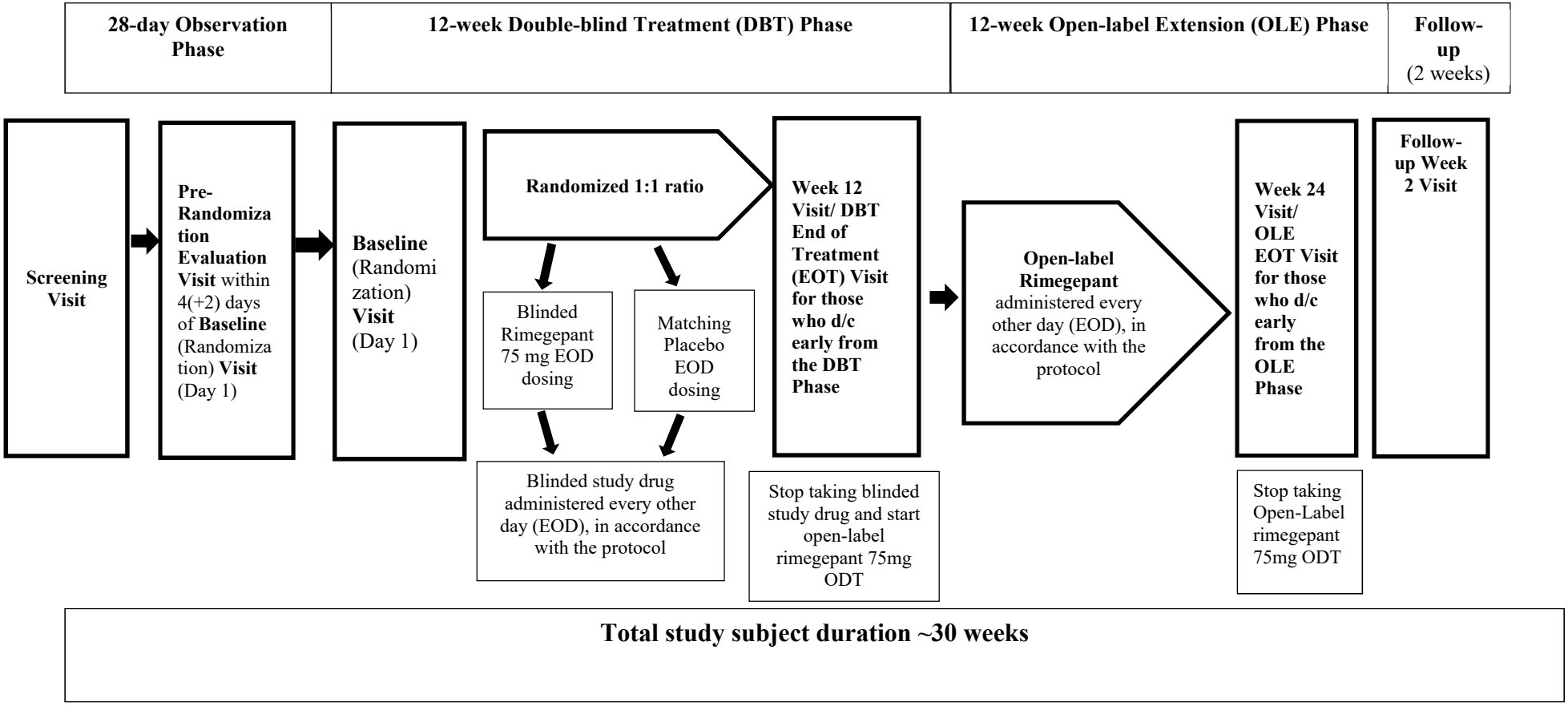
Subjects will record all concomitant medications, including standard of care acute migraine medications (both prescribed and OTC), taken throughout the entire study (Screening Visit to Follow-up Week 2 Visit), in the Concomitant Medication paper diary.

The end of the study is defined as the last visit of the last subject or date of early discontinuation if the last subject is otherwise discontinued from the trial prior to completion of the post-treatment Week 2 Follow-up Visit (e.g., lost to follow-up).

To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Lab results that meet predefined LFT abnormality criteria as potential DILI events should be reported as a serious adverse event (SAE). See Section 8.4 Potential Drug Induced Liver Injury (DILI).

4.2. Study Schematic

STUDY SCHEMATIC



4.3. Schedule of Assessments

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	**Screening Visit**	**Observation Phase**[1] (28 days, + 3 days)	**Pre-Randomization Evaluation Visit:** must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	**Baseline (Randomization) Visit**[2] (Day 1)	**Week 2 Visit**[6] (Day 15 +/- 2 days)	**Week 4 Visit**[6] (Day 29 +3 days)	**Week 8 Visit**[6] (Day 57 + 3 days)	**Week 12 Visit** (Day 86 +3 days) / **End of Treatment (EOT)**[3,8] **Visit for early discontinuation**	**NOTES**
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Eligibility Assessments									
Informed Consent	X								
Inclusion/Exclusion Criteria	X			X					
Medical History	X								
Migraine History (signs/symptoms/ prior treatment/frequency/intensity)	X								
Randomize subject / RTSM and complete the ECOA eligibility report				X					Actual baseline visit date should be used for RTSM enrollment date and eligibility date. Site staff should also complete the ECOA eligibility report.

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Safety Assessments									
Physical Examination	X							X*	*If a subject is eligible to enroll into the OLE Phase, a physical exam at Week 12 DBT is not required. Subjects will undergo a complete physical examination during the Screening Phase and targeted symptom-directed physical exam (physical examinations to include examination of heart, abdomen, and lungs, with review of any other system to be guided by symptoms) at Week 12 DBT/EOT. at EOT
Vital Signs / Physical Measurements	X			X	X	X	X	X	Height measured at Screening Visit only.

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Clinical Safety Laboratory Testing	X		X					X	
Liver Function Test (LFTs)	X		X			X		X	
ECG	X							X*	*If subject is eligible to enroll into the OLE Phase, an ECG at Week 12 visit is not required
Urine Drug Screen for drugs of abuse	X								
Pregnancy Test	X (urine)		X (serum)	X (urine)	X (urine)	X (urine)	X (urine)	X (urine)	
AE, SAE, and Concomitant Procedure assessment	X		X	X	X	X	X	X	SAEs, AEs and Concomitant Procedures must be reported after subject signs informed consent.
Columbia-Suicide Severity Rating Scale (C-SSRS)	X			X		X		X	Paper Assessment

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Clinical Drug Supplies / Study Supplies									
Dispense Study Drug				X		X	X	X	Site staff should review IP taken compared to the ECOA scheduled dosing data at EACH visit. RTSM will dispense enough IP at the baseline, week 4, week 8 and week 12 visits.
Study drug[7] and concomitant medication compliance review	X	X	X	X	X	X	X	X	Site staff should review the IP taken compared to the e-diary dosing data at EACH visit. Site staff should compare the Subject reported standard of care migraine medication use to the e-diary reported "other medication" use. All concomitant medication data should be entered in the database using the paper concomitant

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
									medication log as source. Study Drug medication review is only applicable when study drug is dispensed at the baseline visit.
Electronic Diary (eDiary) dispensed	X								
eDiary completion		X		X*	X*	X*	X*	X*	*Subject to record any acute migraine-specific medication dosing occurrences (i.e., triptan, ergotamine, lasmiditan, or ubrogepant), each migraine occurrence, related migraine pain features, and other associated symptoms during the Observation Phase and everyday during the DBT Phase
Return unused study drug to site for compliance check					X	X	X	X	

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
eDiary returned / reviewed for headache report, PGA and MFIQ assessment completeness		X	X	X	X	X	X	X	Site staff should review headache report, PGA and MFIQ assessments for subject completeness and re-train, if necessary.
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1				X		X	X	X	Paper Assessment
Migraine Interictal Burden Scale (MIBS)				X		X	X	X	Paper Assessment
Work Productivity and Activity Impairment (WPAI) – Migraine				X		X	X	X	Paper Assessment
Headache Impact Test (HIT-6)				X		X	X	X	Paper Assessment
Patient Global Assessment (PGA)[4]				X →	→	→	→	X	Completed by the subject on the handheld eDiary daily.

Table 1. Screening Phase and DBT Phase Schedule of Assessments

Procedure	Screening Visit	Observation Phase[1] (28 days, + 3 days)	Pre-Randomization Evaluation Visit: must occur within 4 days of Baseline (Randomization) Visit (+2 days)[2]	Baseline (Randomization) Visit[2] (Day 1)	Week 2 Visit[6] (Day 15 +/- 2 days)	Week 4 Visit[6] (Day 29 +3 days)	Week 8 Visit[6] (Day 57 + 3 days)	Week 12 Visit (Day 86 +3 days) / End of Treatment (EOT)[3,8] Visit for early discontinuation	NOTES
Visit	**V1**	**-**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	
Migraine Functional Impact Questionnaire (MFIQ)[5]				X →				→ X	Completed by the subject on the handheld eDiary every 7 days.

1. While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s). NOTE: migraine days, headache days and non-migraine headache days reported during the "+3 days" window will not be used for determining eligibility.
2. The duration between the Pre-randomization Evaluation Visit and the Baseline Visit is 4 days. The "+2" days window is included ***for scheduling purposes only***. Every effort should be made to collect the Pre-randomization Evaluation Visit samples as close to, and within, the 4 days prior to the Baseline Visit as possible. However, for scheduling convenience, this window may be up to 6 days (between the Pre-randomization Evaluation Visit and the Baseline Visit).
3. Randomized subjects who discontinue early from the DBT Phase should complete the EOT Visit, except in the case of withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up. Otherwise, subjects should complete the Week 12 Visit.
4. Patient Global Assessment (PGA) will be programmed on the subject handheld device and completed by the subject daily.
5. Migraine Functional Impact Questionnaire (MFIQ) will be programmed on the subject handheld device every 7 days. Subject will have a "+1" day window allowing the subject a total of 48 hours to complete the MFIQ.
6. Every effort should be made to conduct the study visits within the specified windows. However, if necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance. See Sections 4.3.1- 4.3.2 for more information. The following visits may be completed remotely due to COVID-19: Weeks 2, 4, 8 and Follow-up Week 2 visits. The screening, Pre-Randomization Evaluation, Baseline (Randomization) and Week 12 visits must be completed in-person.
7. Subjects must take their study drug every other day (EOD, regardless of whether they have a migraine. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits. Dosing should occur around the same time for each scheduled EOD dose. It is preferred that subjects' dose in the morning; however, it is more important that the subject consistently dose at approximately the same time for each scheduled EOD dose. Subjects will be instructed that they must take one tablet of study drug every other calendar day, regardless of whether they have a migraine on that day or not.
8. All randomized subjects who do not go on to the OLE Phase should complete the Follow-up Week 2 Visit, except those who discontinue early from the DBT Phase due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.

Table 2. OLE Phase and Follow-up Phase Schedule of Assessments

OLE Phase (up to 12 Weeks)			Follow-up Phase	NOTES
Procedure	**Week 14 Visit (Day 99 +/-3 days)**	**Week 24 Visit (Day 169 +/- 3 days) or EOT Visit for early discontinuation [4,5,7]**	**Follow-up Week 2 Visit (+/- 2 days) [5]**	
Safety Assessments				
Physical Examination		X	T	T= Targeted Physical X= Full Physical
Vital Signs / Physical Measurements	X	X	X	
Clinical Safety Laboratory Testing (hematology, chemistry)	X	X		
Liver Function Tests (LFTs)[2]	X	X		
ECG		X		
Pregnancy Test[3]	X (urine)	X (urine)	X(urine)	
AE, SAE and Concomitant Procedure assessment	X	X	X	
Other Assessments				
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1		X		Paper Assessment
Migraine Interictal Burden Scale (MIBS)		X		Paper Assessment
Headache Impact Test (HIT-6)		X		Paper Assessment
Work Productivity and Activity Impairment (WPAI) – Migraine	X	X		Paper Assessment
Patient Global Assessment (PGA)	X	X		Paper Assessment
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X		Paper Assessment

Table 2. OLE Phase and Follow-up Phase Schedule of Assessments

OLE Phase (up to 12 Weeks)			Follow-up Phase	NOTES
Procedure	**Week 14 Visit (Day 99 +/-3 days)**	**Week 24 Visit (Day 169 +/- 3 days) or EOT Visit for early discontinuation [4,5,7]**	**Follow-up Week 2 Visit (+/- 2 days) [5]**	
Clinical Drug Supplies / Study Supplies				
Concomitant medication paper diary[1]	X	X	X	Site staff should compare the subject reported standard of care migraine medication use to the diary reported "other medication" use. All concomitant medication data should be entered in the database using the paper concomitant medication log as source.
Dispense Study Drug[6]	X			Subjects will be dispensed Four wallets containing 8 ODT's
Return used and unused study drug to site for compliance check	X	X		

1. Concomitant medications, including standard of care migraine medications (both prophylactic and acute), taken throughout the study should be recorded by subjects in the concomitant medication paper diary and reviewed by study personnel at each visit.
2. If possible, subjects should be fasting for a minimum of 8 hours before laboratory tests. However, if a subject is not fasting, the blood draw should still be performed, and the non-fasting status must be documented. See section 6.3.4.1 Safety Laboratory Testing.
3. During the OLE Phase, WOCBP must complete a pregnancy test at the Week 14, Week 24/EOT, and Follow-up Week 2 Visits. If a WOCBP suspects that she might be pregnant she must not take any further doses of study drug and immediately contact the study doctor.
4. Subjects who discontinue early from the OLE Phase should complete the EOT Visit, except due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up. Otherwise, subjects should complete the Week 24 Visit.
5. The visit window for the Follow-up Week 2 Visit is 14 days +/- 2 days from EOT visit. All randomized subjects should complete the Follow-up Week 2 Visit, except those who discontinue early from the due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.
6. At the DB EOT visit, subjects will be administered two wallet cards containing 8 ODT's. Subjects are to be instructed to complete a full wallet before taking study drug from a new one.
7. All randomized subjects should complete the Follow-up Week 2 Visit, except those who discontinue early from the DBT Phase due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.

4.3.1. Observation Phase

Approximately 1000 subjects will be screened to randomize approximately 600 subjects to blinded study drug (rimegepant ODT or matching placebo).

The Observation Phase will be 28 consecutive days + 3 days. Note that the "+ 3 days" window is included ***for scheduling purposes only.***

The Observation Phase will have 2 scheduled visits, Screening and Pre-randomization Evaluation, which must be completed in person.

Eligible subjects must report **4–14 migraine days** and **less than 15 headache days** (migraine or non-migraine) and **<7 non-migraine headache days** during the first 28-days of the Observation Phase. NOTE: Migraine days, headache days and non-migraine days reported during the "+3 days" window will not be used for determining eligibility.

Subjects must report each migraine occurrence, related migraine pain features and other associated symptoms, and use of acute standard of care migraine medication in the eDiary every day during the Observation Phase. Subjects who demonstrate poor compliance with the eDiary will be discussed with the Sponsor and corrective training will be completed by the site with the subject.

For LFT testing requirements:

For screening total bilirubin, > 1.5 × ULN may be repeated once for confirmation during the Observation Phase). Bilirubin results > 1.5 x ULN obtained at the Pre-Randomization laboratory Visit cannot be repeated.

For screening ALT/AST >2 × ULN, may be repeated once for confirmation during the Observation Phase. AST and/or ALT results > 2 x ULN obtained at the Pre-Randomization laboratory Visit cannot be repeated.

All subjects may continue to use their acute permitted standard of care migraine medications during the Observation Phase. Subjects will record all concomitant medications, including standard of care acute migraine medications (both prescribed and OTC), taken during the Observation Phase in a Concomitant Medication paper diary.

After completing the 28-day Observation Phase, subjects are to return to the clinic with their eDiary as part of the DBT Baseline (Randomization) Visit. During this visit, both their eDiary and Concomitant Medication paper diary will be reviewed for completeness, and further eligibility for participation in the blinded treatment phase will be assessed prior to randomization and before study drug is initially dispensed.

4.3.1.1. Screening Visit

Before any study procedures are performed, subjects must provide documented informed consent. After informed consent, subjects will be enrolled in the RTSM system. The subject's

migraine history and medical history will be collected at the Screening Visit, which starts at Day 1 of the Observation Phase.

Subjects will undergo all screening procedures as detailed in Section 4.3, Table 1. After completion of all Screening procedures, subjects will be provided an eDiary. If the subject meets study entry criteria (i.e., inclusion/exclusion criteria), then the subject will return to the study site for the Pre-randomization Evaluation Visit.

If the subject does not meet study entry criteria, then the subject will be considered a screen failure and should be recorded as such in RTSM. All subjects who are Screen Failures must return the eDiary to the study site in a timely manner.

Subjects who were considered screen failures may be considered for re-screening provided the ineligibility was due to one of the eligibility criteria that may have changed due to medical intervention or one of the eligibility criteria modified in a protocol amendment. Adequate documentation in source records must support the previously failed criteria. In all possible re-screening circumstances, the situation must be discussed with the sponsor prior to re-screening, with approval in writing from the sponsor prior to re-screening. If a subject is approved for re-screening, a new subject number must be obtained from the appropriate study-related system. Re-screening will only be permitted one time.

4.3.1.2. Pre-randomization Evaluation Visit

Subjects must return to the study site for the Pre-randomization Evaluation Visit within 4-day (+2) days of the Baseline (Randomization) Visit. Note that the "+ 2 days" window is included for scheduling purposes only. Every effort should be made to complete the Pre-randomization Evaluation Visit as close to, and within, the 4 days prior to the Baseline Visit as possible. However, for scheduling convenience, this window may be up to 6 days between the Pre-randomization Evaluation Visit and the Baseline Visit.

Subjects will undergo all pre-randomization procedures as detailed in Table 1 and compliance with the concomitant mediation paper diary and eDiary will be assessed. Subjects with less than 24 completed eDiary reports during the first 28 days in the Observation Phase will not be considered as eligible for participation in the DBT Phase, due to noncompliance with the eDiary.

If the subject continues to meet study entry criteria and laboratory test results are acceptable per protocol, then the subject will be randomized at the Baseline Visit into the DBT Phase.

If the laboratory results are not acceptable per protocol, then the subject is determined to be a screen failure and should be recorded as such in RTSM. All subjects who are Screen Failures must return the eDiary to the study site in a timely manner.

4.3.2. Double-blind Treatment Phase

The DBT Phase will be up to 12 weeks from the Baseline (Randomization) Visit through the Week 12/EOT Visit.

Subjects will be instructed that they must take one tablet of blinded study drug every other calendar day (EOD) during the DBT Phase, regardless of whether they have an acute migraine on that day or not. If subjects have an acute migraine during the DBT Phase, they may treat the headache with permitted acute migraine medication (see Section 16.4 Appendix 4), as needed, and in accordance with the standard of care, to manage acute attacks regardless if the migraine occurs on a study drug dosing day or non-dosing day. Study drug is NOT to be used for the treatment of acute migraine attacks, but regularly dosed EOD, in accordance with the protocol.

Subjects will continue to report each migraine occurrence, related migraine pain features and other associated symptoms, and all use of acute migraine medication in the eDiary every day during the DBT Phase.

The Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ), Columbia-Suicide Severity Rating Scale (C-SSRS), Migraine Interictal Burden Scale (MIBS), Headache Impact Test (HIT-6), Migraine Functional Impact Questionnaire (MFIQ), Work Productivity and Activity Impairment (WPAI) – Migraine, and the Patient Global Assessment (PGA) will be completed, or administered by the Investigator, on paper or eDiary at specified study visits (see Section 4.3, Table 1).

After the Baseline Visit, study visits will be approximately every 2 weeks during the first month, and then every 4 weeks, until Week 12 (see Section 4.3, Table 1). At each visit, the eDiary will be reviewed by site staff for completeness and compliance and collected. Concomitant medication use will be reviewed, where applicable at each visit. Study drug compliance will be reviewed at each visit using the returned study drug wallets, and subjects will be dispensed additional study drug as needed. Additional safety (including laboratory tests and ECGs) will be performed per the schedule outlined in Section 4.3, Table 1.

4.3.2.1. Baseline (Randomization) Visit

Once completing the Observation Phase, subjects will return to the study site for the Baseline (Randomization) Visit, which should be completed in person. Subjects who continue to meet all study entry criteria and have been compliant with the eDiary may enter the DBT Phase, pending review of additional laboratory test results; see Section 4.3.1.1.

Subjects with less than 24 completed eDiary reports during the first 28 days in the Observation Phase will not be considered as eligible for participation in the DBT Phase, due to non-compliance with the eDiary.

At the Baseline Visit, subjects will be randomized 1:1 across 2 treatment groups: blinded rimegepant (75 mg ODT) (n = 300) or matching placebo, dosed EOD (n = 300). Randomization will be stratified by: 1) the number of migraine days reported to have occurred during the first 28-days of the Observation Phase (4-7 or 8-14); and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories).

4.3.3. Week 12 or DBT EOT Visit

Subjects will return to the study site at the Week 12 Visit (Day 86 +3 days) or at the EOT Visit for early discontinuation. At this visit, subjects will undergo the Week 12/DBT EOT Visit procedures as detailed in Table 1; compliance with the concomitant mediation paper diary and eDiary will be assessed. At the Week 12/DBT EOT Visit, subjects will return the eDiary for review and all double-blind study drug, including all wallets with used or unused study drug.

Scheduled every other day (EOD) dosing with blinded study drug (regardless of migraine status) should be continued throughout the entire course of the DBT Phase. If the Week 12 Visit falls on a regularly scheduled dosing day, subjects should take their final dose of blinded study medication on that calendar day.

All randomized subjects ***who discontinue early from the DBT Phase*** should complete the DBT EOT Visit, except in the case of withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up. The assessments associated with the DBT EOT Visit are identical to those conducted as part of the Week 12 Visit (for DBT Phase completers) (see Table 1). Otherwise, subjects should complete the Week 12 Visit.

All randomized subjects should complete the Follow-up Week 2 Visit, except those who discontinue early from the DBT Phase due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.

If the DBT EOT Visit occurs remotely due to the COVID-19 Pandemic, the subject should return to the site for the Follow-up Week 2 Visit to complete all procedures that could not be completed remotely. Procedures completed at the DBT EOT Visit occurring remotely do not need to be repeated.

Subjects who complete the DBT Phase (i.e., Week 12 Visit) will be considered for enrollment into the OLE Phase. For subjects who intend to enroll in the OLE Phase and are considered to be in good-standing, in the opinion of the PI, open-label study drug (rimegepant 75 mg ODT) will be dispensed prior to the conclusion of the Week 12 Visit.

Subjects who (1) discontinue early from the DBT Phase or (2) have already entered the Follow-up Phase are not eligible to enter the OLE Phase. All cases of treatment non-compliance during the DBT Phase are to be discussed with the Sponsor, and corrective training is to be completed and documented, prior to the subject's enrollment into the OLE Phase.

4.3.4. Open-label Extension (OLE) Phase

It is estimated that approximately 480 patients will be entered into the open-label extension phase.

The OLE Phase will be up to 12 weeks and will have scheduled visits at Week 14 and Week 24/ OLE EOT. See Table 2 for schedule of assessments.

Scheduled every other day (EOD) dosing with open-label study drug (regardless of migraine status) should be continued throughout the entire course of the OLE Phase.

Day 1 of the OLE Phase is defined as Week 12 visit date plus 1 calendar day.

Dosing with open-label study drug (rimegepant 75mg ODT) should BEGIN two calendar days after the final scheduled dosing day for blinded study drug, to maintain the EOD dosing schedule throughout the entire course of the trial (DBT and OLE Phases).

Subjects who discontinue early from the DBT Phase or have already entered the Follow-up Phase are not eligible to enter the OLE Phase. Subjects who discontinue who are otherwise not eligible for the OLE Phase, per the discretion of the Investigator, in consultation with the Medical Monitor, should enter the Follow-up Phase. Subjects who successfully complete the DBT Phase, and have not completed the Follow-up Week 2 Visit, may enter the OLE Phase, at the discretion of the Investigator.

4.3.4.1. Week 14 Visit

At the Week 14 Visit, the study drug wallets will be reviewed for compliance and concomitant medication use will be reviewed (and compared to concomitant medication paper diary entries, where applicable). Subjects will be dispensed additional study drug during the visit. Additional safety assessments (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

The Work Productivity and Activity Impairment (WPAI) – Migraine, Patient Global Assessment (PGA) and the Columbia-Suicide Severity Rating Scale (C-SSRS) will be completed, or administered by the Investigator, on paper Week 14 Visit (see Section 4.3, Table 2).

Subjects must continue to record use of concomitant medications in the concomitant medication paper diary through the entire OLE Phase.

4.3.4.2. Week 24 or EOT Visit

Subjects will return to the study site at the Week 24 Visit (Day 169 +/-3 days), or at the OLE EOT Visit for early discontinuation from the OLE Phase.

Subjects will undergo the Week 24/OLE EOT Visit procedures as detailed in Table 2; The subject will return the paper diaries for review and all study drug, including wallets with used or unused open-label drug.

The Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ), Columbia-Suicide Severity Rating Scale (C-SSRS), Migraine Interictal Burden Scale (MIBS), Patient Global Assessment (PGA), Headache Impact Test (HIT-6), and the Work Productivity and Activity Impairment (WPAI) – Migraine will be completed, or administered by the Investigator, on paper Week 24/EOT Visit (see Section 4.3, Table 2).

All randomized subjects ***who discontinue early from the OLE Phase*** should complete the OLE EOT Visit, except in the case of withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up. The assessments associated with the OLE EOT Visit are identical to those conducted as part of the Week 24 Visit (for OLE Phase completers) (see Table 2). Otherwise, subjects should complete the Week 24 Visit.

All randomized subjects should complete the Follow-up Week 2 Visit, except those who discontinue early from the OLE Phase due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.

If the Week 24 /OLE EOT Visit occurs remotely due to the COVID-19 pandemic, the subject should return to the site for the Follow-up Week 2 Visit to complete all procedures that were not able to be completed remotely. Procedures completed at the Week 24/OLE EOT Visit, occurring remotely, do not need to be repeated.

4.3.5. Follow-up Phase

All randomized subjects should complete the Follow-up Week 2 Visit, except those who discontinue early from the study due to withdrawal of consent, loss of a subject's ability to consent freely, death, or when a subject is lost to follow-up.
The Follow-up Phase will have one scheduled visit at Follow-up Week 2 for targeted safety assessment and end-of-study procedures. At this visit, subjects will undergo the follow-up visit procedures as detailed in Table 1 for those subjects that either discontinue early from the DBT Phase or do not enter the OLE Phase, and Table 2 for those subjects completing or discontinuing early from the OLE Phase. In addition, compliance with the concomitant medication paper diary will be assessed. Investigators should assess subjects for AEs consistent with drug dependency or withdrawal effects and report as appropriate (see Section 7.4).

The Follow-up Week 2 Visit is to occur approximately 2 weeks (14 days +/- 2 days) after the last visit in the last treatment phase (i.e., Week 12/DBT EOT Visit if the subject did not enter the OLE Phase; Week 24/OLE EOT Visit if the subject entered the OLE Phase).

Subjects will continue to record all concomitant medications, including standard of care acute migraine medications (both prescribed and OTC), taken during the Follow-up Phase in the Concomitant Medication paper diary.

Due to the COVID-19 Pandemic, some selected study visits may be conducted remotely (Ex: Telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted

remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject participation.

4.4. Post Study Access to Therapy

At the end of the study the sponsor will not continue to supply study drug to subjects or investigators. The Investigator should ensure that the subject receives permitted acute migraine standard of care medication used to treat the condition under study.

5. POPULATION

Individuals entered in this trial will be subjects who suffer from migraines. The treatment setting for these subjects may include clinics, institutions, or private office practices. Subjects may be recruited through a variety of sources, including referrals from physicians and other health care professionals.

5.1. Number of Subjects

Approximately 1,000 subjects will be screened in order to randomize up to approximately 600 eligible adults to either rimegepant or placebo. Subjects will be randomized 1:1 across 2 treatment groups in the DBT Phase: blinded rimegepant (75 mg ODT) (n = 300) or matching placebo (n = 300), dosed EOD. Randomization will be stratified by 1) the number of migraine days reported to have occurred during the first 28-days of the Observation Phase (4-7 or 8-14); and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories).

5.2. Inclusion Criteria

1) Target Population

Minimum 1 year documented history of migraines (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition.[12]

Per self-report, with confirmation from Investigator / supporting medical record, subjects must have:

a) Migraine attacks present for more than 1 year from the Screening Visit

b) Age of onset prior to 50 years of age

c) Migraine attacks lasting about 4–72 hours, if untreated

d) 4 to 14 **migraine days** (based on ICHD-3 criteria), on average, across the 3 months prior to the Screening Visit (a month is defined as 28 days for the purpose of this protocol)

e) 4 to 14 **migraine days** during the first 28-days of the Observation Phase

f) Subjects must be able to distinguish migraine attacks from tension headaches

g) Prior inadequate response, within 10 years of the Screening Visit, to agents across 2-4 categories of recognized, orally-administered migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication) (see Section 16.2 Appendix 2)

h) **For Germany Only** please refer to 16.7.1

2) Age and Reproductive Status

a) Subjects ≥ 18years-old

b) Subject meets reproductive criteria. Refer to Section 16.6 Appendix 6 for reproductive criteria for female subjects (Section 16.6.2).

c) At the Baseline Visit, prior to dispensing investigational study drug, WOCBP must have a negative pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) before dosing with study drug.

5.3. Exclusion Criteria

1. Target Disease Exclusion

a) History of cluster headaches, basilar migraine (migraine with brainstem aura), or hemiplegic migraine

b) Current medication overuse headaches

c) 15 or more **headache days** (migraine or non-migraine) per month in any of the 3-months prior to the Screening Visit or during the first 28-days of the Observation Phase

d) 7 or more non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit or during the first 28-days of the Observation Phase

e) Inadequate response (due to lack of efficacy, prior intolerance, or contraindication) to agents across > 4 categories of recognized, orally-administered, migraine-preventive medications (see Section 16.2 Appendix 2)

2. Medical History and Current Diseases

a) History of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric balloon, etc.), or disease or conditions (e.g., chronic pancreatitis, ulcerative colitis, etc.) that causes malabsorption

b) Body mass index ≥ 35kg/m^2

c) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or subjects who have met DSM-V criteria[13] for any significant substance use disorder within the past 12 months (48 weeks) from the date of the Screening Visit

d) Current diagnosis of major depressive disorder requiring treatment with an atypical antipsychotic

e) Current diagnosis of schizophrenia, bipolar disorder, or borderline personality disorder

f) History or current evidence of other major psychiatric disorder that might interfere with the ability to properly report clinical outcomes

g) Major depressive disorder (MDD) or any anxiety disorder (AD) which requires more than 1 daily medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening Visit.

h) Major depressive episode (MDE) within last 12 months prior to the Screening Visit.

i) Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to the Screening Visit, OR subjects who endorse any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within the last 10 years prior to the Screening Visit, OR subjects who, in the opinion of the Investigator, present a serious risk of suicide (See Section 6.3.5).

j) Active chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, complex regional pain syndrome [CRPS])

k) Other pain syndromes (including trigeminal neuralgia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments of safety or efficacy

l) Current evidence of uncontrolled, unstable or recently (within 6-months [24 weeks] prior to the Screening Visit) diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia

m) Myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) within 6 months (24 weeks) prior to the Screening Visit

n) Uncontrolled hypertension (high blood pressure). Systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg after 10 minutes of rest is exclusionary; this may be repeated once at the Screening Visit to confirm reproducibility.

o) History or current evidence of any unstable medical conditions (e.g., history of congenital heart disease, arrhythmia, or cancer)

p) Positive drug screen for drugs of abuse that in the Investigator's judgment is medically significant, in that it would impact the safety of the subject or the interpretation of the study results. In addition:

i. Detectable levels of cocaine, amphetamine and phencyclidine (PCP) in the drug screen are exclusionary. Retesting is not allowed.

ii. Subjects who are positive for amphetamines, and who are on a prescribed amphetamine medication for an approved indication (e.g., ADHD) will be allowed into the study at the Investigator's discretion. This determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable from 3 months (12 weeks) prior to the Screening Visit though the Week 12 / EOT Visit.

Detectable levels of marijuana in the drug screen are not exclusionary, if in the Investigator's documented opinion the subject does not meet DSM-V criteria[13] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results. Subject must agree to refrain from marijuana use during the study.

3. Allergies and Adverse Drug Reactions

a) History of drug or other allergy which, in the opinion of the investigator, makes the subject unsuitable for participation in the study.

4. Sex and Reproductive Status

a) WOCBP who are unwilling or unable to use required contraception. Refer to Section 16.6 Appendix 6 for Contraceptive and Barrier Guidance). Women who are pregnant or breastfeeding.

b) Women with a positive pregnancy test at Screening Visit or prior to study drug administration

5. ECG and Laboratory Test Findings

a) Any clinically significant abnormality identified on the medical or laboratory evaluation. A subject with a clinical abnormality or laboratory parameters outside the reference range may be included only if the Investigator considers the finding not clinically significant, that it will not introduce additional risk factors, will not interfere with the study procedures, and does not otherwise meet any expressly written exclusionary criterion within the protocol.

b) Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation < 30 ml/min/1.73m^2

c) Total bilirubin > 1.5 x ULN (For Gilbert's syndrome, direct bilirubin >ULN is exclusionary).

d) AST or ALT > 2 x ULN.

e) Serum albumin < 2.8 g/dL

f) Neutrophil count ≤ 1,000/µL (or equivalent)

g) HbA1c > 7.5%

h) The subject has evidence of organ dysfunction or any clinically significant deviation from normal on physical examination, vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory determinations beyond what is consistent with the target population. Abnormal ECG that in the investigator's opinion makes the subject unsuitable for a clinical trial.

6. Prohibited Medications and Devices

a) Recognized migraine-preventive medication taken within 30 days prior the Screening Visit (see Section 16.2 Appendix 2). Note the following exceptions:

i. Biologic migraine medication (such as CGRP antagonist monoclonal antibodies) taken within 6 months (24 weeks) prior to the Screening Visit

ii. Botulinum toxin injections (e.g., Botox®) used for the prevention of migraine taken within 3 months (12 weeks) prior to the Screening Visit

b) Non-Narcotic Analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol [acetaminophen] taken ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit

c) Cefaly™ or any other device for migraine prevention or treatment within 3 months (12 weeks) prior to the Screening Visit

d) Ergotamine taken ≥ 10 days per month on a regular basis for ≥ 3 months (≥ 12 weeks) in the year prior to the Screening Visit

e) Narcotic, such as opioid (e.g., morphine, codeine, oxycodone, hydrocodone) or barbiturate (e.g., butalbital), taken for ≥ 4 days per month during the 3 months (12 weeks) prior to the Screening Visit

f) Permitted acute migraine medication taken ≥ 15 days per month for a non-headache indication during the 3 months (12 weeks) prior to the Screening Visit (see Section 5.5)

   i. Low dose aspirin (e.g., up to 100 mg daily) for documented cardiovascular prophylaxis is allowed.

Note: See Section 5.7 and Section 16.3 Appendix 3 for further details related to prohibited medications and devices

7. Other Exclusion Criteria

a) Non-compliance with or inability to complete eDiary during Observation Phase. Subjects with less than 24 completed eDiary reports during the first 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary.

b) Exposure to non-biological investigational agents within 30 days prior to the Screening Visit

c) Exposure to biological investigational agents (including monoclonal antibodies) within 6 months (24 weeks) prior to the Screening Visit

d) Previous enrollment in any multiple dose BHV3000 (rimegepant) study, such as BHV3000-201, BHV3000-305, BHV3000-405, or BHV3000-406, regardless of the number of doses taken. Subjects may be considered for BHV3000-407 if the subject participated in any of the following single dose studies: BHV3000-301, BHV3000-302, BHV3000-303, but did not participate in any multiple dose rimegepant study. Note that subjects who were considered screen failures in a past BHV3000 study may be considered after discussion with the Sponsor and written approval is received.

e) Participation in any other investigational clinical study while participating in this clinical study.

f) Past participation in a clinical study within 30 days prior to the Screening Visit

g) Failure to complete the Baseline Visit within the timeframe specified in the schedule of assessments

h) The subject is, in the investigator's opinion, considered to be otherwise clinically unsuitable for participation in the study (the reason for exclusion should be documented in the subject's source file).

i) Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

j) **For Germany Only** please refer to 16.7.1

5.4. Definition of Migraine Days

Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥30 minutes, meeting either Criteria A or B (below), and not better accounted for by another clinical diagnosis, in the opinion of the managing Investigator.

A. ≥ 2 of the following pain features:

- Unilateral location,
- Pulsating quality (throbbing),
- Moderate or Severe headache pain intensity,
- Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

B. ≥ 1 of the following associated symptoms:

- Nausea and/or Vomiting,
- Photophobia and phonophobia

During the Observational Phase and DBT Phase, if the subject takes acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, or ubrogepant) to treat a headache (or aura) on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

Of note, the use of ergotamine is prohibited throughout the entire duration of the study. However, all dosing of acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, and ubrogepant) must be reported within the eDiary(DBT) and the Concomitant Medication paper diary, to accurately inform the occurrence of a "migraine day".

A moderate or severe migraine day is a migraine day with a migraine reported with moderate or severe headache pain intensity.

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

A. A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.

B. An attack treated successfully with medication but with relapse within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

For the full definition of Migraine Days, please refer to Section 16.1 Appendix 1.

5.5. Acute Migraine Medication Day:

During the Observational Phase, DBT Phase and OLE Phase, any calendar day during which a subject takes a migraine-specific acute migraine medication (i.e., triptan, ergotamine, lasmiditan, or ubrogepant), the corresponding calendar day will be counted as an "acute migraine medication day" and an “acute migraine-specific medication day”, regardless of the duration and pain features/associated symptoms.

Of note, the use of ergotamine is prohibited throughout the entire duration of the study. However, all dosing of acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, and ubrogepant) must be reported within the eDiary(DBT) and the Concomitant Medication paper diary, to accurately inform the occurrence of a “migraine day”.

In addition, any calendar day during which a subject takes an acute migraine medication (permitted [see Section 16.4 Appendix 4] or non-permitted) for the reported purpose of treating a qualifying migraine headache (or aura), then the corresponding calendar day will be counted as an "acute migraine medication day”.

All use of acute migraine medications (permitted or otherwise) for the purpose of treating a qualified migraine headache will be recorded from the Screening Visit to the Follow-up Week 2 visit on the Concomitant Medication paper diary.

5.6. Definition of Headache Days

A Headache Day is any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- A qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, or ubrogepant), or
- A qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- A headache of any duration for which medication(s) is taken (and recorded on the Concomitant Medication Paper Diary) for the purposes of treating headache-related symptoms

For the full definition of headache days, please refer to Section 16.1 Appendix 1.

5.7. Prohibited and Restricted Concomitant Medications

All medications including vaccinations taken by subjects at the Screening Visit and through the Follow-up Week 2 Visit will be documented as concomitant medications in the appropriate paper diary and shared with the site at each study visit.

See Section 16.3 Appendix 3 for prohibited and restricted concomitant medications and devices during the study.

5.8. Permitted Acute Migraine Medications

Use of standard of care acute migraine medication during the Observation Phase through the Follow-up Week 2 Visit is to be recorded by the subject in the Concomitant Medication paper diary and reported to the site at each study visit.

During the study, subjects may use their permitted acute migraine medication (prescribed or OTC agents) for the management of acute attacks, as needed, and in accordance with the standard of care. See Section 16.4 Appendix 4 for permitted acute migraine medications.

During the DBT Phase and OLE Phase, if a subject takes study drug on a scheduled dosing day and experiences a migraine, then the subject may take permitted acute migraine medication for the management of the acute attack, in accordance with the standard of care.

Note, during the DBT Phase, double-blind study drug is **NOT permitted** for the acute management of migraine symptoms. Also, during the DBT Phase, subjects are NOT allowed to take more than one ODT of study drug EVERY OTHER calendar day (EOD) and are not allowed to take study drug on a non-scheduled dosing day.

Note, during the OLE Phase, subjects are to maintain the EOD dosing schedule established in the DBT Phase. As in the DBT Phase, in the OLE Phase, subjects are to take their open-label study drug every other day (EOD), regardless of whether they have a migraine. In addition, during the OLE Phase, open-label rimegepant is **NOT permitted** for the acute management of migraine symptoms. Subjects may use their permitted acute migraine medication (prescribed or OTC agents) for the management of acute attacks, as needed, and in accordance with the standard of care. See Section 16.4 Appendix 4 for permitted acute migraine medications.

Throughout the entire course of the study (DBT and OLE Phase), study medication (blinded or open-label drug) is NOT to be used as acute migraine attack treatment.

5.9. Contraception

The investigator or designee will inform the subject of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

All WOCBP must complete the pregnancy testing as referenced in the schedule of assessments in Section 4.3, Table 1.

5.10. Other Restrictions and Precautions (if applicable)

Not applicable.

5.11. Significant Deviations

Any significant event that does not comply with the inclusion / exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6. STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1. Study Materials

The following study materials will be provided at the study start:

- Investigator File/Regulatory Binder
- Investigational Product Manual
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant Medication paper diary (take home for subject)
- Investigator Brochure
- Randomization and Trial Supply Management (RTSM) system
- Electronic Case Report Form (eCRF) instructions
    - Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields

- All sites will use an Electronic Data Capture (EDC) tool to submit study data to the CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including queries) will be submitted to the CRO using eCRFs.

- Electronic Diary (eDiary): hand-held electronic device (1 device will be given to each subject)
  - Instructions for the eDiary device and access to the portal.
  - During the DBT Phase, the eDiary will be used daily to record migraine occurrence, migraine pain features, and associated symptoms and use of acute migraine-specific medications (i.e., triptan, ergotamine, lasmiditan, or ubrogepant) (see Section 16.4 Appendix 4.

    Of note, the use of ergotamine is prohibited throughout the entire duration of the study. However, all dosing of acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, and ubrogepant) must be reported within the eDiary(DBT) and the Concomitant Medication paper diary, to accurately inform the occurrence of a "migraine day".
  - During the DBT Phase, the eDiary will be used at select time points to assess the Migraine Functional Impact Questionnaire (MFIQ) and Patient Global Assessment (PGA).

- Laboratory Kits and Laboratory Manual
  - Safety laboratory, plasma, and serum instructions for all specimens collected will be provided by a designated central laboratory.

- ECG Machine and Instructions
  - ECG equipment, supplies, instructions and training materials will be supplied by a centralized ECG vendor.

- SAE forms (to be used only if PSSA is not available) and SAE Reporting instructions
- Exposure during Pregnancy Forms and Pregnant Partner Release of Information
- Columbia-Suicide Severity Rating Scale (C-SSRS) forms
- Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) v 2.1 forms
- Migraine Interictal Burden Scale (MIBS) forms
- Headache Impact Test (HIT-6) forms

- Work Productivity and Activity Impairment (WPAI) – Migraine forms
- Study system access:
  - Electronic Data Capture (EDC) tool to submit study data to Sponsor / CRO
  - RTSM
  - Central Laboratory vendor portal
  - Central ECG vendor portal
  - eDiary vendor portal

6.2. Eligibility Assessments

As outlined in Table 1 and Table 2: Informed consent, inclusion/ exclusion criteria, medical history study procedures, migraine history assessment, Concomitant Medication paper diary, ECG and randomize subject in RTSM.

6.3. Safety Assessments

SAEs should be reported from signing of consent through the 2-week Follow up Visit. Unresolved SAEs at the time of the 2-week Follow-up Visit should be monitored until resolution of the acute aspects of the safety event, per the opinion of the Investigator. The Investigator should report any SAE occurring beyond the 2-week Follow-up Visit when the event is believed to be related to study drug or other protocol-specific procedures.

Non-serious AEs should be reported from signing of consent through 2-Week Follow up Visit.

6.3.1. Vital Signs and Physical Measurements (Height and Weight)

Vital signs, body weight, and height will be recorded at the scheduled visits as outlined in Section 4.3, Table 1 and Table 2 (as applicable).

6.3.2. Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at scheduled visits as outlined in Section 4.3, Table 1 and Table 2 (as applicable). A central ECG service will be utilized for reading all ECGs. The over read from the central ECG vendor should be used to determine eligibility for the study. The Investigator will determine if any ECG abnormalities are clinically significant or not. (See Section 16.5 Appendix 5).

6.3.3. Physical Exam

Subjects will undergo a complete physical examination during the Screening Phase and the Week 12 / EOT Visit, and targeted and symptom-directed physical exam as outlined in Section 4.3, Table 1 and Table 2 (as applicable). Physical examinations to include at

minimum: examination of heart, abdomen and lungs, with review of any other system to be guided by symptoms.

6.3.4. Laboratory Assessments

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory test findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Schedule of Assessments.

6.3.4.1. Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Section 4.3, Table 1 and Table 2 (as applicable) and for clinical laboratory evaluations. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. **If possible, subjects should be fasting for a minimum of 8 hours before laboratory tests.** However, if a subject is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented.

Clinical safety labs:

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets

Chemistry: Sodium, potassium, chloride, bicarbonate, glucose, BUN (urea), serum creatinine

eGFR using the estimated MDRD formula (calculated at central lab) (Screening visit only)

LFTs: AST, ALT, Alkaline Phosphatase and Bilirubin (Total, Direct, Indirect). Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Study Laboratory Manual

Urine Drug Screen: For drugs of abuse

FSH: At screening in female subjects to confirm postmenopausal status, if applicable (FSH level testing is not required for women greater than or equal to 60 years old with amenorrhea of greater than or equal to one year)

Reflex/add-on tests:

If ALT or AST ≥ 3 x ULN *OR* total bilirubin ≥ 2 x ULN at any visit after the Baseline Visit, additional reflex or add-on tests may be performed that may include: CK, GGT,

anti-viral serologies, and more. Subjects may have to return to the study site to provide additional blood samples for these laboratory tests. See section on Potential Drug Induced Liver Injury (Section 8.4).

Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory Manual.

6.3.4.2. Pregnancy Testing

WOCBP must complete pregnancy testing at specified study visits and prior to initial dosing of blinded study medication (Baseline [Randomization] Visit), as outlined in Table 1 and Table 2 (as applicable). If a WOCBP suspects that she might be pregnant, she must not take any further doses of study drug and immediately contact the study doctor.

6.3.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide Assessment. The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[14] will be used at subsequent visits in this study.

The C-SSRS Assessment is intended to help establish a person's immediate risk of suicide. The C-SSRS is a clinician administered scale that should be administered by a certified rater. This scale will be collected on site with a paper form. The C-SSRS should be reviewed by the Investigator or designee before the subject is allowed to leave clinic.

At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit (see Section 5.3).

Any "Yes" responses must be immediately evaluated by the Investigator. If the Investigator determines that a subject is at risk of suicide, self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. In such circumstances, the subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the Investigator and reported within 24 hours to the Sponsor.

6.4. Efficacy Assessments

The eDiary will be used daily to record any acute migraine-specific medication dosing occurrences (i.e., triptan, ergotamine, lasmiditan, or ubrogepant), each migraine occurrence, related migraine pain features, and other associated symptoms during the Observation Phase and everyday during the DBT Phase.

Of note, the use of ergotamine is prohibited throughout the entire duration of the study. However, all dosing of acute migraine-specific medication (i.e., triptan, ergotamine,

lasmiditan, and ubrogepant) must be reported within the eDiary and the Concomitant Medication paper diary, to accurately inform the occurrence of a "migraine day".

Efficacy assessments will be derived from eDiary data and will include the number of migraine days per month by headache pain intensity (total; moderate or severe), and number of acute migraine medication days (see Section 5.5) per month, by study period. A month is defined as 28 days, for the purpose of this protocol.

6.5. Other Assessments

6.5.1. Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1

Impact of treatment on subject-reported quality of life will be assessed using the Migraine-Specific Qualify-of-Life Questionnaire version 2.1 (MSQ v 2.1). The MSQ v 2.1 is a 14-item instrument that has been validated in 3 domains: role function – restrictive, role function – preventive, and emotional function.[15] The MSQ will be completed on a paper form at the site. Please see Table 1 and Table 2 (as applicable) for location and timing of assessment.

6.5.2. Migraine Interictal Burden Scale (MIBS)

The Migraine Interictal Burden Scale (MIBS) is a 4-item self-administered questionnaire that measures: impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress.[16,17] Please see Table 1 and Table 2 (as applicable) for location and timing of assessment.

6.5.3. Patient Global Assessment

The Patient Global Assessment scale captures patient perceptions of treatment that may not be captured by measuring headache pain intensity alone. This is a scale that contains one question relating to subjects' overall assessment of migraine. Please see Table 1 for location and timing of assessment.

6.5.4. Work Productivity and Activity Impairment (WPAI) – Migraine

The Work Productivity and Activity Impairment Questionnaire is a tool used to capture work impairment due to migraine pain. Please see Table 1 and Table 2 (as applicable) for location and timing of assessment.

6.5.5. Headache Impact Test (HIT-6)

The HIT-6 is a global measure of adverse headache impact developed to assess headache severity over the previous month and change in a subject's clinical status over time. For clinical purposes, the HIT-6 provides a validated screening cut-point score for migraine headaches, cut-point score to stratify individuals by headache impact severity, and clinically meaningful thresholds around change in score for the purposes of evaluating improvement or deterioration in headache impact over time.

No recall period is specified for the first 3 items of the HIT-6 scale. The recall period is the past 4 weeks for the last 3 items. Subjects will complete the HIT-6 form within a paper diary

at the time of select study visits. Please see Table 1 and Table 2 (as applicable) for timing of assessments.

6.5.6. Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ was designed to be completed once a week to capture the week-to-week variability of the impact of migraine. A 7-day recall period captures the variability of migraine symptoms and impacts, while being less burdensome than a daily assessment and reducing potential recall bias associated with longer recall intervals.

The MFIQ was developed using methods consistent with the regulatory guidance on patient-reported outcome (PRO) measures to support label claims about the benefit of treatments (FDA 2009). Please see Table 1 for location and timing of assessment.

6.6. Subject Early Discontinuation Criteria

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the Investigator) for any of the following reasons.

- Subjects who discontinue early from the DBT Phase or OLE Phase
- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Pfizer Inc
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Poor compliance with study procedures and visits, including poor completion compliance with evening reports in eDiary
    - Subjects with less than 24 completed eDiary reports during the first 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary
    - Subjects in the DBT Phase will be monitored closely for compliance with the eDiary. Subjects who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.
- Please see Section 6.3.5 for guidance on subject discontinuation based on results from the C-SSRS

- All subjects who discontinue prior to the completion of the DBT Phase or OLE Phase should comply with protocol-specified EOT Visit procedures as outlined in Table 1 or Table 2 (as applicable). The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness), death, or is otherwise lost to follow-up.

- If a subject withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

- If the subject withdraws from the study and also withdraws consent for collection of future information, no further evaluations will be performed and no additional data will be collected, except for publicly available information. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.6.1. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

6.7. Study Early Discontinuation Criteria

The current clinical trial will be completed when the last participant finishes their final pre-specified study assessment or is otherwise permanently discontinued from the trial.

Early discontinuation of the study may occur at the discretion of the Sponsor in the event there is an unacceptable shift in the benefit-risk assessment of the investigational therapy (rimegepant) for the target population under investigation (adults living with migraine who are unsuitable for triptan use). The change in benefit-risk profile of the study drug may be derived from events (adverse events, serious adverse events, etc.) occurring within the

BHV3000-407 study and/or any other rimegepant safety data source, including other clinical trials, toxicological studies, or spontaneous reporting of real-world evidence.

7. STUDY DRUG MANAGEMENT

7.1. Description of Study Drug

7.1.1. Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as follows:

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

During the DBT Phase, investigational product/study drug/study medication is blinded rimegepant (BHV-3000) (PF-07899801) (75 mg ODT) and matching placebo, which will be provided by the Sponsor.

During the OLE Phase, investigational product/study drug/study medication is open label rimegepant (BHV-3000) (PF-07899801) (75 mg ODT), which will be provided by the Sponsor.

NOTE:
During the DBT or OLE Phase, if a dose of study drug for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the Study Drug Compliance Log and should NOT take another dose of study drug until the next scheduled dosing day, in accordance with the planned EOD dosing schedule.

Intervention Name	Rimegepant	Placebo
Type	drug	drug
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Orally disintegrating tablet (ODT)	Orally disintegrating tablet (ODT)

Unit Dose Strength(s)	75 mg	Placebo for 75 mg tablet
Dosage Level(s)	DBT phase: 75 mg OLE phase: 75 mg	DBT phase : Placebo ODT OLE phase: not applicable
Route of Administration	Oral	Oral
Sourcing	Provided by the sponsor	Provided by the sponsor
Packaging and Labeling	Study intervention will be provided in multi-laminated blisters, sealed with a foil backing into wallet cards. Each blister wallet will be labeled as required per country requirement.	Study intervention will be provided in multi-laminated blisters, sealed with a foil backing into wallet cards. Each blister wallet will be labeled as required per country requirement.
SRSD	IB	Not applicable

7.1.2. Concomitant Therapy

In this protocol, concomitant therapy(ies) is/are standard of care for acute treatment and acute migraine medication for migraine treatment. The standard of care and acute migraine medications are not being provided by the Sponsor.

7.1.3. Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature and light) as determined by the sponsor. Please see the Pharmacy Manual/Investigator Brochure for specific conditions. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor/CRO immediately.

In the DBT Phase, subjects will receive blister cards containing 8 tablets of blinded rimegepant 75 mg ODT or matching placebo, heat-sealed into a wallet.

In the OLE Phase, subjects will receive blister cards containing 8 tablets of rimegepant 75 mg ODT, heat-sealed into a wallet.

7.2. Dose and Administration

During the DBT Phase, blinded rimegepant 75 mg ODT or matching placebo will be assigned to subjects at the Baseline Visit via the RTSM system. Subjects will be assigned enough IP at each visit to ensure appropriate supply between monthly (every 4 week) visits. Scheduled every other day (EOD) dosing with blinded study drug (regardless of migraine status) should be continued throughout the entire course of the DBT Phase. If the Week 12 Visit falls on a regularly scheduled dosing day, subjects should take their final dose of blinded study medication on that calendar day.

During the OLE Phase, wallets containing 8 tablets of open label rimegepant 75 mg ODT will be dispensed to subjects. Subjects will receive enough IP at the DBT Week 12 Visit, and

at the OLE Week 14 visit to ensure appropriate supply throughout the open label extension phase. Unscheduled visits to dispense study drug may be scheduled as needed. Scheduled every other day (EOD) dosing with open-label study drug (regardless of migraine status) should be continued throughout the entire course of the OLE Phase.

Day 1 of the OLE Phase is defined as Week 12 visit date plus 1 calendar day.

Dosing with open-label study drug (rimegepant 75 mg ODT) should BEGIN two calendar days after the final scheduled dosing day for blinded study drug, to maintain the EOD dosing schedule throughout the entire course of the trial (DBT and OLE Phases).

7.2.1. Method of Assigning Subject Identification

The Investigator or designee will need to access the Randomization and Trial Supply Management (RTSM) System in order to register each subject. Initially, after informed consent is obtained at the Screening Visit, the Investigator or designee will enter the subject into the study and obtain a subject number assignment.

Once a subject completes the study, or if a subject is discontinued early from the study, the Investigator or designee must access the RTSM to document discontinuation of the subject from participation in the study.

Immediately after written informed consent is obtained and before performing any study-related procedures, the site staff must obtain a subject identification by adding a new subject in the appropriate study-related system. In this study, an RTSM system will be utilized for obtaining subject identification and as the electronic data capture (EDC) system. Each subject will be assigned a unique 8-digit subject number through the appropriate study-related system. The subject number will consist of the 3-digit site number, a hyphen, and a unique 4-digit subject number. This subject number must not be reused for any other subject in the study. Subjects will maintain their subject number assigned at screening throughout the study.

At the Baseline Visit, eligible subjects will be randomized in a 1:1 ratio to blinded rimegepant (75 mg ODT) or matching placebo, dosed EOD. Randomization will be stratified by:1) the number of migraine days reported to have occurred during the first 28-days of the Observation Phase (4-7 or 8-14); and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories).

7.2.2. Selection and Timing of Dose and Administration

After confirming subject eligibility, registering a subject for randomization will trigger kit assignments at the Baseline visit; kit numbers will be obtained by the Investigator (or designee) via the RTSM system.

For the DBT Phase, study drug will be assigned via the RTSM system at Baseline and all subsequent DBT Phase dispensation visits. Subjects will be assigned 2 wallets containing 8

tablets of 75 mg ODT rimegepant or matching placebo at each dispensation visit to ensure appropriate supply between monthly (every 4 week) visits. The system will assign specific kit numbers for all study drug to be dispensed to the subject and there will be no dose adjustment allowed.

Once a kit has been assigned it cannot be dispensed to another study subject. Sites will be responsible for recording the kit numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record.

In the DBT Phase, study drug (rimegepant or matching placebo) will be assigned via the appropriate study-related system. There are no dose adjustments in this study and subjects will receive 8 tablets of study drug in a blister card heat-sealed into a wallet; subjects will be assigned more than 1 wallet at each visit to ensure appropriate supply between visits. Subjects will be dispensed study drug at the Baseline Visit, and the subjects will be instructed that they must take ***one tablet EOD regardless of whether they have a migraine on that day.*** This is the scheduled dosing regimen for the DBT Phase. Site staff should mark each wallet with the scheduled date of each dose to be taken when dispensing the study drug.

In the DBT Phase, subjects will be instructed that they must take ***one tablet EOD regardless of whether they have a migraine on that day.*** Dosing should occur around the same time for each scheduled EOD dose. It is preferred that subjects' dose in the morning; however, it is more important that the subject consistently dose at approximately the same time for each scheduled EOD dose. The time of dosing should be consistent throughout the study. If the subject has a migraine on a day when they ***already took study drug***, then the subject can take permitted acute migraine medication (see Section 16.4 Appendix 4), as needed, and in accordance with the standard of care.

During the DBT Phase, if a dose of study drug for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the Study Drug Compliance Log and should NOT take another dose of study drug until the next scheduled dosing day, in accordance with the planned EOD dosing schedule.

Scheduled every other day (EOD) dosing with blinded study drug (regardless of migraine status) should be continued throughout the entire course of the DBT Phase. If the Week 12 Visit falls on a regularly scheduled dosing day, subjects should take their final dose of blinded study medication on that calendar day.

During the OLE Phase, open label rimegepant 75 mg ODT will be assigned via the RTSM system at the DBT EOT visit and at the Week 14 Visit. Subjects will be instructed that they must take one tablet every other calendar day, regardless of whether they have a migraine on that day or not. If the subject has a migraine on a day when they ***already took open-label drug***, then the subject can take permitted acute migraine medication (see Section 16.4 Appendix 4), as needed, and in accordance with the standard of care.

Scheduled every other day (EOD) dosing with open-label study drug (regardless of migraine status) should be continued throughout the entire course of the OLE Phase.

Day 1 of the OLE Phase is defined as Week 12 visit date plus 1 calendar day.

Dosing with open-label study drug (rimegepant 75 mg ODT) should BEGIN two calendar days after the final scheduled dosing day for blinded study drug, to maintain the EOD dosing schedule throughout the entire course of the trial (DBT and OLE Phase. In both the DBT and OLE Phases, subjects **must** be instructed that they CANNOT take more than one tablet of study drug/open label drug every other day (EOD) during the study, in accordance with the protocol.

7.2.3. Dose Modifications

There will be no dose adjustments in this study.

7.2.4. Dose Interruptions

If a subject experiences an AE that requires interruption in study drug, the Investigator should consult with the Sponsor medical monitor to evaluate the need for any additional tests prior to re-starting study drug.

7.3. Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician.

The BHV3000-407 (C4951012) study is a double-blind placebo-controlled trial being conducted in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH) guidelines, Ethics Committee (EC) requirements, and all applicable regulations. Within the BHV3000-407 (C4951012) study, blinding and randomization are utilized to minimize the influence of bias on the conduct of the trial and its associated outcomes.

At the Baseline Visit, eligible subjects will be randomized 1:1 across two blinded treatment arms (blinded rimegepant 75 mg or matching placebo) for the duration of the Double-Blind Treatment (DBT) Phase. Blinded study drug assignment will be issued by centralized Interactive Response Technology (IRT) to follow block randomization of an undisclosed length. Randomization will be stratified by: 1) the number of migraine days reported to have occurred during the first 28-days of the Observation Phase (4-7 or 8-14) and 2) the number of recognized, orally-administered, preventive medication categories with previous inadequate response within 10 years of the Screening Visit (due to lack of efficacy, prior intolerance, or contraindication) (2 vs. 3-4 categories) (see Section 7.2.1).

BHV3000-407 (C4951012) is a double-blind study in which neither the subject nor the Site staff involved in the conduct of the study or clinical evaluation of subjects are aware of study drug assignment. Sponsor staff too will be blinded to subjects' treatment assignment, except for those sponsor staff involved in the assignment or distribution of blinded study drug.

Blinded treatments (double-blind rimegepant or matching placebo) are packaged and labeled in accordance with the kit list, and supplies are dispensed through the IRT per the randomization schedule. Blinded rimegepant and blinded placebo are both oral disintegrating tablets matched in appearance, texture, and taste, and are supplied to the trial center in a manner that ensures no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject.

Unblinding (breaking the blind for a single subject) should be considered only when knowledge of the treatment assignment is deemed by the Investigator, as essential for the proper care of the subject. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the study Medical Monitor prior to unblinding a subject's treatment assignment unless this could delay further management of the subject. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

In cases of accidental unblinding, the Site should contact the Medical Monitor and ensure every attempt is made to preserve the blind for remaining site personnel.

Sponsor staff will be unblinded after the last subject completes the Double-blind Treatment End of Treatment Visit or, in the event the last subject has discontinued early from the study, completes the Week 12 OLE / End of Treatment Visit, or is otherwise discontinued from the trial (e.g., lost to follow-up) (see protocol Section 6.6). Once the overall study is complete (i.e., after the last subject completes the Follow-up Week 2 Visit or is otherwise discontinued from the study), individual subject assignments will be made available to associated Investigators, upon request.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

7.4. Treatment Compliance

Responsible study personnel will dispense the study drug. Subjects are required to finish a wallet of study drug before starting a new wallet. Accountability and compliance verification should be documented in the subject's study records.

Subjects must be counseled on the importance of taking the study drug as directed (see Section 7.2.2). Treatment compliance and review of study drug doses through review of returned study drug should be assessed by site staff at each study visit. Discrepancies between review of study drug and information provided by subject must be documented in the source record. Investigators should inform subjects that involuntary termination from the study will occur in cases where non-compliance is identified. Study staff should contact a subject between the monthly study visits if the subject demonstrates non-compliance with the

eDiary and document the contact in the source, to identify potential lost to follow-up subjects as early as possible.

Investigators must monitor subjects for possible cases of abuse of study drug (subjects taking study drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should also assess study drug accountability discrepancies (e.g., missing study drug, loss of medication, or non-compliance cases in which more study drug was used, as compared to expected). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies (see Section 8.1.1).

Cases of study drug non-adherence, including subjects who discontinue treatment without returning study drug, should be reported as protocol deviations.

All cases of treatment non-compliance, during the DBT Phase, are to be discussed with the Sponsor, and corrective training is to be completed and documented, prior to the subjects enrollments into the OLE Phase.

Cases of excess dosing (e.g., taking >1 tablet of study drug every other day) should be reported as protocol deviations. In the event that an occurrence(s) of excess dosing is believed, in the opinion of the Principal Investigator, to have possibly caused or exacerbated a clinically-significant adverse outcome or serious adverse outcome, the AE resulting from the excess dosing should be reported as aSAE.

Dosing errors not associated with a SAE (e.g., accidentally taking 2 tablets EOD) need only be reported as deviations.

Compliance with study intervention will be defined as:

- ≥80% (and ideally, up to 100%) of study-supplied intervention from Day 1 through the Treatment Phase are expected to be consumed.
- Post randomization, at each dispensation visit (refer to Table 1), subjects who are <80% compliant must be re-educated on the importance of EOD self administration of study intervention.
- Overall aim: maintain ≥80% compliance over the duration of dosing with randomized study intervention.

7.5. Destruction and Return of Study Drug

All unused and/or partially used study drug can be sent back to the determined destruction facility only after being inspected and reconciled by the responsible Study monitor or the Sponsor's designee. If it is site policy to destroy study drug on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The

unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor or the Sponsor's designee.

8. ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) or symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs. Adverse events should be reported after the first dose of study drug.

If a specific diagnosis or syndrome is identified by the Investigator, this should be recorded as the AE, rather than recording (as separate AEs) the individual signs/symptoms or clinically significant laboratory abnormalities known to be associated with and considered by the Investigator to be a component of, the disease/syndrome.

Definition of terms related to all Adverse Events (serious and non-serious):

Mild: Is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: Is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Severe: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

Assessment for Determining Relationship of AE to Study Drug:

The relatedness of each AE to study drug must be classified based on medical judgement and according to the following categories. The definitions are as follows:

Related: This category applies to AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered related when it follows a temporal sequence from the administration of study drug, it cannot reasonably be explained by the known characteristics of the subject's clinical state, environment, or toxic factors, or other modes of therapy administered to the subject. An AE may be considered related when it follows a known pattern of response to the study drug, or if the AE reappears upon re-challenge.

Possibly related (non-serious AEs only): This category applies to AEs that are considered to have a possible connection to study drug and relationship cannot be ruled out with certainty.

Unlikely related (non-serious AEs only): This category applies to AEs that do not follow a reasonable temporal sequence from the administration of the study drug. The AE may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Unrelated: This category applies to AEs that are considered with a high degree of certainty to be due only to extraneous causes (e.g., subject's clinical state, environment, toxic factors, disease under study, etc.) and does not meet the criteria of other categories above.

There are two types of adverse events, Serious Adverse Events (SAE) and Non-Serious Adverse Events (AEs).

8.1. Serious Adverse Events

8.1.1. Definition of Serious Adverse Event (SAE)

An SAE is any event that meets any of the following criteria at any dose:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received rimegepant
- Other Important Medical Events: that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse
- Potential drug induced liver injury (see Section 8.4)
- Abuse or Overdose of medication
  - Potential study drug abuse (including cases of repeated excess dosing or subjects who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE, as appropriate (see Section 7.4). Investigators must monitor subjects for possible cases of abuse of study drug (subjects taking study drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies.
  - Potential study drug overdose is defined in Section 8.3

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

The following hospitalizations are not considered SAEs in Pfizer clinical studies (but may be considered non-serious AEs):

- A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life-threatening);
- Elective surgery planned prior to signing consent;
- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission (i.e., routine colonoscopy);
- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances).

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

8.1.2. Collection and Reporting Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected from signing of consent through the 2-week Follow-up Visit. Unresolved SAEs at the time of the 2-week Follow-up Visit should be monitored until resolution of the acute aspects of the safety event, per the opinion of the Investigator. The Investigator should report any SAE occurring beyond the 2-week Follow-up Visit when the event is believed to be related to study drug or other protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the Investigator believes that an SAE is not related to the study drug but is potentially related to the conditions of the study (such as a withdrawal of previous therapy or a complication related to study procedure), the relationship should be specified in the narrative section of the SAE Report.

SAEs, whether related or not related to study drug, overdose (see Section 8.3), potential drug induced liver injury, (see Section 8.4) and pregnancies (see Section 8.5.1) must be reported within 24 hours of the Investigator becoming aware of the event. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the SAE information into the Case Report Form (CRF) and/or system (i.e., event term, start/stop dates, causality, and severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to Pfizer Drug Safety Unit (DSU) either via the Pfizer SAE Submission Assistant (PSSA) tool or using the Pfizer CT SAE report form that must be sent by facsimile (fax) to your country's Pfizer DSU. The CT SAE Report Form should only be used as a backup in the event PSSA is not operational.

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug, or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

- Sender of report (Site number, Investigator name)
- Subject identification (subject number)

- Protocol number
- SAE term (if an SAE is being reported)

The Sponsor or specified designee/authorized representative will report suspected unexpected serious adverse reactions (SUSARs) in an expedited manner (without delay) to the Regulatory Authorities and Ethics Committees concerned, in accordance with Food and Drug Administration Code of Federal Regulations (CFR) 21 CFR Parts 312 and 320, Clinical Trials Regulation No 536/2014, and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IPs for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or specified designee/authorized representative shall notify the Investigator of the following information:

Any AE that is both serious and unexpected and is suspected of being related to the use of the IP in this study or in other studies (i.e., SUSAR).

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

8.2. Non-serious Adverse Events

A ***non-serious adverse event*** is an AE not classified as serious.

8.2.1. Collection and Reporting of Non-serious Adverse Events

The collection of non-serious AE information should begin from signing the ICF through the Follow-up Week 2 Visit.

Non-serious adverse events should be followed until conclusion or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

8.2.2. Laboratory Test Abnormalities

The following laboratory test abnormalities should be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

1. Any laboratory test result that is clinically significant or meets the definition of an SAE;

2. Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted;

3. Any laboratory abnormality that required the subject to receive specific corrective therapy.

8.3. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both **excessive** and **medically important**.

There is limited clinical experience with overdose of rimegepant. Treatment of overdose with rimegepant should consist of general supportive measures. There is no known specific antidote for overdose with rimegepant.

Overdose is reportable to Pfizer Safety only when associated with an SAE.

Asymptomatic dosing errors (e.g., accidentally taking multiple tablets instead of the prescribed dose of one tablet in one calendar day) should be reported as deviations.

8.4. Potential Drug Induced Liver Injury (DILI)

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as DILI. Subjects who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are “adaptors” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For subjects with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor. The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

If any potential DILI is identified and meets the criteria above, the Sponsor Medical Monitor (or designee) should immediately be contacted for further instruction on whether the subject must discontinue from the trial and appropriate follow-up requirements. All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental

exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.5.1. Exposure During Pregnancy

If, following the Baseline Visit it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational produce exposure, including during at least 6 half-lives after the product administration, the investigational product will be permanently discontinued in an appropriate manner (i.e., dose tapering if necessary for subject safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The investigator must immediately notify the Pfizer (or designee) Medical Monitor and report the event by either using the PSSA tool and by completing an Exposure During Pregnancy (EDP) Supplemental Form following the SAE reporting procedures as described in Section 8.1.2

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must be reported on an EDP Supplemental Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Pfizer DSU. Information on this pregnancy will be collected on an EDP Supplemental Form, as appropriate.

An EDP occurs if: A female participant is found to be pregnant while receiving or after discontinuing study intervention.

A male participant who is receiving or has discontinued study intervention inseminates a female partner. A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:

A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.

A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form or via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 66 hours after the last dose.

If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form or via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further followup of birth outcomes will be handled on a case by case basis (eg, followup on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.5.2. Exposure During Breastfeeding

An EDB occurs if: A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form or PSSA, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

8.6. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.7. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength. Medication errors are recorded and reported as follows:

Recorded on the Adverse Event Page of the CRF	Reported on the CT SAE Report Form or PSSA to Pfizer Safety Within 24 Hours of Awareness
All medication errors (regardless of whether associated with an AE). Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving subject exposure to the study drug;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study subject.
- The administration of expired study drug;
- The administration of an incorrect study drug;
- The administration of an incorrect dosage:
  - Subjects taking > 2 tablets in one calendar day
  - Subjects who have < 80% study drug compliance between visits
- The administration of study drug that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study drug under question is acceptable for use.

If applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE**.

8.8. Adverse Events of Special Interest

Not applicable for this study.

9. STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the Statistical Analysis Plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where

appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size

The study will randomize approximately 300 subjects per treatment group. Based on data from study BHV3000-305 and subgroup analysis from the galcanezumab Phase 3 program,[6,9,10] we estimate that rimegepant will provide roughly a 1.0-day advantage over placebo on the primary endpoint, and assuming a common standard deviation of 3.6 days. Assuming that roughly 280 subjects per treatment group will contribute to the final migraine analysis dataset, the study will have roughly 90% power on the primary endpoint at a 2-sided alpha level of 0.05.

In study BHV3000-305, rimegepant dosed EOD provided a 1.0-day advantage over placebo dosed EOD in subjects who were not taking prophylactic migraine medication through randomization. Using the data from study BHV3000-305, the standard deviation of the primary endpoint was estimated to be roughly 3.6 days for these subjects.

9.2. Analysis Sets

- Enrolled: Subjects who sign informed consent and are assigned a subject identification number.
- Full: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (rimegepant or placebo) from RTSM.
- DBT safety: Subjects in the enrolled analysis set who take ≥ 1 dose of double-blind study drug (rimegepant or placebo).
- Open-label rimegepant safety: Subjects in the enrolled analysis set who take ≥ 1 dose of open-label rimegepant.
- Double-blind or open-label rimegepant safety: Subjects in the enrolled analysis set who take ≥ 1 dose of double-blind or open-label rimegepant.
- DBT efficacy: Subjects in the full analysis set who are randomized only once and take ≥ 1 dose of double-blind study drug.
- DBT migraine: Subjects in the DBT efficacy analysis set with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the Observation Phase and ≥ 1 month (4-week interval) in the DBT Phase.

9.3. Statistical Methods

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Efficacy Analyses

9.3.1.1. Primary Endpoint

The primary endpoint will be assessed for the DBT migraine analysis set using a linear mixed effects model with repeated measures that will include the following variables: change from the Observation Phase in the number of migraine days per month as the dependent variable; and fixed effects for treatment group, randomization stratum (i.e., 4 levels), month, and month-by-treatment group interaction. Migraine days are of any headache pain intensity. Months are defined using 4-week intervals as Month 1 (Weeks 1 to 4), Month 2 (Weeks 5 to 8), and Month 3 (Weeks 9 to 12). The number of migraine days per month is prorated to 28 days account for days with missing migraine data. The difference estimate (rimegepant – placebo), standard error (SE), p-value, and 95% confidence interval (CI) will be reported for the entire DBT Phase (Weeks 1 to 12).

The repeated measures error structure is assumed to be constant across treatment groups and will be initially specified as unstructured. If the model fails to converge or cannot be fit with an unstructured error structure, then a heterogeneous Toeplitz error structure will be attempted. If the Toeplitz fails, then an autoregressive order 1 error structure will be attempted.

The Huber-White robust "sandwich" estimator will be used for the estimation of SEs, which does not require constant response variances between treatment groups and different baseline covariate values.

9.3.1.2. Secondary Endpoints

The proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days of moderate or severe headache pain intensity per month over the entire DBT Phase (Weeks 1 to 12) will be assessed using Mantel-Haenszel risk estimation with stratification by randomization stratum for the DBT migraine analysis set. Missing data are imputed as non-response (i.e., failure). The difference estimate (rimegepant – placebo), SE, p-value, and 95% CI will be reported.

The mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase will be assessed for the DBT migraine analysis set from the same model used for the primary endpoint.

The mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase will be assessed for the DBT migraine analysis set from the same model used for the primary endpoint.

The mean changes from baseline in MSQ restrictive role function domain score and MIBS score at Week 12 will be assessed for the DBT efficacy analysis set using a linear mixed effects model with repeated measures that will include the following variables: change from baseline in the score as the dependent variable; baseline score as a covariate; and fixed effects for treatment group, randomization stratum, week, and week-by-treatment group interaction. Weeks are 4, 8, and 12. The Week 12 difference estimate (rimegepant – placebo),

SE, 95% CI , and p-value will be reported for each endpoint. The Huber-White "sandwich" estimator will be used for the estimation of SEs.

9.3.1.3. Statistical Hypotheses

The null hypothesis of no difference between rimegepant and placebo will be tested for each primary and key secondary endpoint during the DBT Phase. The alternative hypothesis is that there is a difference between rimegepant and placebo.

Type 1 error is controlled through the use of hierarchical testing. First, the significance of the primary endpoint is evaluated at the 2-sided alpha level of 0.05. If the primary endpoint is not significant, then any further tests on key secondary endpoints will have p-values presented only for descriptive purposes. If the primary endpoint is significant, then key secondary endpoints will be tested, each at the 2-sided alpha level of 0.05, hierarchically in the order specified in Section 3.2.1.

9.3.2. Safety Analyses

Deaths will be listed regardless of onset for the enrolled analysis set.

The frequencies of safety endpoints will be assessed descriptively as the number and percentage of subjects with events/findings separately for the 3 safety analysis sets.

The frequencies of the following safety endpoints will be tabulated on treatment: AEs by intensity (mild, moderate, severe, total); AEs related to study drug; SAEs; AEs leading to study drug discontinuation; laboratory test abnormalities by toxicity grade; LFT elevations based on fold changes above ULN, including ALT or AST > 3x ULN concurrent (on the same laboratory test collection date) with total bilirubin > 2x ULN; and vital sign, physical measurement, and ECG abnormalities.

The investigators will determine the intensity of AEs and the relationship of AEs to study drug. The Investigators' terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated by system organ class and preferred term. In tables by intensity, if a subject has an AE with different intensities over time, then only the greatest intensity will be reported.

Laboratory test abnormalities will be graded according to numeric laboratory test criteria from the following toxicity grading scales:

- Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017). If CTCAE numeric test criteria are not available for a laboratory test, then numeric test criteria from Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017) will be used.
- Food and Drug Administration (FDA) Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported.

In addition, Quality Tolerance Limits (QTLs) are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized.

9.4. Schedule of Analyses

There are 2 planned database locks: (1) primary completion date (PCD) database lock, which will occur after the last subject completes the Week 12/EOT Visit of the DBT Phase; and (2) last subject last visit (LSLV) database lock, which will occur after the last subject completes the Follow-up Week 2 Visit.

The PCD final clinical study report (CSR) will be produced after the PCD database lock. Analyses will focus on efficacy and safety endpoints during the DBT Phase.

The LSLV final CSR will be produced after the LSLV database lock. All endpoints will be assessed.

No interim analysis is planned.

10. ETHICS AND RESPONSIBILITIES

10.1. Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), International Conference on Harmonization guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any Independent Ethics Committee (IEC) requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

The Sponsor is responsible for ensuring that all updated relevant information related to the protocol be submitted to regulatory authorities and Independent Ethics Committees in accordance with local laws and regulations. This includes expedited reporting of suspected unexpected serious adverse reactions per regulatory guidelines.

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

A Serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

The Principal Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any) and the ICFs to regulatory authorities when necessary.

10.2. Data and Safety Monitoring

Not applicable.

This study will not make use of a Data Safety Monitoring Committee (DMC). The study drug rimegepant has been tested and found to be well tolerated. Safety will be closely monitored via oversight by the Investigators, Sponsor and CRO/designee and an Institutional Review Board/Independent Ethics Committee.

10.3. Steering Committee

Not applicable.

10.4. Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure (if any), and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IRB/IEC favorable written approvals for the above-mentioned study documents.

In the event that the protocol is amended, the revised protocol must be approved by the IRB/IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. Such corrections can be communicated as a Protocol Administrative Change Letter (PACL).

10.5. Informed Consent

Investigators must ensure that subjects in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Pfizer (or designee) will provide the Investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and

applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must sign and date an IRB/IEC approved written informed consent form for study. The signed and dated ICF will be retained at the Investigator's site, with a copy provided to the study subject and date will be entered in his or her CRF or appropriate system. The IRB/IEC must review and approve all protocol versions and informed consent form versions and a copy of each version of the IRB/IEC approved protocol and informed consent form is to be retained in the Study Master File. Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and subjects will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IRB/IEC, prior to subsequently obtaining each subject's consent.

If informed consent is initially given by a subject's legal guardian or legally acceptable representative, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then the consent must additionally be obtained from the subject.

The informed consent form must also include a statement that Pfizer and its representatives and regulatory authorities may have direct access to subject records.

10.6. Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation of each study subject. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

Electronic CRFs will be prepared for all data collection fields when EDC is being used.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The Investigator must retain a copy of the CRFs including records of changes and corrections. If EDC is being used, signatures will be obtained electronically and a copy of the electronic CRFs will be provided (or the data from the CRFs) for future reference.

10.7. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or

www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of “bonafide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.8. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Subjects are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

11. RECORDS MANAGEMENT

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor, and CRO. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The Investigator must retain all study records and source documents for the maximum time-period required by the applicable regulations and guidelines, or institution procedures or for the period of time specified by the sponsor, whichever is longer. The Investigator must contact the Sponsor prior to destroying any records associated with this study.

Pfizer will notify the investigators when the study files for this study are no longer needed.

If the Investigator withdraws from the study (i.e., retirement, relocation), the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to Pfizer.

It is the responsibility of the Investigator to ensure that the current disposition record of investigational product (may be supplied by the sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount of study drug received and placed in storage area
- label ID number or batch number or Kit number as specified for the protocol
- amount dispensed to and returned from each subject
- amount transferred to another area or site for dispensing or storage, if applicable
- amount of drug lost or wasted
- amount destroyed at the site, if applicable

- amount returned to sponsor, if applicable
- retain samples for bioavailability/bioequivalence, if applicable
- record of dates and initials of personnel responsible for IM dispensing and accountability

11.1. Source Documentation

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent for all subjects on study.

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical records for each subject for verification of data points, unless otherwise instructed by the Sponsor or designee to enter data directly on the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

11.2. Study Files and Record Retention

The Sponsor does not require original documents that have already been scanned and entered into the eTMF system to be forwarded to the Sponsor. Any original documents (i.e., 1572, signed financial disclosure, signed ICF, etc.) will be retained in the regulatory binder at the study site. The CRO will conduct a final TMF reconciliation to ensure all study files and regulatory documents have been correctly uploaded to the TMF prior to the close or termination of the study. Any materials or documents to support the clinical trial outside of the eTMF (i.e., rater training tapes) should be maintained by the CRO. The Sponsor will be contacted to determine whether the study documents/materials that are retained outside of the TMF will be forwarded to the Sponsor, destroyed, or kept at the CRO or at another facility for a longer period of time at the Sponsor's expense.

The CRO will maintain adequate study records after completion or termination of study. After that period, the Sponsor will be contacted to determine whether the study records will be forwarded to the Sponsor, destroyed, or kept at CRO or at another facility for a longer period of time at the Sponsor's expense.

12. AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Pfizer (or specified designee). A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. Pfizer or specified designee will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or Pfizer, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study subject, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

13. STUDY REPORT AND PUBLICATIONS

Pfizer (or specified designee) is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy is discussed in the investigator's Clinical Research Agreement.

14. STUDY DISCONTINUATION

Both Pfizer and the Principal Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, Pfizer or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the IRB/IEC of the same. In terminating the study, Pfizer and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

15. DATA PROTECTION

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Subjects' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of subjects with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any subject records or data sets that are transferred to the sponsor will contain the numerical code; subject names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, subject specific code. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical

code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of subjects' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

When subject data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

16. APPENDICES

16.1. Appendix 1 – Definition of Migraine and Headache Days

A **Migraine Day** is defined as any calendar day which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting either Criteria A or B:

A. ≥ 2 of the following pain features:

- Unilateral location,
- Pulsating quality (throbbing),
- Moderate or Severe headache pain intensity,
- Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

≥of the following associated symptoms:

- Nausea and/or Vomiting,
- Photophobia and phonophobia

During the Observational Phase, DBT Phase, and OLE Phase, if the subject takes an acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, or ubrogepant) to treat a headache (or aura) on any calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

Of note, the use of ergotamine is prohibited throughout the entire duration of the study. However, all dosing of acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, and ubrogepant) must be reported within the eDiary(DBT) and the Concomitant Medication paper diary, to accurately inform the occurrence of a "migraine day".

A moderate or severe migraine day is a migraine day with a migraine reported with moderate or severe headache pain intensity.

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.

b) An attack treated successfully with medication but with relapse within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

Definition of Headache Days

A Headache Day is any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- A qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication (i.e., triptan, ergotamine, lasmiditan, or ubrogepant), or
- A qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- A headache of any duration for which acute headache treatment is administered.

16.2. Appendix 2 – Recognized, Orally-Administered Migraine-Preventive Medications

Eligible subjects must have experienced, within 10 years of the Screening Visit, inadequate response (due to lack of efficacy or prior intolerance) to specified agents across 2-4 of the following categories of recognized, orally-administered migraine-preventive medications where at least one example of prior inadequate response is due to lack of efficacy or prior intolerance (not contraindication). Within Categories 1-7 this list of medications is specific and exclusive of other medications. Individuals with a history of inadequate response (due to a lack of efficacy, prior intolerance or contraindication) to agents across >4 of the following categories are to be excluded from this study.

- Category 1 Valproic acid: **specifically, divalproex sodium, sodium valproate**
- Category 2 Other anticonvulsant: **specifically, gabapentin, topiramate**
- Category 3 Beta blocker: **specifically, atenolol, bisoprolol, metoprolol, nadolol, propranolol, timolol**
- Category 4 Tricyclic antidepressant: **specifically, amitriptyline**
- Category 5 Serotonin-norepinephrine reuptake inhibitor (SNRI)**: specifically, desvenlafaxine, venlafaxine**
- Category 6 Calcium-channel blocker**: specifically, flunarizine, verapamil**
- Category 7 Angiotensin blocker (angiotensin-converting enzyme [ACE] inhibitor, angiotensin II receptor blocker [ARB]): **specifically, candesartan, lisinopril**
- Category 8 Other: **locally-approved, or otherwise recognized standard of care, oral medications for the preventive treatment of migraine (e.g., methysergide, oxetrone, pizotifen).** If the subject has experienced inadequate response to a medication under this category, supporting documentation is required from the site noting the national or regional published guidelines as to why this medication had been included.

Inadequate Response is defined as meeting any of the following criteria:

- Lack of Efficacy:
    - When previous treatment with a recognized, orally-administered, migraine-preventive medication has yielded no meaningful reduction in headache frequency (e.g., <50% reduction in frequency and/or severity of monthly migraine days) after administration of the respective medication for an adequate period of time (at least 2 - 3 months) at generally accepted therapeutic dose(s) based on the investigator's assessment and documented within the medical/pharmacy record. If the Principal Investigator is not the treating physician and the medical record is not available for documentation purposes, the Principal Investigator can interview the treating physician to confirm the above information and document the interview with date and his/her signature.

When the medical/pharmacy records are available indicating the subject use of previous treatment with a recognized, orally-administered, migraine-preventive medication but there is no documentation on the lack of efficacy, an interview with the subject and documentation with date and time will suffice. This interview must probe on the same indicators of efficacy (e.g., reduction in migraine headache day frequency and severity) described above and such evidence of unsatisfactory efficacy based on interview responses must be documented in sufficient detail to support the conclusion of lack of efficacy.

- Prior Intolerance:
    - When prior treatment with a recognized, orally-administered, migraine-preventive medication has been previously interrupted because of an adverse event(s) that made continuation of the drug unacceptable, as determined by the Principal Investigator and documented within the medical/pharmacy record. If the Principal Investigator is not the treating physician and the medical/pharmacy record is not available for documentation purposes, the Principal Investigator can interview the treating physician to confirm the above information and document the interview with date and his/her signature. When the medical/pharmacy records are available indicating the subject's use of previous treatment with a recognized, orally-administered, migraine-preventive medication but there is no documentation on the lack of prior intolerance, an interview with the subject and documentation with date and time will suffice. This interview must capture a detailed description of the adverse effects from the prior prophylaxis treatment and the reasons the participant found it to be intolerable (e.g., severity, duration, impact on function, etc). Such evidence based on interview responses must be documented in sufficient detail to support the conclusion of intolerance to previous treatment.
- Contraindication:
    - When a recognized, orally-administered, migraine-preventive medication is contraindicated or otherwise considered unadvisable in accordance with locally recognized labelling, practice guidelines, and/or the current standard of care, as determined by the Principal Investigator with rationale documented within the medical record. If the Principal Investigator is not the treating physician and the medical record is not available for documentation purposes, the Principal Investigator can interview the treating physician to confirm the above information and document the interview with date and his/her signature. When the medical records or other objective evidence on screening are available indicating the subject's use of previous treatment with a recognized, orally-administered, migraine-preventive medication but there is insufficient documentation on the contraindication, a supplemental interview with the subject and documentation with date and time will suffice.

16.3. Appendix 3 – Prohibited and Restricted Concomitant Medications and Devices

Use of the following medications and devices is prohibited or restricted during the study (i.e., starting from the Screening Visit and through the Follow-up Week 2 Visit), unless otherwise specified.

- Use of the following recognized migraine-preventive medications within 30 days prior to the Screening Visit and throughout the study, unless otherwise specified:
  - All prophylactic treatments targeting the CGRP pathway
    - Oral small molecules (e.g., atogepant, non-study rimegepant, etc.)
    - Injectable monoclonal antibodies (e.g., eptinezumab, erenumab, fremanezumab, galcanezumab, etc.)- these particular medications must be discontinued at least **6 months** (24 weeks) prior to the Screening Visit and throughout the study
  - ACE inhibitors / Angiotensin receptor blockers: candesartan, lisinopril
  - Alpha-adrenergic agonists: clonidine, guanfacine
  - Antidepressants: amitriptyline, desvenlafaxine, duloxetine, milnacipran, nortriptyline, protriptyline, venlafaxine
  - Antiepileptics: gabapentin, topiramate, valproic acid (sodium valproate, divalproex sodium)
  - Beta-blockers: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol
  - Calcium channel blockers: flunarizine, lomerizine, nifedipine, nimodipine, verapamil
  - Onabotulinumtoxin A (Botox®) taken within **3 months** (12 weeks) prior to the Screening Visit and throughout the study
  - Serotonin antagonists: methysergide, oxetrone, pizotifen
  - Vitamins / Supplements: butterbur, feverfew, magnesium citrate (>=600 mg/day), riboflavin (Vitamin B2; >=100 mg/day)
  - Other locally-approved, or otherwise recognized standard of care, medications used for the preventive treatment of migraine, unless otherwise specified
- Note: Stable use (consistent dosing frequency and strength at least 3 months [12 weeks] prior to the Screening Visit and afterward) of the above migraine preventive medications for non-headache indication is allowed, unless otherwise specified. The above medications are NOT permitted to be newly initiated at any time during the course of the study (e.g., Screening, DBT, or OLE Phases)

- All devices and/or invasive interventions used for the preventive treatment of migraine (e.g., nerve blocks, occipital nerve stimulators, transcranial magnetic stimulation, etc.) administered within 3-months(12 weeks) of the Screening Visit and throughout the study

- Cefaly™ or any other device for migraine prevention or treatment within **3 months** (12 weeks) prior to the Screening Visit

- Paracetamol (acetaminophen) or paracetamol-containing products for **non-headache indications**

    - Paracetamol and paracetamol-containing products as acute headache medication (including Excedrin Migraine) is allowed during study up to 2,000/mg day for a maximum of 2 consecutive days at a time (i.e., if administer paracetamol 2,000 mg/day, only allowed to do this on 2 consecutive days at a time) (see Section 16.4 Appendix 4).

- Atypical antipsychotics

    - Aripriprazole

    - Olanzapine

    - Quetiapine

    - Ziprasidone

    - Risperidone

- Non-narcotic analgesics (e.g., NSAIDs, gabapentin, etc.) taken ≥ 15 days per month for **non-headache indications**

    - Low dose aspirin (e.g. up to 100 mg daily) for documented cardiovascular prophylaxis is allowed.

- Ergotamine

- Lamotrigine

- Marijuana and all forms of ingested or inhaled cannabidiol (CBD) and THC-containing products

- Narcotics

    - Opioid (e.g., morphine, codeine, oxycodone and hydrocodone)

    - Barbiturate/barbiturate-containing product (e.g., Fioricet, Fiorinal, butalbital, phenobarbital, etc.)

- Any investigational agent other than rimegepant (provided for the purpose of this clinical study)

Prohibited Concomitant Medications That May Result in DDI

Drugs that are known strong inhibitors or moderate or strong inducers of CYP3A4 may impact the exposure of EOD dosing of rimegepant.

The prohibited concomitant medications listed below should not be taken with study intervention for the period of time at least equal to the required washout period listed in the table, and during the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs) if the overall benefit/risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs	Washout Period Requirement
Strong CYP3A4 Inhibitors	Boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir, mifepristone, mibefradil, telithromycin, troleandomycin	2 weeks or 5 half-lives whichever is longer
Strong CYP3A4 Inducers	Apalutamide, avasimibe, carbamazepine, phenytoin, rifampin, rifapentine, St. John's Wort	5 half-lives plus 14 days
Moderate CYP3A4 Inducers	Bosentan, efavirenz, etravirine, lopinavir, modafinil, nafcillin, rifabutin, phenobarbital	5 half-lives plus 14 days

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Any of the medications listed above are permitted during the study if administered as a topical agent or eye drops and if applied in a routinely accepted manner.

16.4. Appendix 4 – Permitted Acute Migraine Medication

The medications listed below are the only acute migraine medications allowed during the entire study.

- Simple analgesic
  - Non-steroidal anti-inflammatory drugs, including, but not limited to:
    - Aspirin
    - Ibuprofen
    - Naproxen
  - Acetaminophen and acetaminophen-containing combination agents (e.g., acetaminophen/aspirin/caffeine)
    - Maximum allowable daily dose of paracetamol (acetaminophen) in this study is 2,000 mg for a maximum of 2 consecutive days at a time
- Triptans
  - Imitrex (Sumatriptan)
  - Zomig (Zolmitriptan)
  - Maxalt (Rizatriptan)
  - Relpax (Eltriptan)
  - Treximet (Sumatriptan and Naproxen Sodium Tablets)
  - Amerge (Naratriptan)
  - Frova (Frovatriptan)
  - Axert (Almotriptan)
  - Sumavel DosePro (Sumatriptan)
  - Onzetra (Sumatriptan nasal powder)
- Antiemetics
  - Metoclopramide
  - Promethazine

- Other:
    - Baclofen
    - Locally-approved, or otherwise recognized standard of care, medications used for the acute treatment of migraine (e.g., lasmiditan, ubrogepant), unless otherwise specified.

The above listed medications are the only acute migraine medications allowed.

If a subject experiences a migraine after dosing with study drug for the day during the DBT or OLE Phase, the subject may take their acute migraine medication as described above in this section of the protocol.

16.5. Appendix 5 - ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs
• QTcF prolongation >500 ms. • Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms. • New ST-T changes suggestive of myocardial ischemia. • New-onset LBBB (QRS complex >120 ms). • New-onset right bundle branch block (QRS complex >120 ms). • Symptomatic bradycardia. • Asystole • In awake, symptom-free subjects in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node; • In awake, symptom-free subjects with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-second duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is to be reported as AEs/SAEs.

16.6. Appendix 6 - Contraceptive and Barrier Guidance

16.6.1. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.2) and specify the reproductive requirements for including female subjects. Refer to Section 16.6.3 for a complete list of contraceptive methods permitted in the study.

A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 16.6.2).
    - OR
- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

16.6.2. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
  - A high FSH level in the postmenopausal range (> 35 mIU/mL) must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
  - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

16.6.3. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

<u>Highly Effective Methods That Have Low User Dependency</u>

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
   - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
   - Oral;
   - Intravaginal;
   - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
   - Oral;
   - Injectable.
8. Sexual abstinence
   - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Other Effective Methods

1. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
2. Male or female condom, with or without spermicide.
3. Cervical cap, diaphragm, or sponge with spermicide.
4. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

16.7. Appendix 7 – Country Specific Requirements

16.7.1. Germany

Inclusion Criteria 1h:

Written informed consent must be obtained from the subject in accordance with requirements of the study center's institutional review board (IRB) or ethics committee and in accordance with local regulations, prior to the initiation of any protocol-required procedures (as described in Section 10.5)

Exclusion Criteria 7j:

i. Prisoners or subjects who are involuntarily incarcerated.

ii. Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

16.7.2. European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents. The sponsor will notify EU Member States concerned of the following:

- Any SUSAR via reporting to the EudraVigilance database
- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event
- Any serious breach, as described in **Section 10.1** no later than 7 days of becoming aware of that breach
- Any urgent safety measure, as described in **Section 10.1**, no later than 7 days of the measure being taken
- Any inspection report of a third-country authority concerning the study

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

16.8. Appendix 7 - Protocol Amendment History

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	15-Jul-2022
Version 2.0	There was an administrative error with the study schematic section 4.2 when rendering the final PDF version of the BHV3000-407 protocol. The first occurring schematic was correct, an inconsistency in the second study schematic (section 4.2) was identified after sign off and approval. Version 1 of the BHV3000-407 will not be distributed to any sites or IRBs/ECs. The study will be initiated with all sites receiving version 2 of the protocol. Version 1 will be retained to demonstrate version control. Corrected bulleting in exclusion criteria in Section 6 Prohibited Medications and Devices as required. Updated primary endpoint section in the protocol synopsis to match section 2.1 of the protocol. Updated secondary endpoint section in the protocol synopsis to match section 2.2 in protocol. Added Headache Impact Test (HIT-6) to all applicable areas of the protocol including protocol body, schedule of assessments and Section 6. Added lasmiditan and ubrogepant to the list of migraine-specific medications used to define Migraine Days and Headache Days. Further emphasized the requirement that all dosing of acute migraine-specific medications must be properly recorded within the eDiary and Concomitant Medication paper diary (including ergotamine and lasmiditan), in all applicable areas of the protocol including	16-Aug-2022

Version Number	Brief Description Summary of Changes	Date
	Sections 5.4, 5.5, 5.6, 6.1, 6.4, and 17.2 Appendix 2. Clarified that "acute migraine medication days" is defined as any calendar day in which an acute migraine medication(s) (permitted or non-permitted) is taken for the reported purpose of treating a migraine headache or aura, section 5.5. Refined list of recognized, orally administered migraine-preventive medications to further align with published expert opinion, section 17.3 Appendix 3. Reorganized and amended list of prohibited migraine-preventive medications to align with published expert opinion and for ease of application, section 17.4 Appendix 4. Removed *Strong Inhibitors of P-gp transporter* and *Moderate Inhibitors of CYP3A4* from the list of prohibited medications in accordance with the rimegepant label, section 17.4 Appendix 4. Per BHV3000-407 protocol, study drug is to be provided no more frequently than every-other-day. Corrected inconsistencies, typographical errors throughout the protocol for readability.	
Version 3.0	Updated Section 4.1, Study Design and Duration to define the end of study. Clarified definition of HIT exploratory endpoints, Section 2.3. Specified the time frame (6 months [24 weeks]) for considering "recently" diagnosed cardiovascular disease for the	25-Oct-2022

Version Number	Brief Description Summary of Changes	Date
	purposes of considering the eligibility of Screening candidates, Section 5.3 (2p) Clarified low dose aspirin use for cardiovascular prophylaxis is permitted during the course of this study, Section 5.3 (6f) Clarified, subjects with suicidal ideation and/**or suicidal behavior(s), per C-SSRS assessment, are not eligible for participation in the study, Section 5.3 (7f)** Clarified the exclusionary provision which permits Investigators to exclude individuals from participation in the study based on documented clinical concern, beyond the strict confines of the protocol defined I/E criteria, Section 5.3 (7k) Updated the definition of WOCBP (women of childbearing potential) (Section 5.9) and contraception requirements (Section 5.2 [3b] and Section 5.3 [4a]) to more closely align with CTFG (Clinical Trials Facilitation and Coordination Group) Guidance Removed routine collection of: albumin, calcium, CK, LDH, total protein, uric acid, and urinalysis due to lack of safety signal across the rimegepant clinical development program, Section 6.3.4.1 Provided further clarification on the pregnancy testing requirements for WOCBP in the study and stressed the importance of WOCBP interrupting further dosing of blinded study medication and immediately contacting the Investigator when there is any concern for possible pregnancy, Section 6.3.4.2	

Version Number	Brief Description Summary of Changes	Date
	Clarified, in the case of Potential Drug Induced Liver Injury (pDILI), the disposition of the subject is left to the discretion of the managing Investigator, and provided further detail on the management of abnormal liver tests in treated subjects during the conduct of the study, Section 8.5 Clarified variables included in GLMEM model for the primary endpoint analysis, Section 9.3.1.1. Clarified variables included in the GLMEM model for the secondary endpoint of MSQ restrictive role function analysis, Section 9.3.1.2. Updated Sections 16 and 17.1 with updated medical monitor contact information. Clarified conditions associated with the "stable" use of recognized migraine-preventive therapies; Provided further detail on the restrictions of paracetamol (acetaminophen) use during the study; Clarified prohibition of atypical antipsychotics and valproic acid during the conduct of the study; Updated the non-inclusive list of strong CYP3A4 inhibitors in accordance with recognized DDI risk profile of concomitant medications, Section 17.4, Appendix 4. Added section ANNEX 1., Benefit Risk Assessment	
Version 4.0	Protocol updated to add an Open-Label Extension whereas upon successful completion of the DBT Phase, eligible subjects will be given the opportunity to enroll into a 12-week Open-label	01 Mar 2023

Version Number	Brief Description Summary of Changes	Date
	Extension (OLE) Phase. It is estimated that approximately 480 subjects will enter the OLE Phase of the study. Updated Study Design section of the synopsis so that it offers more of a brief summary of the protocol. Study Schematic, Schedule of Events, and Study Design Rationale updated to include details of the OLE Phase Secondary Endpoints and Exploratory Objectives updated to include analysis to be done for OLE Exclusion Criteria 1. Target Disease Exclusion addition of the following exclusion: • 1.d. 7 or more non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit or during the 28-day Observation Phase clusion Criteria 2. Medical History and Current Diseases deletion of the following exclusions: • 2.b. History or diagnosis of Gilbert's Syndrome or any other active hepatic or biliary disorder • 2.c. History of HIV disease • 2.d. History of gallstones or cholecystectomy • 2.t. History of acute hepatitis within 6 months of Screening or chronic hepatitis (including nonalcoholic steatohepatitis) or a positive result on anti-hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface	

Version Number	Brief Description Summary of Changes	Date
	antigen (HbsAg), or anti-hepatitis C antibody testing (HCV Ab+ with detectable HCV RNA on reflex testing) at Screening clusion Criteria 2. Medical History and Current Diseases modification of the following exclusion: • 2.e. Body mass index ≥ 33 kg/m^2 To the following: • 2.e. Body mass index ≥ 35 kg/m^2 Exclusion Criteria 5. ECG and Laboratory Test Findings updates: • 5.c. Serum bilirubin (Total, Direct or Indirect) >1 ULN (only abnormal values between 1-1.5x ULN may be repeated once for confirmation during the screening period). Abnormal bilirubin results obtained at the Pre-Randomization Laboratory Visit may not be repeated. To the following: • 5.c. Serum bilirubin (Total, Direct or Indirect) > 1.5 x ULN (Only abnormal values with clinical justification (e.g., elevated direct bilirubin with a documented event of gallstones), may be repeated once for confirmation during the Screening Phase). Bilirubin results > 1.5 x ULN obtained at the Pre-Randomization laboratory Visit cannot be repeated. • 5.e. Changed AST, ALT, > 1.0 x ULN. (Only abnormal values of	

Version Number	Brief Description Summary of Changes	Date
	between 1-1.5x ULN may be repeated once for confirmation during the screening period). To the following: • 5.e. AST, ALT, total bilirubin > 1.5 x ULN. (Only abnormal values with clinical justification (e.g., elevated AST with documented exercise), may be repeated once for confirmation during the Screening Phase). AST and/or AST results > 1.5 x ULN obtained at the Pre-Randomization laboratory Visit cannot be repeated. • 5.g. Changed HbA1c ≥ 6.5% To the following: • HbA1c ≥ 7.5% • Section 5.9 Women of Childbearing Potential addition of Bilateral Tubal Occlusion as permitted highly effective forms of contraception • Section 6.3 Safety Assessments and Section 8.1.2 updated to add clarification regarding unresolved SAEs follow-up after the Week 2 Follow-up Visit • Addition of Section 6.7 Study Early Discontinuation Criteria • Section 7.2 Dose and Administration updated to include updates for the transition from the DBT to the OLE for open label drug dosing and dispensing.	

Version Number	Brief Description Summary of Changes	Date
	• Section 7.3 Clarifications and updates to the Blinding and Unblinding section • Section 7.4 Treatment Compliance clarification added for treatment non-compliance by subjects and corrective action implementation • Section 9.2 Analysis Sets updated to accommodate OLE • Section 9.3.2 Safety Analysis updated to include vital sign, physical measurement, and ECG abnormalities as defined as a safety endpoint for which the frequencies will be tabulated on treatment. • Section 9.4 Schedule of Analysis updated to clarified to include OLE	
Version 5.0	Referenced study number BHV3000-407 to C4951012 and compound name BHV3000 to PF-07899801 to reflect identification changes by sponsor. Inclusion criterion #1 "Signed written Informed Consent" deleted Inclusion criterion #3.b and Exclusion criterion #4.a for reproductive status updated Inclusion criterion #3a removed upper age limit Exclusion criterion #2.c for "History of hematologic or solid malignancy diagnosis within 5 years prior to screening" deleted	09-Aug-2023

Version Number	Brief Description Summary of Changes	Date
	Exclusion criterion #2.b for body mass index changed to ≥ 35.0 kg/m2 (instead of > 35.0 kg/m2). Exclusion criterion #5.g for HbA1c changed to > 7.5 % (instead of ≥ 7.5%) Exclusion criterion #5.f for liver enzymes (ALT and AST) changed to >2 x ULN (instead >1.5xULN) Exclusion criteria #5.i-iv for "QTcF, Left Bundle Branch Block, Right Bundle Branch Block and Intra Conduction defect" deleted and replaced with "Abnormal ECG that in the investigator's opinion makes the subject unsuitable for a clinical trial" added Exclusion criterion #5.b for eGFR criteria changed to < 30 ml/min/1.73m2 Exclusion criterion 6 ii Changed the term onabotulinumtoxinA to botulinum injection Exclusion criterion #6f increase dosage of low dose asprin from 81mg to up to 100mg Exclusion criterion #7f deleted Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members. Changed term non-migraine to non-headache. Guidance relative to Women of Childbearing Potential replaced with Contraception section and Appendix 6 Potential DILI cases identification and management update	

Version Number	Brief Description Summary of Changes	Date
	Added Appendix for ECG findings of Potential Clinical Concern Clarified definition of Sponsor's Medically Qualified Individual. Included detailed information about the known and expected benefits and risks and reasonably expected AEs of rimegepant and referenced to the Investigator Brochure. Updated Serious Adverse Event (SAE) reporting destination and electronic reporting system administrative changes and clarifications Updated Overdose section Updated text for Data Protection. Added compliance aim for IP of 80% Updated Non-Investigational Product section to Concomitant Therapy Removal of “humidity” from environmental condition requirements Updated to include US, UK, EU reference and investigator brochure reference. Clarified study drug destruction Removed Clinical Protocol Approval Form Removed PI declaration page Change statistical method from Kenward Roger to Huber-White robust ‘sandwich’ estimator, and method for determination of secondary endpoints. Clarified schedule of analyses	

Version Number	Brief Description Summary of Changes	Date
	Added reference to quality tolerance limits Removed Phase 1 study exception. Removed statement regarding Principal Investigator and the Sponsor's representative signatory. Added Sponsor's regulatory and ethics responsibilities. Added AE information on lack of efficacy and medication errors Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure Moved Pregnancy AE safety section to 8.5.1 Added Pfizer standard text for Dissemination of Clinical Study Data. Moved prior Protocol Amendment Summary of Changes to Appendix Updated List of abbreviations Schedule of Activities DBT Phase Table clarified eDiary completion timepoints Addressed typographical errors Clarified the protocol restriction around the use of acetaminophen and paracetamol-containing products for non-migraine indications during the study Increased the daily dosage of Paracetamol (acetaminophen) and paracetamol-containing products from 1000 mg/day to 2000 mg/day Removal of diltiazem from Prohibited and Restricted Concomitant Medications and Devices	

Version Number	Brief Description Summary of Changes	Date
	Re-screening policy updated Updated instances of 'participant' to 'subject' Clarified that subject must sign and date an IRB/IEC approved written informed consent form for study Removed statement that IRB/IEC has to be notified at least 5 days prior to implementing protocol change Section 15 "Confidentiality" renamed to "Data Protection" and updated Clarified that subject must sign and date an IRB/IEC approved written informed consent form for study	
Version 6,0	Added Inclusion Criteria 1h specific to Germany due to request from German Regulatory Authority Added Exclusion Criteria 7j specific to Germany due to request from German Regulatory Authority	06 Feb 24

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