DRUG:	Rimegepant (BHV-3000) (PF-07899801)
STUDY NUMBER(S):	BHV3000-406 (C4951004)
PROTOCOL TITLE:	BHV3000-406 (C4951004): A Phase 4, Randomized, Double-blind Placebo-Controlled, Efficacy and Tolerability Trial of Rimegepant for the Acute Treatment of Migraine in Adults Unsuitable for Triptan Use
US IND NUMBER:	109886
EU CT NUMBER:	2024-513269-37-00
ClinicalTrials.gov ID:	NCT05509400
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	14-July-2022
VERSION NUMBER:	Version 6.0
VERSION DATE:	29-August-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(s).

SUMMARY OF CHANGES

Amendment Version 6.0

Overall Rationale for the Amendment: Alignment with the Clinical Trials Regulation EU No 536/2014 (CTR). Amendment also includes protocol administrative change letters (dated 06 Dec 2023; 07 Mar 2024) and edits to align with the SAP and Pfizer protocol template

Description of change	Brief Rationale	Section # and Name
Non Substantial Modification(s)		
Addition of various sponsor reporting responsibilities per EU CTR	Alignment with EU CTR requirements	16.7.3 European Union
Clarification of procedures relative to Urgent Safety Measures and Serious Breaches	Alignment with EU CTR requirements	10.1 Good Clinical Practice
Procedures relative to collection of data regarding withdrawn subjects clarified	Alignment with EU CTR requirements	6.6 Subject Early Discontinuation Criteria
Clarification regarding timelines for clinical trial results publication on CTIS	Alignment with EU CTR requirements	10.7 Dissemination of Clinical Study Data
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
IOL=F algorithm added	Alignment with Statistical Analysis Plan	9.3.1 Efficacy Analyses
Reliability of rimegepant effect in the OLE Phase endpoint definition modified	Alignment with Statistical Analysis Plan	3.2.2 Other Secondary Endpoints 9.3.1.2 Secondary Endpoints
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

Description of change	**Brief Rationale**	**Section # and Name**
FDA laboratory test toxicity grading scale added	Alignment with Statistical Analysis Plan and FDA request	9.3.2 Safety Analyses
"ALT and AST > 2xULN" replaced by "ALT or AST >2xULN" in exclusion criterion 5d	Alignment with rimegepant program-level exclusion criteria	5.3 Exclusion criteria
"Non-migraine" indication replaced with "Non headache" indication in exclusion criterion 6g	For consistency with exclusion criterion 6a	5.3 Exclusion criteria
Addition of muscle relaxants Inclusion of an updated list of CYP3A4 inhibitors/ inducers and P-gp inhibitors, and specification of the washout period in case of concomitant use of CYP3A4 inhibitors/inducers or P-gp inhibitors.	Alignment with updated product-level DDI Master List and Sponsor's standard approach	16.1 Prohibited and Restricted Concomitant Medications and Devices
Addition of FSH post menopausal range (>35 mIU/mL)	Reinstatement of FSH menopausal range deleted by mistake in prior amendment	16.5.2 Woman of Childbearing Potential
Study intervention table added	To align with Pfizer's protocol template	7.1.1 Investigational product
Definition of rescue medications clarified	Clarification that rescue medications are concomitant medications used per standard of care to treat persistent migraine symptoms	6.4.4 Rescue medication
Primary and Secondary Endpoints added in the synopsis	To align with Pfizer's protocol template	Synopsis
Study drug dosing regimen and treatment duration clarified	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

Description of change	**Brief Rationale**	**Section # and Name**
Ethical considerations regarding placebo use rationale; treatment duration and burden for subjects clarified	To align with Pfizer's protocol template	Synopsis
Clarification that rimegepant dose, population and indication in the study are covered by Marketing Authorization	Alignment with EU CTR requirements	1.1.2 Product Development Background
Number of subjects involved in rimegepant clinical development updated	Alignment with Investigator's Brochure v3.0, April 2024	1.1.2 Product Development Background
Reference to European directive 2001/20/EC replaced by reference to EU CTR No 536/2014	Alignment with EU CTR requirements	8.1.2 Collection and Reporting Serious Adverse Events
Eudra CT number replaced by EU CT number	Alignment with EU CTR requirements	Cover page, synopsis
Reference to 24h dosing interval in the OLE phase deleted	Incorporation of nonsubstantial changes described in previous PACL dated 06 Dec 2023	Synopsis 4.1 Study design and duration 7.1.5.2 Open-label Extension phase
MQOL collection clarified	Incorporation of nonsubstantial changes described in previous PACL dated 06 Dec 2023	4.1 Study design and duration 4.3 Schedule of Assessments 4.3.3.3 OLE Week 12/OLE EOT visit 6.5.2 Migraine Quality of Life Questionnaire (MQOL)
Clarification regarding Medication Errors reporting	Incorporation of nonsubstantial changes described in previous PACL dated 06 Dec 2023	8.5.5 Medications Errors
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	Incorporation of nonsubstantial changes described in previous PACL dated 07 Mar 2024	10.8 Sponsor's Medically Qualified Individual

Description of change	**Brief Rationale**	**Section # and Name**
Contact List. Emergency Contact Card replaced by a study information card		
Addition that the CT SAE Report Form should only be used as a backup in the event PSSA is not operational	Incorporation of nonsubstantial changes described in previous PACL dated 06 Dec 2023	8.1.2 Collection and Reporting Serious Adverse Events
List of references updated	Ensuring complete alignment with protocol updates	17 References
List of Abbreviations updated	Ensuring complete alignment with protocol	List of abbreviations
Minor typographic and spelling corrections	Corrections	Throughout the document

STUDY SUMMARY (SYNOPSIS)

PROTOCOL SUMMARY

Synopsis

Protocol Title: A Phase 4, Randomized, Double-blind Placebo-Controlled, Efficacy and Tolerability Trial of Rimegepant for the Acute Treatment of Migraine in Adults Unsuitable for Triptan Use.

Brief Title: A Phase 4 Study Evaluating Efficacy and Tolerability of Rimegepant for the Treatment of Migraine in Adults Unsuitable for Triptan Use.

Regulatory Agency Identification Number(s):

US IND Number:	109886
EU CT Number:	2024-513269-37-00
ClinicalTrials.gov ID:	NCT05509400
Pediatric Investigational Plan Number:	N/A
Protocol Number:	BHV3000-406 (C4951004)
Phase:	4

Rationale:

Rimegepant is approved for the acute treatment and prevention of episodic migraine in the United States (US), United Kingdom (UK), and European Union (EU). 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 postdose. Rimegepant effectiveness for the preventive treatment of migraine was also 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 (MOH), abuse potential, cardiovascular events, or hepatotoxicity.

This study is being conducted to evaluate the efficacy and tolerability of rimegepant in a population of adult subjects that are unsuitable for triptan medications due to previous intolerance, lack of efficacy, or contraindication (including a history of clinically-relevant cardiovascular disease). Rimegepant (75mg once daily as needed) will be further evaluated in this population during the trial's 12-week open-label extension phase.

Objectives and Endpoints:

Objectives	Endpoints
Primary objective:	**Primary endpoint:**
To compare the efficacy of rimegepant with placebo in the acute treatment of migraine, as measured by migraine headache pain relief at 2 hours postdose during the Double Blind Treatment (DBT) Phase	Percentage of subjects with a headache pain intensity of none or mild at 2 hours postdose in the DBT Phase. Migraine headache pain intensity will be measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).
Key secondary objectives:	**Key secondary endpoints**
To compare rimegepant with placebo for migraine headache pain freedom at 2 hours postdose during the DBT Phase.	Percentage of subjects with a headache pain intensity of none at 2 hours postdose in the DBT Phase
To compare rimegepant with placebo for rescue medication use within 24 hours postdose during the DBT Phase	Percentage of subjects who take rescue medication within 24 hours after taking study drug in the DBT Phase. Rescue medication is defined in the protocol.
To compare rimegepant with placebo for return to normal function, as measured by the functional disability scale, at 2 hours postdose during the DBT Phase	Percentage of subjects with a functional disability level of normal at 2 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing. Functional disability level will be measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest).
To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 24 hours postdose during the DBT Phase	Percentage of subjects with functional disability levels of normal at all time points from 2 to 24 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing
To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 48 hours postdose during the DBT Phase	Percentage of subjects with functional disability levels of normal at all time points from 2 to 48 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing
To compare rimegepant with placebo for sustained migraine headache pain relief from 2 to 24 hours postdose during the DBT Phase	Percentage of subjects with headache pain intensities of none or mild at all time points from 2 to 24 hours postdose in the DBT Phase
To compare rimegepant with placebo on sustained migraine headache pain relief from 2 to 48 hours postdose during the DBT Phase	Percentage of subjects with headache pain intensities of none or mild at all time points from 2 to 48 hours postdose in the DBT Phase
To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 24 hours postdose during the DBT Phase	Percentage of subjects with headache pain intensities of none at all time points from 2 to 24 hours postdose in the DBT Phase

Objectives	Endpoints
To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 48 hours postdose during the DBT Phase	Percentage of subjects with headache pain intensities of none at all time points from 2 to 48 hours postdose in the DBT Phase
To compare rimegepant with placebo for freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose during the DBT Phase	Percentage of subjects with an MBS that is reported on study before dosing and is absent at 2 hours postdose in the DBT Phase. The MBS on study before dosing will be reported as nausea, phonophobia, or photophobia. Symptom status will be reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).
Other secondary objectives	**Other secondary endpoints**
To evaluate reliability of rimegepant effect in the Open-label extension (OLE) Phase, as measured by Migraine Quality of Life Questionnaire (MQoL) Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose in the DBT Phase and after each of the first 5 qualifying migraine attacks in the OLE Phase	Percentages of subjects achieving response after (1) the single evaluable qualifying migraine attack in the DBT Phase for those randomized to rimegepant, and (2) each of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase. Reliability of rimegepant effect during the OLE Phase is defined as percentages for at least 4 of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase being no more than 7% less than the percentage in the DBT Phase. Response is defined as a category of “moderately better” or “very much better” for MQoL Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose. Evaluable qualifying migraine attacks are defined in the protocol
To evaluate the mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase	Mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase
To evaluate the proportions of subjects with ≥ 50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase	Percentages of subjects with ≥ 50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase
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.	Number and percentage of subjects with AEs by intensity (mild, moderate, severe, total), SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases
To evaluate the mean change from baseline in the Migraine Interictal Burden Scale (MIBS) score over time during the OLE Phase	Mean changes from baseline in the MIBS score at Weeks 4, 8, and 12 of the OLE Phase

Overall Design:

This is a multicenter, phase 4, randomized, double-blind placebo-controlled study, with an OLE phase to assess the efficacy and tolerability of rimegepant for the acute treatment of migraine in a population of adult subjects that are unsuitable for the use of triptan medications due to previous intolerance, lack of efficacy, or contraindication (including a history of clinically significant cardiovascular disease)

The total study duration for each subject will be up to ~24 weeks.

- In the DBT Phase, subjects will be dispensed one single blister card containing one tablet of blinded study drug consisting of rimegepant 75 mg oral disintegrating tablet (ODT) or matching placebo. The DBT Phase will last approximately 11 weeks (including a 3 to 28-day screening period, a treatment phase that can last up to 45-days or until the subject experiences a qualifying migraine attack [whichever comes first], and an end-of-treatment visit ~7 days after the administration of study drug). Subjects will take blinded study drug as the first treatment for a migraine attack of moderate or severe headache pain intensity, and are not to take permitted acute migraine medication before taking blinded study drug.

- In the OLE Phase, lasting up to 12 weeks, subjects will be able to take up to 1 tablet of open-label study drug (75 mg ODT rimegepant) per calendar day as needed for acute treatment of migraine for a maximum of 18 doses per month (month is 28 days).

    - ***During the OLE Phase***

        - Subjects are to use open-label study drug as the first treatment of migraine attacks of moderate or severe headache pain intensity, and should not take acute migraine medication before taking open-label study drug

        - In association with each of the ***First 5 Qualifying Migraine Attacks*** , subjects are required to complete the MQoL Questionnaire within the eDiary at 24 hours after dosing with open-label study drug

        - If migraine-associated symptoms persist beyond 2 hours after dosing with open-label study drug, subjects may use permitted acute migraine medication for the purposes of rescue, as needed and in accordance with the standard of care. *All dosing of rescue medication (permitted or exclusionary), is to be recorded on the Rescue Medication paper diary.*

Number of Subjects:

Approximately 600 subjects will be randomized in a 1:1 ratio to blinded rimegepant or matching placebo in the DBT Phase. Randomization will be stratified by history of clinically relevant cardiovascular (CV) disease (yes, no). In addition, randomization of subjects in the

CV subgroup ("yes" category) will be capped at 15%. In the OLE Phase, the study drug will be 75 mg ODT of open label rimegepant as needed, up to once per calendar day.

Study Population:

The study will recruit subjects ≥18 years of age with a minimum 1 year documented history of migraine attacks (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. Less than 15 headache days (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and throughout the Screening Phase

5. Less than 7 non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit

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

7. Subjects on prophylactic migraine medication (excluding calcitonin gene-related peptide [CGRP] antagonists) are permitted to remain on therapy if they have been on a stable dose for at least 3 months (12 weeks) prior to the Screening Visit, and if the dose is not expected to change during the course of the study.

8. Be Triptan unsuitable.

Moreover, subjects must not have:

9. History of cluster headache, basilar migraine (migraine with brainstem aura), or hemiplegic migraine

10. Current Medication-overuse headaches

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. 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 EOD. 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. The design of the study, including the use of a placebo control, is in accordance with the most current International Headache Society (IHS) guidelines on the conduct of controlled trials in the acute treatment of migraine attacks in adults. Specifically, the document states, “Drugs intended for the acute treatment of migraine attacks can only be reliably evaluated in randomized, double-blind, placebo-controlled trials”.

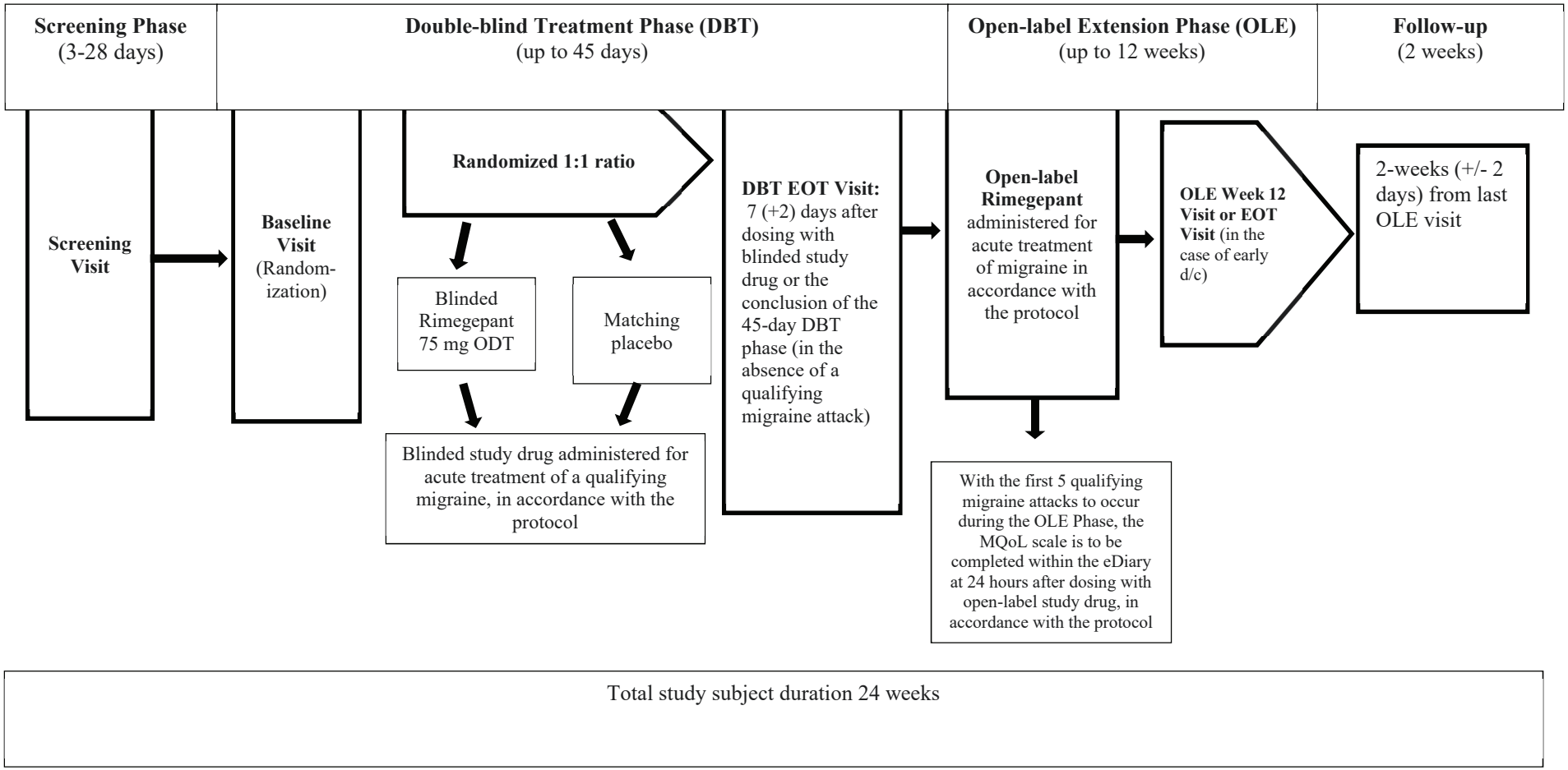
During the DBT phase, subjects randomized to placebo are not expected to obtain any specific benefit beyond close monitoring of their medical condition and safety. Subjects continuing to the OLE phase will have the opportunity to receive open-label rimegepant for 12 weeks (regardless whether they received placebo or rimegepant in the DBT phase) and may potentially derive benefit from the pharmacological effects of rimegepant in regards to the acute treatment of migraine.

Additionally, during both phases of the study, subjects may use their permitted acute migraine medication (prescribed or over-the-counter [OTC] agents) for the management of acute attacks, as needed, and in accordance with the standard of care.

During the study, subjects will undergo electrocardiograms (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
AST	Aspartate aminotransferase
AV	atrioventricular
AxMP	Auxiliary Medicinal Product
BHV	Biohaven
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CAD	coronary artery disease
CBD	cannabidiol
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CI	Confidence interval
CK	Creatine kinase
COVID-19	coronavirus disease of 2019
CRF	Case report form
CRO	Contracted Research Organization
CRPS	complex regional pain syndrome
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
CV	Cardiovascular

CVA	Cerebrovascular accident
CYP	cytochrome P450
DAIDS	Division of AIDS
DBT	Double-blind Treatment
DDI	drug-drug interaction
DILI	Drug Induced Liver Injury
DMC	Data Safety Monitoring Committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSU	Drug Safety Unit
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case report form
EDB	Exposure During Breastfeeding
EDC	Electronic Data Capture
eDiary	Electronic Diary
EDP	Exposure During Pregnancy
EFD	embryo-fetal development
eGFR	Estimated glomerular filtration rate
EOD	Every Other Day
EOT	End of Treatment
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
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HbA1c	glycated haemoglobin
HCG	Human chorionic gonadotropin

HR	Heart rate
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IHS	International Headache Society
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IOL=F	Intervening OL Rimegepant = Failure
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU/L	International Units Per Liter
kg	Kilogram
L	Liters
LBBB	Left Bundle Branch Block
LFT	Liver function test
LSLV	Last Subject Last Visit
MBS	Most bothersome symptom
MDD	Major depressive disorder
MDE	major depressive episode
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	myocardial infarction
MIBS	The Migraine Interictal Burden Scale
min	Minute
mL	millilitres

mmHg	Millimeters mercury
MOH	Medication Overuse Headache
MQI	Medically Qualified Individual
MQoL	Migraine Quality of Life Questionnaire
MSQ	Migraine-Specific Quality-of-Life Questionnaire
NC=F	Non-completer = Failure
NIMP	Non Investigational Medicinal Product
NOAEL	No Observed Adverse Event Level
NSAID	Non-steroidal anti-inflammatory drug
ODT	Oral disintegrating tablet
OL	Open-label
OLE	Open-label Extension
OTC	Over-the-Counter
PACL	Protocol Administrative Clarification Letter
PCD	Primary Completion Date
PCI	percutaneous coronary intervention
PCP	phencyclidine
P-gp	P-glycoprotein
PI	Principal investigator
PRN	as needed
PSSA	Pfizer SAE Submission Assistant
PVC	Premature Ventricular Contraction
QTcF	QTc corrected using Fridericia's formula
QTL	Quality Tolerance Limit
RM=F	Rescue Medication = Failure
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SRSD	Single Reference Safety Document

SUSAR	Suspected Unexpected Serious Adverse Reaction
T Bili	Total bilirubin
THC	Tetrahydrocannabinol
TIA	transient ischemic attack
TMD	temporomandibular disorders
TMF	Trial Master File
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WOCBP	Woman/women of childbearing potential
WPW	Wolff-Parkinson-White

1. INTRODUCTION AND RATIONALE

1.1. Background

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe headache pain intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.[1]

BHV-3000 (rimegepant) (PF-07899801) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of migraine. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a key role in migraine pathophysiology. For example, 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 show that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors, are effective in aborting migraine attacks. Treatment with a CGRP receptor antagonist is believed to relieve migraine through the possible mechanisms of 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 [PF-07899801]) is an oral, small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist approved in the United States (US) and the European Union (EU) for the acute treatment of migraine and the preventive treatment of episodic migraine in adults.[2,3] 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)

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

1.1.2. Product Development Background

Details of the clinical and preclinical studies are provided in the current Investigator Brochure. A summary of the relevant data to the study are presented below.[4]
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 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 and tolerability of rimegepant for the acute and preventive treatment of migraine in the pediatric

population is currently being evaluated. In this study, rimegepant is used in adults at the dose (75 mg) and in the indication (acute treatment of migraine) which are covered by the Marketing Authorization.

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

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 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. Also, in all 3 studies, significant results were achieved on photophobia freedom, phonophobia freedom, and pain relief 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 LFTs, vital signs, and 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 for up to 52 weeks in the open-label phase was well tolerated, with no new safety signals observed in the open-label-extension phase.

Across the 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 Appendix 5). The potential risk of exposure to rimegepant in a sexual partner of a male subject 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.

1.3. Study Rationale

Rimegepant is approved medication for the acute treatment of migraine attacks and preventive treatment 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 single-attack Phase 3 trials using the current registrational co-primary endpoints of migraine headache pain freedom and freedom from most bothersome symptom at 2 hours postdose. Rimegepant

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).[6] EOD dosing was also well tolerated with no signals of medication-overuse headache, abuse potential, cardiovascular events, or hepatotoxicity.

Rimegepant represents an alternative treatment option for migraine sufferers who are not well served by existing standard of care (e.g., triptans), due to either a poor or inconsistent therapeutic response, prior intolerance, or due to the presence of contraindications. Subgroup analysis of subjects enrolled in Phase 3 pivotal trials who were identified having discontinued one or more triptans indicated that rimegepant demonstrated a similar degree of efficacy as for the general study population. Therefore, the primary aim of this study is to confirm the efficacy of rimegepant in a population deemed unsuitable for triptan use and in whom an alternative treatment option would be most advantageous.

1.3.1. Study Design Rationale

This study is being conducted to evaluate the efficacy and tolerability of rimegepant for the acute treatment of migraine among adults considered unsuitable for triptan use because of prior intolerance, lack of efficacy or contraindication (including a history of clinically relevant cardiovascular disease). The double-blind, placebo-controlled, parallel group design to assess the efficacy and tolerability of rimegepant in this population in a primary migraine attack is in accordance with international guidelines for such an evaluation.[7] Additional information on the effectiveness and safety of rimegepant will also be obtained across additional attacks when used as needed in the 12-week open-label extension. The inclusion of the 12-week OLE Phase allows for the evaluation of safety and tolerability of rimegepant across multiple migraine attacks in a population of triptan-unsuitable adults. In addition, the OLE Phase allows for the potential to evaluate consistency of effect (as measured by improvement in quality of life [MQoL Question 16]), at the population level, among adults in need of effective alternative treatments for the management of acute migraine.

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 current study will evaluate the efficacy and tolerability of the acute treatment of multiple migraine attacks in adults unsuitable for triptan use.

1.3.3. Research Hypothesis

Rimegepant is a safe and effective treatment for acute treatment of migraine in adults who are unsuitable for triptan use because of prior intolerance, lack of efficacy, or contraindication (including a history of clinically relevant cardiovascular disease).

2. STUDY OBJECTIVES

2.1. Primary Objectives

To compare the efficacy of rimegepant with placebo in the acute treatment of migraine, as measured by migraine headache pain relief at 2 hours postdose during the DBT Phase.

2.2. Secondary Objectives

2.2.1. Key Secondary Objectives

1. To compare rimegepant with placebo for migraine headache pain freedom at 2 hours postdose during the DBT Phase.

2. To compare rimegepant with placebo for rescue medication use within 24 hours postdose during the DBT Phase.

3. To compare rimegepant with placebo for return to normal function, as measured by the functional disability scale, at 2 hours postdose during the DBT Phase.

4. To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 24 hours postdose during the DBT Phase.

5. To compare rimegepant with placebo for sustained return to normal function, as measured by the functional disability scale, from 2 to 48 hours postdose during the DBT Phase.

6. To compare rimegepant with placebo for sustained migraine headache pain relief from 2 to 24 hours postdose during the DBT Phase.

7. To compare rimegepant with placebo on sustained migraine headache pain relief from 2 to 48 hours postdose during the DBT Phase.

8. To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 24 hours postdose during the DBT Phase.

9. To compare rimegepant with placebo for sustained migraine headache pain freedom from 2 to 48 hours postdose during the DBT Phase.

10. To compare rimegepant with placebo for freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose during the DBT Phase.

2.2.2. Other Secondary Objectives

1. To evaluate reliability of rimegepant effect in the OLE Phase, as measured by Migraine Quality of Life Questionnaire (MQoL) Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose in the DBT Phase and after each of the first 5 qualifying migraine attacks in the OLE Phase.

2. To evaluate the mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

3. To evaluate the proportions of subjects with ≥ 50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

4. 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.

5. To evaluate the mean change from baseline in the Migraine Interictal Burden Scale (MIBS) score over time during the OLE Phase.

2.3. Exploratory Objectives

1. To evaluate the Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose during the DBT Phase

2. To evaluate the Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose after each of the first 5 qualifying migraine attacks during the OLE Phase.

3. To evaluate migraine headache pain relief at all scheduled time points postdose during the DBT Phase.

4. To evaluate migraine headache pain freedom at all scheduled time points postdose during the DBT Phase.

5. To evaluate MBS freedom at all scheduled time points postdose during the DBT Phase.

6. To evaluate return to normal function, as measured by the functional disability scale, at all scheduled time points postdose during the DBT Phase.

7. To evaluate photophobia freedom at all scheduled time points postdose during the DBT Phase.

8. To evaluate phonophobia freedom at all scheduled time points postdose during the DBT Phase.

9. To evaluate nausea freedom at all scheduled time points postdose during the DBT Phase.

10. To evaluate pain relapse from 2 to 48 hours postdose during the DBT Phase.

11. To evaluate time to migraine headache pain relief through 48 hours postdose during the DBT Phase.

12. To evaluate the mean number of acute migraine medication (rescue or non-rescue) days per month in each month and over the entire OLE Phase.

13. To evaluate the proportion of subjects who use rescue medication after each of the first 5 qualifying migraine attacks during the OLE Phase.

14. To evaluate the frequencies of hepatic-related adverse events and hepatic-related adverse events leading to study drug discontinuation in subjects treated with rimegepant during the DBT and OLE Phases.

15. To evaluate the mean changes from baseline in the Migraine-Specific Quality-of-Life Questionnaire v2.1 (MSQ) domain scores at Week 12 of the OLE Phase.

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

17. To evaluate primary and key secondary efficacy endpoints during the DBT Phase and high-level safety endpoints during the DBT and OLE Phases by history of clinically relevant CV disease (yes, no).

18. To evaluate primary and key secondary efficacy endpoints during the DBT Phase by history of documented failure to ≥ 2 triptan medications with ≥ 1 failure due to lack of efficacy (yes, no).

3. STUDY ENDPOINTS

Efficacy endpoints based on scales (migraine headache; presence or absence of nausea, phonophobia, or photophobia; functional disability level), and MQoL scores during the DBT and OLE Phases are derived from the eDiary.

Adverse events (AEs) and acute migraine medication use are determined from 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.

During the DBT Phase, the intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication (see Section 6.4.4) will be classified as failures for all efficacy assessments that are reported at or after taking acute migraine medication as rescue.

The RM=F method will apply to all binary efficacy endpoints listed below (including reliability of rimegepant effect) except the key secondary endpoint of rescue medication use within 24 hours postdose.

3.1. Primary Endpoints

Percentage of subjects with a headache pain intensity of none or mild at 2 hours postdose in the DBT Phase. Migraine headache pain intensity will be measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).

3.2. Secondary Endpoints

3.2.1. Key Secondary Endpoints

1. Percentage of subjects with a headache pain intensity of none at 2 hours postdose in the DBT Phase.

2. Percentage of subjects who take rescue medication within 24 hours after taking study drug in the DBT Phase. Rescue medication is defined in Section 6.4.4.

3. Percentage of subjects with a functional disability level of normal at 2 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing. Functional disability level will be measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest).

4. Percentage of subjects with functional disability levels of normal at all time points from 2 to 24 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing.

5. Percentage of subjects with functional disability levels of normal at all time points from 2 to 48 hours postdose in the DBT Phase in the subset of subjects with functional disability at the time of dosing.

6. Percentage of subjects with headache pain intensities of none or mild at all time points from 2 to 24 hours postdose in the DBT Phase.

7. Percentage of subjects with headache pain intensities of none or mild at all time points from 2 to 48 hours postdose in the DBT Phase.

8. Percentage of subjects with headache pain intensities of none at all time points from 2 to 24 hours postdose in the DBT Phase.

9. Percentage of subjects with headache pain intensities of none at all time points from 2 to 48 hours postdose in the DBT Phase.

10. Percentage of subjects with an MBS that is reported on study before dosing and is absent at 2 hours postdose in the DBT Phase. The MBS on study before dosing will be reported as nausea, phonophobia, or photophobia. Symptom status will be reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).

3.2.2. Other Secondary Endpoints

1. Percentages of subjects achieving response after (1) the single evaluable qualifying migraine attack in the DBT Phase for those randomized to rimegepant, and (2) each of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase. Reliability of rimegepant effect during the OLE Phase is defined as percentages for at least 4 of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase being no more than 7% less than the percentage in the DBT Phase. Response is defined as a category of "moderately better" or "very much better" for MQoL Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose. Evaluable qualifying migraine attacks are defined in Section 9.3.1.2.

2. Mean change from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

3. Percentages of subjects with ≥ 50% reduction from historical baseline in the number of migraine days per month by headache pain intensity (total; moderate or severe) in each month and over the entire OLE Phase.

4. Number and percentage of subjects with AEs by intensity (mild, moderate, severe, total), SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases.

5. Mean changes from baseline in the MIBS score at Weeks 4, 8, and 12 of the OLE Phase.

4. STUDY PLAN

4.1. Study Design and Duration

This is a multicenter, phase 4, randomized, double-blind placebo-controlled study, with an open label extension (OLE) phase to assess the efficacy and tolerability of rimegepant for the acute treatment of migraine in subjects who are unsuitable for triptan use (see Section 16.4, Appendix 4, for triptan unsuitable).

The total study duration for each subject will be up to ~24 weeks. The end of the study is defined as the last visit of the last subject.

- In the DBT Phase, subjects will be dispensed 1 blister card and instructed to take 1 tablet (75 mg ODT) of blinded rimegepant or matching placebo when they have a migraine attack of moderate or severe headache pain intensity that they have not already treated with acute migraine medication (see Section 16.3 Appendix 3).
    - The DBT Phase will last approximately 11 weeks (including a 3 to 28-day screening period, a treatment phase that can last up to 45 days or until the subject experiences a qualifying migraine attack (see definition below) [whichever comes first], and an end-

of-treatment visit that is to occur ~7-days after the administration of blinded study drug).

- **A qualifying migraine attack in the DBT Phase is defined as a migraine attack of moderate or severe headache pain intensity that is first treated with blinded study drug, i.e., acute migraine medication is not taken before taking blinded study drug.**

- Subjects who do not have a qualifying migraine attack (see above for definition) during the 45-day DBT Phase will not be eligible for the OLE Phase.

- In association with a qualifying migraine attack, subjects are required to use the eDiary to complete (1) efficacy-related questions though 48 hours after dosing with blinded study drug, and (2) the MQoL Questionnaire at 24 hours after dosing with blinded study drug.

- In the OLE Phase, subjects will be able to take up to 1 tablet of open-label study drug (75 mg ODT rimegepant) per calendar day as needed for acute treatment of migraine for a maximum of 18 doses per month (month is 28 days).

  - ***During the OLE Phase,***

    - Subjects are to use open-label study drug as the first treatment for migraine attacks of moderate or severe headache pain intensity, and should not take acute migraine medication before taking open-label study drug (see Section 16.3 Appendix 3).

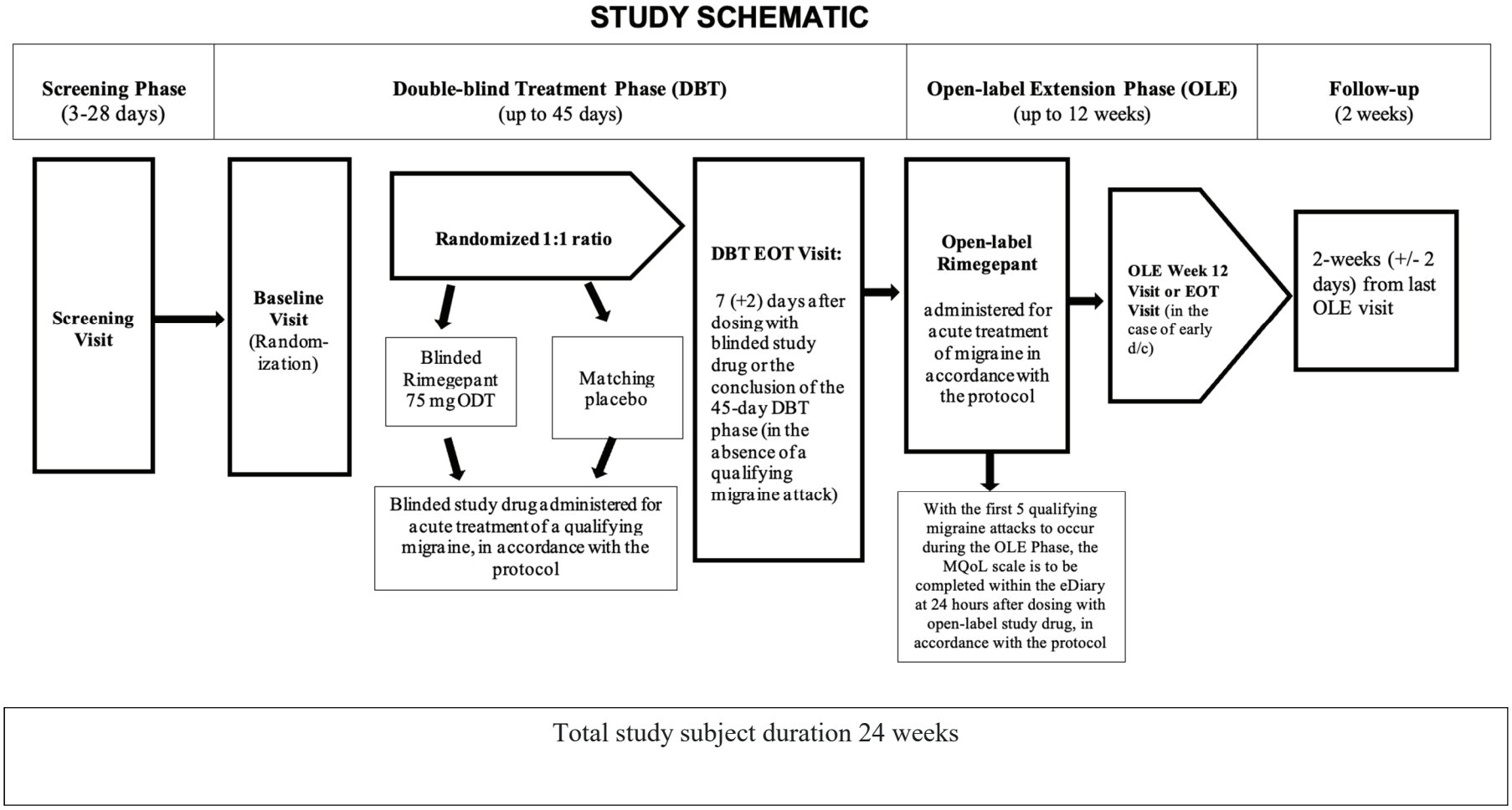
    - **A qualifying migraine attack in the OLE Phase is defined as a migraine attack of moderate or severe headache pain intensity that is first treated with open-label study drug, i.e., acute migraine medication is not taken before taking open-label study drug.**

    - In association with each of the ***First 5 Qualifying Migraine Attacks***, subjects are required to use the eDiary to complete the MQoL Questionnaire at 24 hours after dosing with open-label study drug. In the event an MQoL Questionnaire is not completed for any of the first 5 qualifying migraine attacks (eg, inadvertently missed), MQoL Questionnaires will be collected for subsequent qualifying migraine attacks until a total of 5 MQoL Questionnaires are completed.

    - If migraine-associated symptoms persist beyond 2 hours after dosing with open-label study drug, subjects may use permitted acute migraine medication (see Section 16.3, Appendix 3) for the purposes of rescue, as needed and in accordance with the standard of care. *All dosing of rescue medication (permitted or exclusionary), as defined in* Section 6.4.4*, is to be recorded on the Rescue Medication paper diary.*

In the DBT Phase, the study drug will be blinded 75 mg ODT of rimegepant or matching placebo. The study will randomize approximately 600 subjects in a 1:1 ratio to blinded rimegepant or matching placebo in the DBT Phase. Randomization will be stratified by history of clinically relevant CV disease (yes or no; see Section 7.1.6). In addition, randomization of subjects in the CV subgroup ("yes" category) will be capped at 15%. In the OLE Phase, the study drug will be 75 mg ODT of open-label rimegepant.

4.2. Study Schematic



4.3. Schedule of Assessments

Table 1. Screening Phase and DBT Phase Schedule of Assessments

	Screening Phase (3-28 days)	DBT Phase (up to 45 days in duration)				
Procedure	**Screening Visit**	**Baseline/ Randomization (Day 1)[1]**	**Moderate or Severe Migraine Before Study Drug**	**Post Study Drug: Administration 15, 30, 45, 60, 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours**	**End of Treatment – (DBT Phase) (7 days +2 days after dosing)[2]**	**Notes**
Eligibility Assessments						
Informed consent	**X**					Subject must be entered in the RTSM after informed consent is collected to obtain their study subject identification number.
Inclusion/ Exclusion criteria assessed	**X**	**X**				
Medical history	**X**					
Migraine history assessment (signs/ symptoms/ prior treatment/ frequency/ intensity)	**X**					
Concomitant medication paper diary	**X**	**X**		**X**	**X**	See Section 5.4 for additional details
Rescue Medication paper diary		**X**	**X**	**X**		

1 The **Baseline Visit** may only occur ***after*** all screening procedures are completed and the subject meets all inclusion/exclusion criteria. If the subject does not meet all eligibility requirements, the subject is to be counted as a Screen Failed within the RTSM system.

2 All subjects will return to the site (after assessments in the eDiary are completed) within 7 (+2) days after dosing with study drug in this phase. The "+2" day window is included for scheduling purposes only. Every effort should be made to conduct the DBT EOT Visit and maintain the 7 (+2) day window. However, due to concerns related to the COVID-19 pandemic, or any natural catastrophe, the DBT EOT Visit window may be modified beyond the 7 (+2) day window. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis.

	Screening Phase (3-28 days)	DBT Phase (up to 45 days in duration)				
Procedure	**Screening Visit**	**Baseline/ Randomization (Day 1)[1]**	**Moderate or Severe Migraine Before Study Drug**	**Post Study Drug: Administration 15, 30, 45, 60, 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours**	**End of Treatment – (DBT Phase) (7 days +2 days after dosing)[2]**	**Notes**
Randomize subject in RTSM		**X**				Obtain subject ID
Safety Assessments						
Physical Examination	**X**				**X***	*If subject is eligible to enroll into the OLE Phase, a physical exam at DBT EOT 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 DBT EOT. see Section 6.3.3.
Vital Signs/ Physical Measurements	**X**	**X**			**X**	Height will only be captured at the Screening Visit. Weight, body temperature, respiratory rate, blood pressure and heart rate will be collected at all time points where indicated. Sitting arterial systolic and diastolic blood pressure and pulse rate will be measured.
ECG	**X**				**X***	*If subject is eligible to enroll into the OLE Phase, an ECG at DBT EOT is not required
Urine drug screen for drugs of abuse	**X**					

	Screening Phase (3-28 days)	**DBT Phase (up to 45 days in duration)**				
Procedure	**Screening Visit**	**Baseline/ Randomization (Day 1)[1]**	**Moderate or Severe Migraine Before Study Drug**	**Post Study Drug: Administration 15, 30, 45, 60, 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours**	**End of Treatment – (DBT Phase) (7 days +2 days after dosing)[2]**	**Notes**
AE, SAE, and Concomitant Procedure assessment	**X**	**X**		**X**	**X**	SAEs and AEs are reported from the time of signed informed consent (See Section 8.2.1 and 8.1.2). All ongoing non-serious AEs and SAEs will be followed to resolution or until the Investigator deems there will be no further status change. AEs that occur during the treatment period must be reported to the site in real time. Non-serious AEs that occur during the treatment period must be reported to the site at each study visit.
Clinical Safety Laboratory Testing (hematology, chemistry)[3]	**X**				**X**	
Liver Function Tests (LFTs)[3]	**X**				**X**	
Pregnancy Test[4]	**X (serum)**	**X (urine)**	**X (urine)[4]**		**X (serum or urine)**	

3 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

4 During the DBT Phase, WOCBP must complete a pregnancy test at Screening, Baseline, prior to taking blinded study medication, and at the DBT EOT Visit. 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.

	Screening Phase (3-28 days)	DBT Phase (up to 45 days in duration)				
Procedure	**Screening Visit**	**Baseline/ Randomization (Day 1)[1]**	**Moderate or Severe Migraine Before Study Drug**	**Post Study Drug: Administration 15, 30, 45, 60, 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours**	**End of Treatment – (DBT Phase) (7 days +2 days after dosing)[2]**	**Notes**
Clinical Drug Supplies/ Study Supplies						
eDiary assigned to subject		**X**				
Subject education: eDiary subject training/ device training		**X**				
Dispense study drug		**X**				Subjects are to use blinded study drug to first treat a migraine attack of moderate or severe headache pain intensity. Subjects are to use the eDiary to indicate when it is time to take study drug.
Collect study drug					**X**	Collect used and unused study drug.
Subject administers study drug			**X**			Subject administers study drug ONLY after completion of the eDiary pre-dose migraine assessments.
eDiary completion				**X**		
eDiary reviewed for completeness					**X**	Subject will return with eDiary. Site staff to review and confirm all data points are transferred from the eDiary. After study personnel review, the eDiary should be re-dispensed to the subject.
eDiary re-training for OLE subjects					**X**	

	Screening Phase (3-28 days)	**DBT Phase (up to 45 days in duration)**				
Procedure	**Screening Visit**	**Baseline/ Randomization (Day 1)[1]**	**Moderate or Severe Migraine Before Study Drug**	**Post Study Drug: Administration 15, 30, 45, 60, 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours**	**End of Treatment – (DBT Phase) (7 days +2 days after dosing)[2]**	**Notes**
Efficacy and Outcomes Research Assessments						
Assessments of migraine pain, migraine symptoms Most Bothersome Symptoms (MBS) * (phonophobia, photophobia, and nausea) and functional disability			**X***	**X**		*MBS is captured before study drug administration
Other Assessments						
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1		**X**				Paper assessment – recall 4 weeks
Migraine Quality of Life Questionnaire (MQoL)				**X (24 hours only)**		eDiary
Columbia-Suicide Severity Rating Scale (C-SSRS)	**X**	**X**			**X**	Paper assessment Screening assessment for the Screening Visit and Since the last assessment for all other timepoints.
Migraine Interictal Burden Scale (MIBS)		**X**				Paper assessment. Recall for this scale is every 4 weeks.

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

	Open-label Extension Phase					**Follow-up Phase**	
Procedure	**Eligibility Confirmation Phone Visit**[1]	**Week 2 Visit** (OLE Day 15 +/- 2 days)	**Week 4 Visit** (OLE Day 29 +/- 2 days)	**Week 8 Visit** (OLE Day 57 +/- 2 days)	**Week 12 Visit (**OLE Day 85 +2 days) or **EOT** for early discontinuation	**Follow-up Week 2 Visit (+/- 2days)**	**NOTES**
Confirm DBT EOT laboratory test results	**X**						
Rescue Medication paper diary		**X**	**X**	**X**			
Concomitant medication paperdiary		**X**	**X**	**X**	**X**	**X**	Concomitant medications, including prophylactic migraine medications (both prescribed and OTC), taken during the OLE Phase and Follow-up Phase are to be recorded in the subject's Concomitant Medication paper diary, reviewed by study personnel at each visit, and a copy made at each study visit to be maintained in source records. At end of study, the Concomitant Medication paper diary must be collected at the Follow-up Week 2 Visit.

1 The DBT-EOT Visit represents OLE Day 1. While on study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to their original visit schedule by calculating the visit window interval from the DBT EOT Visit.

	Open-label Extension Phase					**Follow-up Phase**	
Procedure	**Eligibility Confirmation Phone Visit**[1]	**Week 2 Visit** (OLE Day 15 +/- 2 days)	**Week 4 Visit** (OLE Day 29 +/- 2 days)	**Week 8 Visit** (OLE Day 57 +/- 2 days)	**Week 12 Visit** (OLE Day 85 +2 days) or **EOT** for early discontinuation	**Follow-up Week 2 Visit (+/- 2days)**	**NOTES**
Safety Assessments							
Physical Examination					**X**		Targeted symptom directed physical examination to include examination of heart, abdomen, and lungs, with review of any other system to be guided by symptoms. See Section 6.3.3
Vital Signs / Physical Measurements		**X**	**X**	**X**	**X**	**X**	Height will only be captured at the Screening Visit. Weight, body temperature, respiratory rate, blood pressure and heart rate will be collected at all time points where indicated. Sitting arterial systolic and diastolic blood pressure and pulse rate will be measured.
Clinical Safety Laboratory Testing (hematology, chemistry)[2]					**X**		
Liver Function Test (LFTs)[2]			**X**		**X**		
ECG					**X**		
Pregnancy Test[3]		**X (urine)**	**X (urine)**	**X (urine)**	**X (serum)**	**X (urine)**	

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 2, Week 4, Week 8, Week 12/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

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	Open-label Extension Phase					**Follow-up Phase**	
Procedure	**Eligibility Confirmation Phone Visit**[1]	**Week 2 Visit** (OLE Day 15 +/- 2 days)	**Week 4 Visit** (OLE Day 29 +/- 2 days)	**Week 8 Visit** (OLE Day 57 +/- 2 days)	**Week 12 Visit (**OLE Day 85 +2 days) or **EOT** for early discontinuation	**Follow-up Week 2 Visit (+/- 2days)**	**NOTES**
AE, SAE, and ConcomitantProcedure assessment		**X**	**X**	**X**	**X**	**X**	AEs and SAEs are collected through the Follow-up Week 2 Visit
Clinical Drug Supplies /Study Supplies							
Dispense study drug[4]		**X**	**X**	**X**			
Administer study drug		**X**	**X**	**X**			Subjects cannot take more than 1 ODT of study drug (rimegepant) per day, and no more than 18 tablets of rimegepant per 28 days. Study drug is NOT to be used for rescue.
Return used and unused study drug to site for compliance check		**X**	**X**	**X**	**X**		
eDiary returned / reviewed for completeness[5]		**X**	**X**	**X**	**X**		Subject will return eDiary. Site staff to review and confirm all data points are transferred, PRIOR to the subject leaving the study center.

4 At the DBT Phase EOT Visit, subjects will be administered 2 wallet cards containing 8 ODTs. Subjects are to be instructed to complete a full wallet, as directed, before taking study drug from a new one. Day 1 of the OLE Phase = DBT EOT Visit.
5 eDiary will be used to record the occurrence of migraine attacks and headaches during the OLE Phase

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	Open-label Extension Phase					**Follow-up Phase**	
Procedure	**Eligibility Confirmation Phone Visit**[1]	**Week 2 Visit** (OLE Day 15 +/- 2 days)	**Week 4 Visit** (OLE Day 29 +/- 2 days)	**Week 8 Visit** (OLE Day 57 +/- 2 days)	**Week 12 Visit (**OLE Day 85 +2 days) or **EOT** for early discontinuation	**Follow-up Week 2 Visit (+/- 2days)**	**NOTES**
Other Assessments							
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1					**X**		Paper assessment.
Migraine Interictal Burden Scale (MIBS)			**X**	**X**	**X**		Paper assessment. Recall for this scale is every 4 weeks.
Migraine Quality of Life Questionnaire (MQoL)		**X** →	→	→	→ **X**		Scale will populate on the eDiary 24 hours after each qualifying migraine attack until 5 are completed.
Columbia-Suicide Severity Rating Scale (C-SSRS)			**X**		**X**		Paper assessment. Since the last assessment will be used for all OL timepoints.

4.3.1. Screening Phase

Approximately 900 subjects will be screened to randomize approximately 600 subjects to blinded study drug (rimegepant ODT or matching placebo).

Before any study procedures are performed, subjects must sign informed consent. After informed consent is signed, subjects will be enrolled in the RTSM system. The subject's migraine history and medical history will be collected at the Screening Visit. Subjects will also undergo all screening procedures as detailed in Table 1. Within 3-28 days from the Screening Visits, subjects will return to the site for the Baseline/Randomization Visit; if the subject does not meet all eligibility criteria, the subject will be considered a Screen Failure.

For LFT testing requirements:

For total bilirubin, > 1.5 × ULN may be repeated once for confirmation during the Screening Phase.

For ALT/AST >2 × ULN, may be repeated once for confirmation during the Screening Phase. Screening Phase will have one screening visit that must be completed in person.

Subjects on prophylactic migraine medication are permitted to remain on therapy (excluding CGRP antagonists) provided they have been on a stable dose for 3 months prior to the Screening Visit and the dose is not expected to change throughout the course of the study (DBT through OLE). The list of acceptable prophylactic migraine medications can be found in Section 16.2, Appendix 2.

A Concomitant Medication paper diary will be provided to subjects at the Screening Visit. Subjects are to keep track of all concomitant medications including acute migraine medications (*used for non-rescue purposes only*, see Section 6.4.4) and standard prophylactic migraine medications (see Section 16.2, Appendix 2), through the DBT EOT and OLE Week 12/ EOT Visits on an IRB-approved Concomitant Medication paper diary. All paper diaries (the Concomitant Medication and the Rescue Medication paper diaries) are to be returned to the investigational site at each visit for review and electronic data capture (EDC) entry. The paper diaries must be kept as source documentation. See the Acute Migraine Medication section of the protocol (Section 5.5) for additional information.

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.

4.3.2. Double-blind Treatment Phase

The DBT Phase will have 2 scheduled clinic visits, Baseline (Randomization) and DBT EOT. Both visits must be completed in person. Eligible subjects will be randomized at the Baseline (Randomization) Visit of the 45-day DBT Phase. Subjects will be dispensed a single dose of double-blind study drug for the DBT Phase.

During the DBT Phase, subjects will record efficacy data in their assigned eDiary. Subjects will be instructed to take study drug as an outpatient. Subjects are not permitted to dose with study drug until the migraine headache pain reaches moderate or severe headache pain intensity. The eDiary will instruct the subject to take study drug after the initial assessments are completed in the device. The following will be recorded in the eDiary:

- Migraine headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe) before taking study drug and after taking study drug at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours postdose
- The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and functional disability level (4-point numeric rating scale: normal, mildly impaired, severely impaired, requires bedrest) recorded at the same time points as migraine headache pain intensity
- MBS before taking study drug (with or without aura)
- Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose

Subjects who experience reduction of migraine headache pain intensity to a level of none or mild will be considered to have achieved migraine headache pain relief. Subjects will be allowed to take permitted acute migraine medication (specified in Section 16.3, Appendix 3), for the purposes of rescue, as needed and in accordance with the standard of care, ***only after the 2-hour postdose and after the 2-hour assessments have been completed within the eDiary***.

Subjects will be instructed to contact the study center immediately if a severe or serious adverse event occurs. At select study visits (see Table 1), subjects will be requested to complete the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ), MIBS (The Migraine Interictal Burden Scale) and the Columbia-Suicide Severity Rating Scale (C-SSRS) on paper forms.

Subjects will continue to record all concomitant medications, including acute migraine medications (*used for non-rescue purposes only*, see Section 5.5.2) and standard prophylactic migraine medications (see Section 16.2, Appendix 2), taken during the DBT Phase in the Concomitant Medication paper diary. All rescue medications, as defined in Section 6.4.4, are to be documented on the Rescue Medication paper diary.

4.3.2.1. Baseline (Randomization) Visit

Subjects are to return to the study site for the Baseline (Randomization) Visit, which must be completed in person. Subjects who continue to meet all study entry criteria may be randomized in the RTSM system and entered into the DBT Phase.

At the Baseline Visit, subjects will be randomized 1:1 across 2 treatment groups: blinded rimegepant 75 mg (n = 300) or matching placebo for rimegepant 75 mg (n = 300). Randomization will be stratified by history of clinically relevant CV disease (yes or no; see Section 7.1.6). In addition, randomization of subjects in the CV subgroup ("yes" category) will be capped at 15%.

4.3.2.2. DBT EOT Visit

Subjects will return to the study site within 7 (+2) days after administration of double-blind study drug, for review of the eDiary data, assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and ECG). If a subject does NOT have a qualifying migraine attack (see Section 4.1) within 45 days after randomization, they still are required to complete all DBT EOT Visit procedures including assessment of medication compliance and monitoring of tolerability and safety (including vital signs, laboratory tests, and ECG). Subjects who do not have a qualifying migraine attack (see Section 4.1) during the 45-day DBT Phase will not be eligible for the OLE Phase.

At the DBT EOT Visit, the subject will return the eDiary for review and all study drug, including wallets with used or unused study drug. Subjects will also be evaluated at this visit for entry into the 12-week OLE Phase following laboratory results within acceptable ranges per protocol (see Table 2). Subjects in the DBT Phase who demonstrate poor compliance will be discussed with the Sponsor, corrective training will be completed by the site with the subject prior to the OLE Phase (see Sections 6.6 and 7.3).

4.3.3. Open-label Extension Phase

4.3.3.1. OLE Eligibility Confirmation Phone Visit

Study eligibility must be confirmed by DBT EOT Visit laboratory results prior to the first dose of open-label rimegepant. The site must contact the subject by phone to confirm OLE Phase eligibility prior to subject taking the first dose of open-label rimegepant.

4.3.3.2. OLE Day 1

Day 1 of the OLE Phase is the same day as the DBT EOT Visit. Sites are to instruct subjects to refrain from dosing with open-label study drug until they have received a phone call from the site confirming their eligibility to enter the OLE Phase.

4.3.3.3. OLE Week 12 / OLE EOT Visit

The OLE Phase will last 12 weeks from the DBT EOT Visit through the OLE Week 12 / OLE EOT Visit.

In the OLE Phase, subjects will be able to take up to 1 tablet of open-label study drug (75 mg ODT rimegepant) per calendar day as needed for acute treatment of migraine of moderate or severe headache pain intensity for a maximum of 18 doses per month (month is 28 days).

- ***During the OLE Phase***

    - Subjects are to use open-label study drug as the first treatment for migraine attacks of moderate or severe headache pain intensity, and should not take acute migraine medication before taking open-label study drug (see Section 16.3, Appendix 3).

    - In association with each of the ***First 5 Qualifying Migraine Attacks*** (see Section 4.1), subjects are required to complete the MQoL Questionnaire within the eDiary at 24 hours after dosing with open-label study drug. In the event an MQoL Questionnaire is not completed for any of the first 5 qualifying migraine attacks (eg, inadvertently missed), MQoL Questionnaires will be collected for subsequent qualifying migraine attacks until a total of 5 MQoL Questionnaires are completed.

    - If migraine-associated symptoms persist beyond 2 hours after dosing with open-label study drug, subjects may use permitted acute migraine medication (see Section 16.3, Appendix 3) for the purposes of rescue, as needed and in accordance with the standard of care. *All dosing of rescue medication (permitted or exclusionary), as defined in* Section 6.4.4*, is to be recorded on the Rescue Medication paper diary.*

Subjects will record the following about their migraine attacks in the eDiary:

- migraine occurrence (yes, no);
- migraine headache pain intensity (mild, moderate, severe);
- study drug dosing (yes, no);
- Migraine Quality of Life Questionnaire (MQoL) at 24 hours postdose (until 5 are completed)

Subjects will continue to record all concomitant medications, including acute migraine medications (*used for non-rescue purposes only*, see Section 5.5.2) and standard prophylactic migraine medications (see Section 16.2, Appendix 2) taken during the OLE Phase in the Concomitant Medication paper diary.

Subjects will return to the study site at the OLE Week 12 / OLE EOT Visit (OLE Day 85 +2 days) for assessment of medication compliance and assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 2). Subjects must return the eDiary, unused study drug to the study site at each visit.

All subjects ***who discontinue early from the OLE Phase*** are to complete the OLE Week 12 / EOT Visit (see Table 2).

In the event that the feasibility of study visits is impacted due to COVID-19, 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. During the OLE Phase, the following visits may be completed remotely due to COVID-19: Week 2, Week 4, Week 8 and the Follow-up Week 2 Visit. The following visits must be completed in-person: Week 12/ EOT Visit.

4.3.4. Follow-up Phase

The Follow-up Phase will have 1 scheduled visit at Follow-up Week 2, which will occur approximately 2 weeks (14 days +/- 2 days) after the OLE Week 12 / EOT Visit. Subjects will return to the study site to collect vital signs, assessment of AEs/SAEs, and to have a urine pregnancy test performed (WOCBP). Investigators are to assess subjects for AEs consistent with drug dependency or withdrawal effects and report as appropriate (see Section 7.4).

All subjects who enter the OLE Phase are to complete the Follow-up Week 2 Visit (regardless of completing the OLE Phase), except those who discontinue early from the OLE Phase due to withdrawal by subject or lost to follow-up.

Subjects will continue to record all concomitant medications, including acute migraine medications (used for non-rescue purposes only, see Section 5.5.2) and standard prophylactic migraine medications (see Section 16.2, Appendix 2), taken during the Follow-up Phase in the Concomitant Medication paper diary.

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 is to 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 migraine attacks. 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

It is anticipated that approximately 900 subjects will be screened in order to randomize approximately 600 subjects. The subjects will be randomized in a 1:1 ratio to blinded rimegepant or matching placebo during the Double-blind Treatment (DBT) Phase. It is

estimated that approximately 510 subjects will be entered into the Open-label Extension (OLE) Phase.

5.2. Inclusion Criteria

1. Target Population

   Minimum 1 year documented history of migraine attacks (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition.[8]

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

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

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

   c. 4 to 14 migraine days (see Section 6.4.5) 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).

   d. Subjects must be able to distinguish migraine attacks from tension headaches.

   e. Subjects on prophylactic migraine medication (excluding CGRP antagonists) are permitted to remain on therapy if they have been on a stable dose for at least 3 months (12 weeks) prior to the Screening Visit, and if the dose is not expected to change during the course of the study.

2. Triptan unsuitable (see Appendix 4).

3. Age and Reproductive Status

   a. Subjects ≥18 years of age.
   b. Subject meets reproductive criteria. Refer to Appendix 5 for reproductive criteria for female (Section 16.5.1) subjects.

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

4. Subjects must be able to fully comply with the prohibitions and restrictions on the concomitant use of medications and therapies (including moderate to strong inhibitors and inducers of the CYP3A4 enzyme and strong inhibitors of the P-gp transporter) detailed in Section 16.1, Appendix 1.

5. For Germany only: 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); refer to Section 16.7.2.

5.3. Exclusion Criteria

1. Target Disease Exclusion:

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

    b. Current Medication-overuse headaches

    c. Headaches occurring 15 or more days per month (migraine or non-migraine) in any of the 3 months prior to the Screening Visit

    d. 7 or more non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit

2. History and Concurrent Diseases

    a. History of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or other disease or condition (e.g. chronic pancreatitis, ulcerative colitis, etc.) that causes malabsorption

    b. Body mass index ≥35 kg/m^2

    c. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria[9] for any significant substance use disorder within the past 12 months prior to the Screening Visit

    d. Current diagnosis of schizophrenia, bipolar, or borderline personality disorder

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

    f. Major depressive (MDD) or any anxiety disorder (AD) which requires more than 1 daily medication for each disorder, or major depressive episode (MDE) within last 12 months. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for ≥3 months (12 weeks) prior to the Screening Visit

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

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

i. Current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality

j. History with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease (including, but not limited to: ischemic heart disease, coronary artery vasospasm, myocardial infarction [MI], acute coronary syndrome [ACS], percutaneous coronary intervention [PCI], cardiac surgery), cerebral ischemia (including, but not limited to: stroke or transient ischemic attack [TIA]) during the 6 months (24 weeks) prior to the Screening Visit

k. Systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg after 10 minutes of rest. This may be repeated once at the Screening Visit to confirm reproducibility.

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

m. 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 test 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 Baseline Visit until the OLE Week 12 or OLE EOT Visit occurs.

iii. 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[9] 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. “Rimegepant is contraindicated in subjects with a hypersensitivity to any component of its formulation.”

4. Sex and Reproductive Status

    a. WOCBP who are unwilling or unable to use required contraception (Refer to Section 16.5 Appendix 5 for Contraceptive and Barrier Guidance).

    b. Women who are pregnant, lactating or breastfeeding

    c. Women with a positive pregnancy test at the Screening Visit or prior to study drug administration

5. ECG and Laboratory Test Findings

    a. Any clinically significant abnormality identified on the medical, ECG 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, nor interfere with the study procedures (not including exclusion criteria listed in Section 5.3).

    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 <2.8g/dL

    f. Neutrophil count ≤ 1000/µL (or equivalent)

    g. HbA1c >7.5%

    h. 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.

6. Prohibited Medications and Devices

    a. Non-Narcotic Analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol [acetaminophen], gabapentin, etc.) taken >= 15 days per month for a non-headache indication during the 3 months (12 weeks) prior to the Screening Visit

b. Other CGRP antagonists (beyond rimegepant), including:

   i. CGRP antagonist monoclonal antibodies taken within 6 months (24 weeks) prior to the Screening Visit

   ii. CGRP antagonist small molecules taken within 10 days prior to the Screening Visit

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

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

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

f. Narcotics, such as opioids (e.g., morphine, codeine, oxycodone, hydrocodone) or barbiturates (e.g., butalbital) taken ≥4 days per month during the 3 months (12 weeks) prior to the Screening Visit

g. 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 5.5.2)

7. Other Exclusion Criteria:

   a. For France and Germany only: Persons deprived of their liberty by a judicial or administrative decision. (Refer to Section 16.7 for France and Germany)

   b. For France and Germany only: Adults subject to a legal protection measure (guardianship, curatorship, and safeguard of justice). (Refer to Section 16.7 for France and Germany)

   c. For France only: Persons not affiliated to a social security scheme or equivalent. (Refer to Section 16.7 For France)

   d. Exposure to non-biological investigational agents within 30 days prior to the Screening Visit

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

   f. Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to screening, 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 screening, OR subjects who, in the opinion of the Investigator, present a serious risk of suicide (See Section 6.3.5).

g. Previous enrollment in any multiple dose BHV3000 (rimegepant) (PF-07899801) study, such as BHV3000-201, BHV3000-305, BHV3000-404, BHV3000-405, or BHV3000-407, regardless of the number of doses taken. Subjects may be considered for BHV3000-406 (C4951004) 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 BHV-3000 (PF-07899801) study may be considered after discussion with the Sponsor and written approval is received.

h. Participation in any other investigational clinical trial while participating in this clinical trial.

i. Past participation in a clinical study within 30 days prior to the Screening Visit.

j. Failure to complete the Baseline Visit within the timeframe specified in the schedule of assessments.

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

l. 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.

m. For Germany only: Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness (refer to Section 16.7.2).

5.4. Prohibited and Restricted Concomitant Medications and Devices

All non-study medications, including vaccinations taken by subjects throughout the study (i.e., starting from the Screening Visit though the Follow-up Week 2 Visit) will be documented as concomitant medications in the Concomitant Medication paper diary. The only exception is the use of acute migraine medication (permitted or exclusionary) for the purposes of rescue (i.e., for the management of unresolved migraine-related symptoms following primary treatment with study medication [blinded or open-label]). All dosing with rescue medications should be recorded in the Rescue Medication paper diary.

See Section 16.1, Appendix 1 for a full list of concomitant medications and devices prohibited during the study.

5.5. Permitted Non-study Standard of Care Migraine Medications

Non-study standard of care migraine medications (both acute and prophylactic) will be documented in paper diaries throughout the study. Subjects are to record all concomitant medications, including acute migraine medications (*used for non-rescue purposes only*, see Section 5.5.2) and standard prophylactic migraine medications (see Section 16.2, Appendix 2), taken throughout the study (DBT and OLE Phases), in the Concomitant Medication paper diary. All rescue medications, as defined in Section 6.4.4, are to be documented on the Rescue Medication paper diary.

5.5.1. Prophylactic Migraine Medications

Subjects may take standard prophylactic migraine medication throughout the study (see Section 16.2, Appendix 2). Doses must be stable for 3 months (12 weeks) prior to the Screening Visit and throughout the study.

5.5.2. Acute Migraine Medications

Acute migraine medications are those agents recognized as having efficacy in the treatment of acute migraine. Permitted acute migraine medications are presented in Section 16.3, Appendix 3.

Subjects are to keep track of all concomitant medications including acute migraine medications (*used for non-rescue purposes only*, see Section 6.4.4), throughout the course of the study, on an IRB-approved Concomitant Medication paper diary.

Subjects are allowed to use permitted acute migraine medications (see Section 16.3, Appendix 3), as needed, for the treatment of migraine attacks of mild or no headache pain intensity.

5.5.2.1. Acute Migraine Medications in the DBT Phase

In the DBT Phase, subjects should use blinded study drug to first treat a migraine attack of moderate or severe headache pain intensity. After dosing with blinded study drug for the treatment of a moderate or severe migraine attack, no acute migraine medications are permitted through 2 hours postdose AND completion of the 2-hour assessments within the eDiary.

Subjects who do not experience relief of their migraine-related symptoms at 2 hours postdose but have completed the requisite 2-hour assessments within the eDiary, may take permitted acute migraine medication (see Section 16.3, Appendix 3) for the purposes of rescue, as needed and in accordance with the standard of care. In addition, if a moderate or severe migraine attack is relieved with study drug at 2 hours postdose but then returns to a moderate or severe headache pain intensity level between 2 and 48 hours (and prior to completion of 48-hour postdose assessments within the eDiary), subjects may use permitted acute migraine medication as rescue. All dosing of rescue medication (permitted or exclusionary), as defined in Section 6.4.4, is to be recorded on the Rescue Medication paper diary.

After completing all assessments associated with a qualifying migraine attack (see Section 4.1) in the eDiary (through 48 hours postdose and before returning to the clinical site for DBT EOT Visit), if subjects have a migraine, then they may take permitted acute migraine medication (see Section 16.3, Appendix 3), as needed. If a subject takes a permitted acute migraine medication after the 48-hour postdose assessment and before returning to the study site for the DBT EOT Visit, this must be documented on the Concomitant Medication paper diary.

During the 45-day DBT Phase, subjects are not permitted to use blinded study drug for the treatment of a migraine attack of mild or no headache pain intensity. Subjects are only permitted to use non-study acute migraine medication to treat a migraine attack of mild or no headache pain intensity (see Section 16.3, Appendix 3). This dosing must be recorded on the Concomitant Medication paper diary.

5.5.2.2. Acute Migraine Medications in the OLE Phase

In the OLE Phase, subjects are to use open-label study drug as the first treatment of migraine attacks of moderate or severe headache pain intensity. After dosing with open-label study drug for the treatment of a moderate or severe migraine attack, no acute migraine medications are permitted through 2 hours postdose.

Subjects who do not experience relief of their migraine-related symptoms at 2 hours post-dosing with open-label study drug may take permitted acute migraine medication (see Section 16.3, Appendix 3) for the purposes of rescue, as needed and in accordance with the standard of care. In addition, if a moderate or severe migraine attack is relieved with study drug at 2 hours postdose but then returns to a moderate or severe headache pain intensity level between 2 and 24 hours (and prior to the completion of the 24-hour MQoL assessment within the eDiary), subjects may use permitted acute migraine medication as rescue. All dosing of rescue medication (permitted or exclusionary), as defined in Section 6.4.4, is to be recorded on the Rescue Medication paper diary.

During the 12-week OLE Phase, subjects are only permitted to use open-label study drug for the treatment of a migraine attack of moderate or severe headache pain intensity. Subjects are permitted to use non-study acute migraine medication (see Section 16.3, Appendix 3) for the primary management of migraines of mild or no headache pain intensity and/or as rescue medication. All dosing with concomitant (non-study) medication, including permitted and non-permitted acute migraine medications used for the primary treatment (non-rescue) of a migraine, must be recorded on the Concomitant Medication paper diary. All dosing with study medication throughout the course of the study (DBT and OLE Phases) must be recorded in the eDiary.

5.5.2.3. Migraine Medications in the Follow-up Phase

During the Follow-up Phase, subjects may take permitted acute migraine medication (see Section 16.3, Appendix 3) as needed. If a subject takes a permitted acute migraine medication at any time during the Follow-up Phase, this must be documented on the Concomitant Medication paper diary.

5.6. 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 subject's affirmation in the subject'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 subject to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the subject will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the subject or partner.
All WOCBP (see Section 16.5) must complete the pregnancy test schedule outlined in Table 1 and Table 2.

5.7. Deviation from Inclusion/ Exclusion Criteria

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
- Pharmacy Binder
- Investigational Product Manual
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant Medication paper diary (take home for subject)
- Rescue Medication paper diary (take home for subject)
- Investigator Brochure
- Interactive Web-based Response System (RTSM)

- 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 will be assigned to each subject)
    - Instructions for the eDiary device and access to the portal
- Laboratory kits and laboratory manual
    - Safety laboratory, plasma, urine, and serum instructions for 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 (MSQ) v 2.1 form
- The Migraine Interictal Burden Scale (MIBS) form
- 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: 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 the ICF through the Follow up Week 2 Visit. Unresolved SAEs at the time of the Follow-up Week 2 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 Follow-up Week 2 Visit when the event is believed to be related to study drug or other protocol-specific procedures.

Non-serious Adverse events must be reported from signing the ICF through the Follow-up Week 2 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 Table 1 and Table 2.

6.3.2. Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at scheduled visits as outlined in Table 1 and Table 2. A central ECG service will be utilized for all ECGs. The overread from the central ECG vendor is to be used to determine eligibility for the study. The investigator will determine whether any ECG abnormalities are clinically significant based on the overread from the central ECG vendor (see Appendix 6).

6.3.3. Physical Exam

Subjects will undergo a complete physical examination during the Screening Phase and targeted symptom-directed physical exam at all scheduled visits as outlined Table 1 and Table 2.

Physical examinations to include at minimum examination of heart, abdomen and lungs, with review of any other system to be guided by symptoms. The Physical exam will be performed by the Investigator or medically qualified delegate.

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 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 Table 1 and Table 2 for clinical laboratory evaluations. Unless otherwise noted approximately 15mL of venous blood will be obtained at each laboratory testing timepoint. This will include a pregnancy test if the subject is a woman that may be able to become pregnant. The result of the pregnancy test must be negative to qualify for the study. Additional diagnostic testing will be completed including blood tests to assess the general health, and wellness of the subject's kidneys and liver. At the screening visit, end of treatment visit (in the double blind phase), and at the 12 week visit in the open-label phase, the subject will have a venous blood sample (approximately 15mL collected at each of these visits). A chemistry panel and hematology panel to assess general health, a blood test to check for liver function and a pregnancy test (if applicable) will be done. During the Open Label extension -week 4 visit the subject will have blood work to check their liver function. This venous blood draw will be approximately 5mL. 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 appropriately documented.

1. **Clinical safety labs**:
    a. **Hematology**: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets.
    b. **Chemistry**: Sodium, potassium, chloride, bicarbonate, glucose, BUN (urea), serum creatinine
    c. **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 Study laboratory manual.
2. **Urine Drug Screen**: For drugs of abuse (Screening Visits only)
3. **eGFR** estimated using the MDRD formula (calculated at central lab) (Screening Visit only)
4. **FSH**: in female subjects to confirm postmenopausal status, if applicable (Screening Visit only)
5. **Reflex/ add-on tests:**
    a. If ALT or AST $\geq$ 3x ULN or total bilirubin $\geq$ 2x 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 required to evaluate eligibility, or in-study 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 (in the DBT Phase), as outlined in Table 1 and Table 2. 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.[10] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[11] 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 is to 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 (reference Table 1 and Table 2).

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 must 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 and paper questionnaires will be used in the DBT and OLE Phases of the study.

6.4.1. Pain

Subjects record their migraine headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe) in the eDiary at the time points indicated in Table 1 and Table 2.

6.4.2. Nausea, Phonophobia and Photophobia

During the DBT Phase, subjects will record the status (present or absent) of their migraine-associated symptoms of photophobia, phonophobia and nausea in the eDiary at the time points indicated in Table 1. In addition, subjects will record the intensity of the symptoms on

a 4-point numeric rating scale (none, mild, moderate, or severe) in the eDiary at the same time points. Subjects will also record their current MBS (nausea, phonophobia or photophobia) and aura status (present or absent) in the eDiary before taking study drug.

6.4.3. Functional Disability

During the DBT Phase, subjects will record their functional disability level using the functional disability scale, a 4-point numeric rating scale (normal, mild impairment, severe impairment, required bedrest), in the eDiary at the time points indicated in Table 1.

6.4.4. Rescue Medication

Rescue medication is recognized acute migraine concomitant medication (see Section 16.3, Appendix 3) used for the management of persistent migraine-related symptoms as per standard of care following dosing with study drug.

The use of rescue medication is NOT permitted within 2 hours of dosing study drug.

In the DBT Phase, rescue medication includes acute migraine medication (permitted or exclusionary) (see Section 16.3, Appendix 3) dosed after blinded study drug (rimegepant 75 mg ODT or matching placebo) **AND** prior to 48 hours postdose and completion of the 48-hour assessments within the eDiary.

In the OLE Phase, rescue medication includes acute migraine medication (permitted or exclusionary) (see Section 16.3, Appendix 3) dosed after open-label study drug (rimegepant 75 mg ODT) **AND** prior to 24 hours postdose and completion of the 24-hour assessments within the eDiary.

All non-study medications used as rescue (i.e., for the management of unresolved migraine-related symptoms following primary treatment with study medication [blinded or open-label]) (permitted or exclusionary) must be recorded on the Rescue Medication paper diary. All other non-study drugs should be recorded on the Concomitant Medication paper diary.

Study medication (blinded or open-label) is not permitted to be used as rescue medication.

All dosing of rescue medication (permitted or exclusionary), as defined above, is to be recorded on the Rescue Medication paper diary.

Permitted acute migraine medications are presented in Section 16.3, Appendix 3.

Non-permitted acute migraine medication include: opioids, ergotamines, lasmiditan, triptans, ubrogepant, barbiturates/barbiturate-containing products, and muscle relaxants (except baclofen) and other CGRP antagonists. A full list of restricted and exclusionary medications is located in Section 16.1 , Appendix 1*).*

6.4.5. Migraine Days

For the purposes of this study, a migraine day is defined as any calendar day during which the subject experiences a migraine (regardless of headache pain intensity). Additionally, if a subject uses a migraine-specific standard of care medication (i.e., triptans, ergotamine, ubrogepant, lasmiditan, etc.), the corresponding dosing day will be counted as a migraine day.

"Historical baseline" number of migraine days, for the purposes of inclusion and to determine the change in monthly migraine days, is the average number of days per month that subjects experience a migraine (of any headache pain intensity) over the 3 months prior to the Screening Visit, as reported by the subject and confirmed by the Investigator / supporting medical record. As above, if a subject uses a migraine-specific standard of care medication (i.e., triptans, ergotamine, ubrogepant, lasmiditan, etc.), the dosing day will automatically get counted as a migraine day

Of note, the use of triptans, ergotamine, ubrogepant, and lasmiditan is prohibited throughout the duration of the study. However, all dosing with acute migraine-specific medication (including non-permitted medications such as triptans, ergotamine, ubrogepant, and lasmiditan) must be reported within the appropriate (Concomitant or Rescue) medication paper diary (see Section 6.4.4), to help ensure accurate accounting of "migraine days".

6.4.6. 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.

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.[12] The MSQ will be completed on a paper form at the site at the Baseline and OLE Week 12/ EOT Visits.

6.5.2. Migraine Quality of Life Questionnaire (MQoL)

The Migraine Quality of Life Questionnaire (MQoL) version 3.0 is a 16-item instrument that has been validated in migraine sufferers to assess the effect of migraine and its treatment on health-related quality of life in the following 5 migraine-specific domains: work functioning, social functioning, energy/vitality, feelings and concerns, and migraine headache symptoms.[13] During the DBT Phase, subjects will complete the MQoL using the eDiary at 24 hours post-dose for a qualifying migraine attack (see Section 4.1) (see Table 1).

During the OLE Phase, subjects will complete the MQoL 24 hours postdose in the eDiary for each qualifying migraine attack until 5 MQoL Questionnaires are completed (see Section 4.1) (see Table 2).

6.5.3. 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.[14]

During the DBT and OLE Phase, subjects will complete the MIBS using a paper form at site.

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:

- 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 or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Pfizer.
- 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
    - Subjects in the DBT Phase will be monitored closely for compliance with the eDiary and may not be considered for the OLE Phase, based on PI and/or Sponsor discretion if compliance is low. Subjects who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.

- Subjects in the OLE Phase will be monitored closely for compliance with the eDiary.

- Please see Section 6.3.5 for guidance on subject discontinuation based on results from the C-SSRS.

- All subjects who discontinue the DBT Phase must comply with protocol specified DBT EOT procedures as outlined in Table 1. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (e.g., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

- All subjects who discontinue the OLE Phase are to comply with protocol-specified OLE Week 12/EOT Visit procedures as outlined in Table 2. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (e.g., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

- If a participant 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 participant 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 must be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she 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 subject finishes their final pre-specified study assessment or is otherwise permanently discontinued from the trial.

Early discontinuation of the study (in its entirety) 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 BHV3000-406 (C4951004) study and/or any other rimegepant safety data source, including other clinical trials, toxicological studies, or spontaneous reporting of real-world evidence.

Both Pfizer and the Principal Investigator at a specific study site reserve the right to terminate the study at a given study site at any time (see Section 14).

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 must 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 or matching placebo as directed.

- During the OLE Phase, investigational product (study drug/ study medication) is open-label rimegepant (BHV-3000) (PF-07899801) 75 mg ODT as directed.

Intervention Name	Rimegepant	Placebo
Type	drug	drug
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	Oral disintegrating tablet	Oral disintegrating tablet
Unit Dose Strength(s)	75 mg	placebo for 75-mg tablet
Dosage Level(s)	DBT phase: 75 mg (single dose) OLE phase: 75 mg per day, maximum 18 tablets per month	DBT phase : 0 mg (single dose) 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. Formulation

Rimegepant (BHV-3000) (PF-07899801) is formulated as 75mg oral disintegrating tablets for which there is a matching placebo.

7.1.4. Packaging, Shipment and Storage

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

For the DBT Phase, subjects will receive 1 tablet (ODT) of blinded rimegepant 75mg or matching placebo within a blister card, heat-sealed into a wallet.

For the OLE Phase, subjects will receive blister cards containing 8 tablets (75mg ODT) of open-label Rimegepant, heat-sealed into a wallet. Subjects will receive enough IP at each dispensation visit to ensure appropriate supply between visits.

7.1.5. Dose and Administration

7.1.5.1. Double-blind Treatment Phase

In the DBT Phase, subjects will be instructed to take 1 tablet (75 mg ODT) of blinded rimegepant or matching placebo when they have a migraine attack of moderate or severe headache pain intensity that they have not already treated with acute migraine medication (see Section 16.3 Appendix 3).

7.1.5.2. Open-label Extension Phase

In the OLE Phase, subjects will receive study drug in a blister card that is heat-sealed into a wallet. Subjects will be permitted to take up to 1 tablet of open-label study drug (75 mg ODT rimegepant) per calendar day as needed for acute treatment of migraine for a maximum of 18 doses per month (month is 28 days).

- ***During the OLE Phase***
    - Subjects should use open-label study drug as the first treatment of moderate or severe headache pain intensity that they have not already treated with acute migraine medication (see Section 16.3 Appendix 3).
    - Throughout the 12-week OLE Phase, subjects are not permitted to use open-label study drug for the treatment of a migraine of mild or no headache pain intensity or as a rescue medication. If subjects treat a migraine of mild intensity during the OLE Phase, they are to only use permitted non-study acute migraine medication. This dosing must be recorded on the Concomitant Medication paper diary.

7.1.6. 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.

At the Baseline Visit, eligible subjects will be randomized in a 1:1 ratio to rimegepant or placebo. Randomization will be stratified by history of clinically relevant CV disease (yes or no). In addition, randomization of subjects in the CV subgroup (“yes” category) will be capped at 15%. Subjects are to be categorized as “yes” if they meet the criteria for being in the CV subgroup (see Section 16.4, Appendix 4, Contraindication: Cardiovascular Events, Conditions, and Procedures). Otherwise, subjects are to be categorized as “no”.

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.

7.1.7. Selection and Timing of Dose and Administration

Study drug will be assigned via the RTSM system; the system will assign specific kit numbers for all blinded study drug to be dispensed to the subject. 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.

For the DBT Phase, rimegepant 75 mg ODT or placebo will be assigned to subjects at the Baseline (Randomization) Visit via the RTSM system. Subjects will be instructed to administer 1 ODT when they have a migraine that is moderate or severe in headache pain intensity.

For the OLE Phase, rimegepant 75 mg ODT will be dispensed at study dispensation visits. Subjects must completely finish study drug wallets before starting new wallets.

There are no dose adjustments in this study.

Subjects **must** be instructed that they CANNOT take more than 1 tablet of study drug daily during the study and no more than 18 tablets of rimegepant per month (28 days).

7.1.8. Dose Modifications

There will be no dose adjustments in this study.

7.2. 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 BHV3000-406 (C4951004) study is a double-blind placebo-controlled trial being conducted in accordance with Good Clinical Practice (GCP), International Conference on Harmonisation guidelines, Ethics Committee (EC) requirements, and all applicable regulations. Within the BHV3000-406 (C4951004) study, randomization and blinding 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 history of clinically relevant cardiovascular (CV) disease (yes or no; see Section 7.1.6 and 16.4, Appendix 4).

BHV3000-406 (C4951004) 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, as described in Section 9.4 Once the study is complete (i.e., after the last subject completes the Follow-up Week 2 Visit) or has otherwise permanently discontinued from the trial, 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.

7.3. Treatment Compliance

Responsible study personnel will dispense the study drug. Accountability and compliance verification must be documented in the subject's study records.

DBT Phase:

Subjects have to be counseled on the importance of taking the study drug as directed for a migraine attack of moderate or severe headache pain intensity, and not taking acute migraine medication before taking study drug (see Section 16.3, Appendix 3). A qualifying migraine attack is defined in Section 4.1. If the subject does not have a qualifying migraine attack within 45-days of the Baseline Visit, they are to return to the clinic for their DBT EOT Visit and return their study drug. If a subject does not have a qualifying migraine attack in the DBT Phase, they are not eligible for 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 subjects' enrollments into the OLE Phase.

OLE Phase:

- Treatment compliance and review of study drug doses through review of returned study drug must 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 are to inform subjects that involuntary termination from the study will occur in cases where non-compliance is identified.

- 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). Also, Investigators are to 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 are to obtain more information and explanation from subjects when there are study drug accountability discrepancies.

7.4. 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 the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) 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. Non-serious Adverse events and Serious Adverse events whether related or not related to study drug, must be collected after written informed consent to participate in the study.

If a specific diagnosis or syndrome is identified by the Investigator, this must 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, in accordance with the protocol. 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
  i. Potential study drug abuse (including cases of excessive non-compliance with study drug dosing instructions or subjects who discontinue treatment without returning study drug) is to be documented in the source record and reported as an AE or SAE, as appropriate. 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 are to obtain more information and explanation from subjects when there are study drug accountability discrepancies
  ii. 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 is to 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 Follow-up Week 2 Visit. Unresolved SAEs at the time of the Follow-up Week 2 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 Follow-up Week 2 Visit when the event is believed to be related to study drug or other protocol-specific procedures.

All SAEs must be followed to resolution or stabilization.

An SAE report must 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 must be specified in the narrative section of the SAE Report Form.

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).

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to Pfizer Drug Safety Unit (DSU) within 24 hours of learning of the event. Pfizer DSU will then immediately notify the Medical Monitor of the event. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB)/ EC as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the SAE information in the Electronic Data Capture (EDC) system (i.e., event term, start/stop dates, causality, severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to Pfizer DSU either via the Pfizer SAE Submission Assistant (PSSA) tool or as a written description 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 must 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 is to 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 EU 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 is to begin from signing the ICF through the Follow-up Week 2 Visit.

Non-serious adverse events are to 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 are to be captured on the non-serious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

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

c. 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.

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

- Cases of excess dosing (e.g., taking >1 tablet of study medication in a single day) are to 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, such event(s) are to be reported as an AE or SAE, respectively, of "Overdose".

- Asymptomatic dosing errors (e.g., accidentally taking >1 tablet of study drug in one calendar day) need only 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) must be immediately 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 subject 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 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 subject is found to be pregnant while receiving or after discontinuing study intervention.
- A male subject who is receiving or has discontinued study intervention inseminates a female partner.

- A female subject 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 subject/subject's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form and EDP supplemental 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 and EDP supplemental form or via PSSA. Since the exposure information does not pertain to the subject 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, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject 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 subject is found to be breastfeeding while receiving or after discontinuing study intervention.

- A female non subject 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 or PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the subject 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 subject 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.

8.5.4. 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.

8.5.5. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong subject, 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 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

*The CT SAE Report Form should only be used as a backup in the event PSSA is not operational

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

- 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**.

8.6. 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

It is anticipated that about 90% of the 300 subjects randomized to each treatment group will have a migraine in the allotted time period of the DBT Phase, resulting in approximately 270 subjects evaluable for efficacy in each treatment group. The sample size calculation is based on pooled results from Phase 3 single-dose migraine studies BHV3000-301, BHV3000-302, and BHV3000-303. Pooled response rates for migraine headache pain relief at 2 hours postdose were 57.9% for rimegepant 75 mg and 43.9% for placebo in these studies.

A total sample size of 540 evaluable subjects (270 per treatment group) will provide approximately 90% power for the primary endpoint of migraine headache pain relief at 2 hours postdose in the DBT Phase. This is based on a chi-square test with a 2-sided alpha level of 0.05 and assumes that the true response rates in the subjects unsuitable for triptan use will be equivalent to the overall pooled response rates above.

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 double-blind study drug (rimegepant or placebo).

- OL rimegepant safety: Subjects in the enrolled analysis set who take ≥ 1 dose of OL rimegepant (75 mg ODT).

- DBT efficacy: Subjects in the full analysis set who: (1) are randomized only once; (2) take double-blind study drug; (3) have a qualifying migraine attack at the time of double-blind study drug dosing (see Section 4.1); and (4) have double-blind postdose efficacy data (i.e., nonmissing headache pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level after taking double-blind study drug).

- OL rimegepant efficacy: Subjects in the DBT efficacy analysis set who take ≥1 dose of OL rimegepant (75 mg ODT).

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

In the DBT Phase, the intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication (see Section 6.4.4) will be classified as failures for all efficacy assessments that are reported at or after taking acute migraine medication as rescue.

The RM=F method will apply to all binary efficacy endpoints (including reliability of rimegepant effect) except the secondary endpoint of rescue medication use within 24 hours postdose.

In the OLE Phase, the intercurrent event of intervening OL rimegepant use will be handled using Intervening OL Rimegepant = Failure (IOL=F), i.e., for a given migraine attack, subjects who take intervening OL rimegepant will be classified as failures for an MQoL assessment that is reported at or after taking intervening OL rimegepant. The IOL=F method will apply only to the secondary endpoint of reliability of rimegepant effect during the OLE Phase.

9.3.1.1. Primary Endpoint

Rimegepant will be tested for superiority against placebo at a 2-sided alpha level of 0.05 for the primary endpoint of migraine headache pain relief at 2 hours postdose during the DBT Phase using the DBT efficacy analysis set. Treatment groups will be compared using Mantel-Haenszel risk estimation with stratification by history of clinically relevant CV disease (yes, no), to estimate the difference in percentages of subjects achieving the endpoint response criteria (rimegepant – placebo). The percentage of subjects achieving the endpoint response criteria will be presented with a 95% confidence interval (CI) by treatment group. The

stratified difference in percentages between treatment groups will be presented with a 95% CI and p-value.

Subjects with missing data at 2 hours postdose will be classified as failures (i.e., Non-completer = Failure; NC=F).

Sensitivity analyses will be described in the SAP.

9.3.1.2. Secondary Endpoints

The same statistics for key secondary endpoints during the DBT Phase (i.e., those listed in Section 3.2.1) will be presented as those for the primary endpoint.

For endpoints based on a single time point during the DBT Phase, such as migraine headache pain freedom at 2 hours postdose, subjects with missing data at a single time point will be classified as failures.

For endpoints based on multiple time points during the DBT Phase, such as sustained migraine headache pain relief from 2 to 48 hours postdose, subjects with missing data at (1) 2, 24, or 48 hours postdose, or (2) more than 1 time point from 3 to 8 hours postdose will also be classified as failures.

Reliability of rimegepant effect during the OLE Phase will be assessed using the percentages of subjects achieving response after (1) the single evaluable qualifying migraine attack in the DBT Phase (i.e., π_{DBT}) for the DBT efficacy analysis set randomized to rimegepant, and (2) each of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase (i.e., π_{OLEi}, $i = 1,\ldots,5$) for the OL rimegepant efficacy analysis set.

- Reliability of rimegepant effect during the OLE Phase is defined as percentages for ≥4 of the first 5 evaluable qualifying migraine attacks ≥23 hours apart in the OLE Phase being no more than 7% less than the percentage in the DBT Phase, i.e., $\pi_{DBT} - \pi_{OLEi} \leq 7\%$ for ≥4 of the 5 π_{OLEi}. The cutoff of 23 hours aligns with the lower bound of the 24-hour postdose analysis window for eDiary MQoL data collection.

- Response is defined as a category of "moderately better" or "very much better" for MQoL Question 16 (overall change in migraine symptoms since taking study medication) at 24 hours postdose.

- An evaluable qualifying migraine attack is defined as a qualifying migraine attack (see Section 4.1) with a nonmissing MQoL Question 16 category at 24 hours postdose.

The percentages of subjects achieving response will be presented descriptively using "n/N" and 95% CI by evaluable qualifying migraine attack.

A frequency table will display the number and percentage of subjects in each MQoL Question 16 category (plus additional categories for RM=F and IOL=F) by evaluable qualifying migraine attack.

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 2 safety analysis sets (DBT and OL rimegepant).

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; CV AEs by intensity; grade 3 to 4 laboratory test abnormalities; and LFT elevations based on fold changes above ULN, including ALT or AST >3x ULN concurrent (i.e., on the same laboratory test collection date) with total bilirubin >2x ULN.

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) available at the start of the study. 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 results 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 DBT EOT Visit; 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).

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 Committee

Not applicable.

This study will not make use of a Data Safety Monitoring Committee (DMC). The study medication 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.

10.5. Informed Consent

Investigators must ensure that subjects, or, 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 related to the clinical trial in which they are considering voluntary participation.

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.

10.7.1. Data sharing

Pfizer provides researchers secure access to subject 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. Subject 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.

Participants 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 include:

1. amount of study drug received and placed in storage area
2. label ID number or batch number or Kit number as specified for the protocol
3. amount dispensed to and returned from each subject
4. amount transferred to another area or site for dispensing or storage if applicable
5. amount of drug lost or wasted

6. amount destroyed at the site if applicable

7. amount returned to sponsor, if applicable

8. retain samples for bioavailability/bioequivalence, if applicable

9. record of dates and initials of personnel responsible for IMP 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) must 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 (or specified designee), 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 at a specific study site reserve the right to terminate the study at a given study 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 at the specified site and the reasons for its termination. The affected Principal Investigator will inform the IRB/IEC of the same. In terminating the study at a specific trial site, 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 subject 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, subjects will be assigned a single, subject 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 – 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.

- Paracetamol (acetaminophen) and paracetamol-containing products (e.g., paracetamol/aspirin/caffeine, etc.) for non-headache indications (See Section 5.5.2)
    - Paracetamol (acetaminophen) and paracetamol-containing products are permitted for the treatment of headache indications only
    - Paracetamol (acetaminophen) and paracetamol-containing products, for the treatment of headache indications, are permitted up to a maximum dose of 2,000 mg of paracetamol per calendar day, up to 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)
- Non-narcotic analgesics (e.g., NSAIDs, gabapentin, etc.) taken ≥ 15 days per month for non-headache indications
- Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, etc.)
- CGRP antagonists (e.g., oral or injectable: atogepant, non-study rimegepant, ubrogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, etc.)
- Botulinum toxin injection (Botox®)
- Ergotamine
- Lamotrigine
- Muscle relaxants (except baclofen)
- 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.)

- Atypical antipsychotics
  - Aripriprazole
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Risperidone

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

- Prohibited Concomitant Medications That May Result in DDI:

Drugs that are known strong or moderate inhibitors or inducers of CYP3A4, as well as drugs that inhibit P-gp transporters may impact the exposure 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
Moderate CYP3A4 Inhibitors	Amprenavir, aprepitant, casopitant, ciprofloxacin, conivaptan, diltiazem, dronedarone, erythromycin, fluconazole,	2 weeks or 5 half-lives whichever is longer

Drug Category	Drugs	Washout Period Requirement
	isavuconazole, lefamulin, letermovir, netupitant, ravuconazole, verapamil	
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
Strong P-gp Inhibitors	Amiodarone, clarithromycin, cyclosporine, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ritonavir, verapamil	2 weeks or 5 half-lives whichever is longer

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

All medications listed above are permitted to be used during the course of the trial, if administered as a topical agent or eye drops, and if applied in a routinely accepted manner.

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

Approved vaccinations including COVID-19 vaccines and treatments with local emergency use authorization are permitted throughout the study, unless otherwise specified.

16.2. APPENDIX 2 – Permitted Prophylactic Migraine Medication

- ACE inhibitors/Angiotensin receptor blockers: lisinopril, candesartan
- 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 blocker: flunarizine, lomerizine, nifedipine, nimodipine
- Vitamins: butterbur, feverfew, magnesium citrate, riboflavin (Vitamin B2)
- Other locally-approved, or otherwise recognized standard of care, medications used for the preventative treatment of migraine (e.g. methysergide, oxetrone, pizotifen, etc), unless otherwise specified.

Standard prophylactic migraine medication(s) listed above are only permitted under the following conditions:

- Drug dosing (frequency and strength) has been stable for at least 3 months prior to the screening visit
- Drug is being taken consistently (at regular dosing intervals; e.g., daily, etc.)
- Drug dosing (frequency and strength) remains unchanged throughout the course of the study (e.g., Screening, DBT, or OLE Phases)
    - Discontinuation or dose-reduction of standard prophylactic migraine medication is permitted for valid and documented safety reasons only
- Drug is NOT newly initiated at any time during the course of the study (e.g., Screening, DBT, or OLE Phases)

16.3. APPENDIX 3 – Permitted Acute Migraine (Rescue) Medications

- Simple analgesics:
    - Non-steroidal anti-inflammatory drug, including, but not limited to:
        - Aspirin, Ibuprofen, Naproxen
        - Low dose aspirin use for cardiovascular prophylaxis is permitted during the course of this study**.**
        - Paracetamol (acetaminophen) and paracetamol-containing products (e.g., paracetamol/aspirin/caffeine, etc.)
            - Paracetamol (acetaminophen) and paracetamol-containing products, for the treatment of headache indications, are permitted up to a maximum dose of 2,000 mg of paracetamol per calendar day, up to 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)
    - Antiemetics, including but not limited to:
        - Metoclopramide
        - Promethazine
    - Other:
        - Baclofen
        - Other approved pharmacological treatment with established efficacy in the acute treatment of migraine, including locally-recognized standard of care, unless otherwise specified (See Section 16.2, Appendix 2)

These are the only acute migraine medications allowed for rescue treatment at ≥2 hours postdose study drug and after completing the 2-hour eDiary entry.

16.4. APPENDIX 4 – Triptan-unsuitable Criteria

Triptan-unsuitable - Documented failure (due to lack of efficacy or prior intolerance) on at least 2 triptan medications, or documented contraindication to the use of triptans

- **Lack of Efficacy**[a]:
- **Prior Intolerance**[b], including, but not limited to:
    - Prior triptan-associated overuse headache
    - Arrhythmia associated to prior triptan use
    - Chest/throat/neck/jaw pain, tightness, pressure, or heaviness associated with prior triptan use
    - Gastrointestinal ischemia or peripheral vasospastic reaction associated with prior triptan use
    - Serotonin syndrome associated with prior triptan use
- **Contraindication**[c], including but not limited to:
    - Documented hypersensitivity to triptans
    - History of cardiovascular event, condition, or procedure[d]
    - Uncontrolled hypertension for the purposes of the -406 study, “uncontrolled hypertension” is being defined as: "an active diagnosis of uncontrolled hypertension that is documented within the medical record and, in the opinion of the Principal Investigator, an indication for not using triptan medications.

NOTES

a Lack of Efficacy:

- When previous treatment with a triptan medication(s) has yielded no, unsatisfactory, or inconsistent therapeutic effect (e.g., recurrent, incomplete relief of migraine-related symptoms [including pain, nausea, photophobia, phonophobia, etc.] at 2 hours postdose, non-sustained relief of migraine-related symptoms through 24 hours postdose, etc.), after repeated dosing (≥2 attempts) at recommended dose levels, as determined by the managing 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 triptan 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., 2-hour pain freedom, sustained pain freedom, freedom from disability, freedom from associated symptoms) 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.

b Prior Intolerance:

- When treatment with a triptan medication(s) has been previously interrupted because of an adverse event(s) that made continuation of the drug intolerable for the individual, as determined by the managing 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 triptan but there is no documentation on the lack of 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 triptan use and the reasons the subject 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.

c Contraindication:

- When triptan medications are contraindicated, in accordance with locally recognized labelling, practice guidelines, and/or the current standard of care, as determined by the managing 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 presence of a triptan contraindication, but there is insufficient documentation on the details of this contraindication, a supplemental interview with the subject and documentation with date and time will suffice.

- d **Cardiovascular Events, Conditions, and Procedures -** Cardiovascular events, conditions, and procedures considered contraindications to the use of triptan medications. Within the current protocol, eligible subjects with any of the following events, conditions, or procedures (as confirmed by information within the medical record) will be included within the study's "CV Subgroup" for the purposes of stratification and subgroup analysis

    - Events:

        - Myocardial infarction (MI)

- Cerebrovascular accident (CVA; e.g., Intracerebral hemorrhage, Intracranial hemorrhage, Subarachnoid hemorrhage, Ischemic stroke, etc.)
- Prior cardiac arrest
- Transient ischemic attack(s) (TIA)

- Conditions:
  - Angina pectoris (myocardial ischemia)
  - Cardiac conduction disorder (e.g., Wolff-Parkinson-White [WPW], other life-threatening arrhythmia/heart block)
  - Coronary artery vasospasm (Prinzmetal's angina)
  - Ischemic coronary artery disease (CAD)
  - Ischemic bowel disease
  - Peripheral artery disease (including claudication)

- Procedures:
  - Angioplasty (with or without stent placement)
  - Coronary artery bypass grafting (CABG)
  - Carotid endarterectomy

16.5. Appendix 5: Contraceptive and Barrier Guidance

16.5.1. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 3 (Age and Sex; Section 5.2) and specify the reproductive requirements for including female participants. Refer to Section 16.5.3 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 16.5.2).

  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.

16.5.2. 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.

16.5.3. 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

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

16.6. APPENDIX 6 - 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, symptomfree 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, symptomfree 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.

16.7. Appendix 7: Country-Specific Requirements

16.7.1. France

Contrat Unique

1. Study Intervention

   No participants or third-party payers will be charged for study intervention.

2. Urgent Safety Measures

   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 ICH GCP that the investigator becomes aware of.

3. Termination Rights

   Pfizer retains the right to discontinue development of BHV-3000 (PF-07899801) at any time.

4. Exclusion Criteria

   - Persons deprived of their liberty by a judicial or administrative decision,
   - Adults subject to a legal protection measure (guardianship, curatorship, and safeguard of justice),
   - Persons not affiliated to a social security scheme or equivalent

   Covered by Articles 1121-6, 1121-8 and L1122-2 of the Public Health Code.

The investigator agrees to abide by the ethical principles set forth in the World Health Organization's *Guiding Principles for Human Cell, Tissue and Organ Transplantation* (WHA63.22) with regard to the study.

16.7.2. Germany

1. Inclusion criteria

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).

2. Exclusion criteria

Persons deprived of their liberty by a judicial or administrative decision.

Adults subject to a legal protection measure (guardianship, curatorship, and safeguard of justice).

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

16.7.3. 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 8– Protocol Amendment History

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	14-July-2022
Version 2.0	Updated the wording and provided further details in some objectives in Sections 2.2.1, 2.2.2 and 2.3 to improve readability and understanding of the objectives Clarified that the RM=F method will apply to all binary efficacy endpoints in Sections 3 and 9.3.1 Updated the wording and provided further details in some endpoints in Sections 3.2.1 and 3.2.2 to improve readability and understanding of the secondary endpoints Updated Section 4.1, Study Design and Duration to define the end of study. Further clarified the pregnancy testing requirements for WOCBP in the DBT (Section 4.2, Table 1) and OLE (Section 4.2, Table 2) Phases and throughout the study, Section 6.3.4.2 Removed footnote 2 from Section 4.3, Table 2 (OLE Phase and Follow-up Phase Schedule of Assessments). All dosing of study medication (both blinded and open-label) is to be recorded in the eDiary Clarified that chronic Hepatitis C viral infection will be determined at Screening by the combination of a positive HCV antibody plus positive HCV RNA, Section 5.3 (2q) Clarified low dose aspirin use for cardiovascular prophylaxis is permitted during the course of this study, Sections 5.3 (6c) and 17.4 Appendix 4 Clarified that exposure to investigational biological agents (including monoclonal	20-Oct-2022

Version Number	Brief Description Summary of Changes	Date
	antibodies) is prohibited within 6 months (24 weeks) of the Screening Visit, Section 5.3 (7d) Added failure to complete Baseline Visit as an exclusion criterion, Section 5.3 (7i) 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 (7j) Further emphasized: subjects are permitted to use non-study acute migraine medication for the primary treatment of migraine headaches of mild pain intensity (Sections 5.5.2 and 7.1.7); that study medication is not to be used as rescue medication (Section 7.1.7); and the proper recording of all dosing with concomitant (non-study) medication, both rescue and non-rescue (on Rescue and Concomitant Medication paper diaries, respectively, Sections 5.4 and 6.4.4) Updated the definition of WOCBP (women of childbearing potential) (Section 5.6) and contraception requirements (Section 5.2 [4b] and Section 5.3 [4a]) to more closely align with CTFG (Clinical Trials Facilitation and Coordination Group) Guidance Removed routine collection of creatine kinase blood samples due to lack of safety signal across the rimegepant clinical development program, Section 6.3.4.1 Clarified, during the OLE Phase, rescue medication is non-study acute migraine medication dosed after open-label study medication and prior to 24 hours postdose and completion of the 24-hour assessments within the eDiary, and clarified proper recording of rescue and non-rescue concomitant (non-study) medications (in the Rescue and Concomitant	

Version Number	Brief Description Summary of Changes	Date
	Medication paper diaries, respectively), Section 6.4.4 Added Section 6.4.6 to clearly define what constitutes a Headache Day in the current study 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 Provided further details about the definition and assessment of reliability of rimegepant effect during the OLE Phase in Section 9.3.1.2 Updated Sections 16 and 17.1 with updated medical monitor contact information, and signatory section. Reordered text and provided further detail to improve readability and understanding on proper study conduct. Made updates to list of prohibited medications to comply with current understanding of the rimgepant DDI profile; provided further detail on the restrictions of acetaminophen use during the study, Section 17.2 Appendix 2 Reordered text and provided further detail to improve readability and understanding on proper study conduct. Added recognized herbals and vitamins to the list of permitted prophylactic migraine medication; Provided further detail on the restrictions of permitted prophylactic medication use during the study, Section 17.3 Appendix 3 Provided further detail on the restrictions of paracetamol (acetaminophen) use during the study, Section 17.4 Appendix 4	

Version Number	Brief Description Summary of Changes	Date
	Re-arranged text, corrected typographical errors, added detail, and addressed potential inconsistencies in messaging throughout the document to improve readability and intended study conduct Added section ANNEX 1., Benefit Risk Assessment	
Version 3.0	The following modifications have been made to study exclusion criteria: • Added a provision which excludes individuals who experience 7 or more non-migraine headache days per month, on-average, across the 3-months prior to the Screening Visit, in accordance with current CHMP Guidelines on Clinical Investigation of Medicinal Products for the Treatment of Migraine, Section 5.3 (Exclusion Criteria 1, Target Disease Exclusion; criterion 1d) • Removed exclusion criteria related to the following: History of gallstones or cholecystectomy; History or diagnosis of Gilbert's Syndrome or any other active hepatic or biliary disorder); History of HIV disease; and History of acute hepatitis within 6 months of Screening or chronic hepatitis [including nonalcoholic steatohepatitis]. Restrictions were considered unwarranted per rimegepant labelling, Section 5.3 (Exclusion Criteria 2, History and Concurrent Diseases) • Modified exclusion criteria related to: Body Mass Index (BMI) (increased exclusionary cutoff from ≥ 33 kg/m^2 to ≥ 35 kg/m^2). Degree of restriction was considered unwarranted per rimegepant labelling, Section 5.3 (Exclusion Criteria 2, History and Concurrent Diseases; criterion 2b) • Modified exclusion 3a: Added Rimegepant is contraindicated in	6-Apr-2023

Version Number	Brief Description Summary of Changes	Date
	subjects with a hypersensitivity to any component of its formulation. • Modified exclusion criteria related to: Serum bilirubin (increased exclusionary cutoff from >1x ULN to >1.5x ULN); Serum transaminases (increased exclusionary cutoff from >1x ULN to >1.5x ULN); and HbA1c (increased exclusionary cutoff from ≥ 6.5% to ≥7.5%). Degrees of restrictions were considered unwarranted per rimegepant labelling, Section 5.3 (Exclusion Criteria 5, ECG and Laboratory Test Findings; criteria 5c, 5d, and 5g, respectively) • Inclusion Criterion 5 in Section 5.2 (Inclusion Criteria) was added. It states, Subjects must be able to fully comply with the prohibitions and restrictions on the concomitant use of medications and therapies (including moderate to strong inhibitors and inducers of the CYP3A4 enzyme and strong inhibitors of the P-gp transporter) detailed in Section 17.2, Appendix 2. Updated Section 4.3.3.2 to clarify that Day 1 of the OLE Phase is the same day as the DBT EOT Visit. Sites are to instruct subjects to refrain from dosing with open-label study drug until they have received a phone call from the site confirming their eligibility to enter the OLE Phase. Clarified that hysterectomy and bilateral salpingectomy plus bilateral oophorectomy are considered sterilizing procedures with regards to the definition of Women of Childbearing Potential and contraceptive requirements during participation in the trial, Section 5.6 (Women of Childbearing Potential)	

Version Number	Brief Description Summary of Changes	Date
	Clarifying text was added with regards to complete abstinence and associated contraception requirements of subjects in the clinical trial, Section 5.6 (Women of Childbearing Potential) Clarified that bilateral tubal ligation is an acceptable highly effective contraception for Women of Childbearing Potential, Section 5.6 (Women of Childbearing Potential) Provided clarifying text regarding reporting of Serious Adverse Events, Section 6.3 (Safety Assessments) and Section 8.1.2 (Collection and Reporting Serious Adverse Events) Modified the title of Section 6.6 from "Early Discontinuation from the Study" to "Subject Early Discontinuation Criteria", to more accurately reflect key messaging in that respective section, Section 6.6 (Subject Early Discontinuation Criteria) Provided further detail regarding conditions determining the termination of the overall trial, including unacceptable shift in benefit-risk, in accordance with ICH Guideline E6 (R2), Section 6.7 (Study Early Discontinuation Criteria) Provided clarifying text regarding strategies used to minimize bias in the conduct of the trial, in accordance with ICH E6 (R2), Section 7.2 (Blinding and Unblinding) Provided clarifying text regarding the definition of treatment non-compliance by subjects and corrective actions to be implemented in response subject non-compliance, Section 6.6 (Subject Early Discontinuation Criteria) and 7.3 (Treatment Compliance)	

Version Number	Brief Description Summary of Changes	Date
	Corrected typographical errors and provided detail to proactively address potential inconsistencies in messaging throughout the document in an effort to improve readability and intended study conduct Updated wording for blood sampling in section 6.3.4.1	
Version 4.0	**Substantial Modification(s)** Referenced study number BHV3000-406 to C4951004 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 #3.a -removed upper age limit Addition of an exclusion criterion #7.j “Subject unable to complete eDiary independently in the opinion of the Investigator.” Exclusion criterion #2.c for “History of hematologic or solid malignancy diagnosis within 5 years prior to screening” deleted 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.c for liver enzymes (ALT and AST) changed to >2 x ULN (instead >1.5xULN)	07-Aug-2023

Version Number	Brief Description Summary of Changes	Date
	Exclusion criteria #5.i 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/1.73m^2 Exclusion criterion #6c Changed the term onabotulinumtoxinA to botulinum toxin injection Guidance relative to Women of Childbearing Potential replaced with Contraception section and Appendix 5 Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members. Added exclusion criterion #7a, b, and c for France only Changed term non-migraine to non-headache and migraine to headache. Potential DILI cases identification and management update 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. **Non-substantial Modification(s)**	

Version Number	Brief Description Summary of Changes	Date
	Updated Serious Adverse Event (SAE) reporting destination and electronic reporting system administrative changes and clarifications Updated Overdose section Section 15 “Confidentiality” renamed to “Data Protection” and updated and updated text for Data Protection. Addition of exploratory objective for pain relapse in the DBT phase Addition of 2 exploratory objectives for subgroups Updated to include US, UK, EU reference and Investigator’s Brochure reference. Clarified study drug destruction Updated Non-Investigational Product section to Concomitant Therapy Removal of “humidity” from environmental condition requirements Increased the daily dosage of Paracetamol (acetaminophen) and paracetamol-containing products from 1000mg/day to 2000mg/day Clarified definition of Qualifying Migraine and simplified subsequent references in protocol Removed Clinical Protocol Approval Form Removed PI declaration page Clarified definition of analysis sets Added reference to quality tolerance limits Removed Phase I study exception. Removed statement regarding Principal Investigator and	

Version Number	Brief Description Summary of Changes	Date
	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 1 updated to add line item for eDiary completion and re-training at the EOT visit for subjects eligible for the OLE phase for clarity Clarified the blood volumes in mL from tablespoons and teaspoons Addressed typographical errors Clarified the protocol restriction around the use of acetaminophen and paracetamol-containing products for non-migraine indications during the study Clarified how medical documentation for previous failed treatment is to be recorded. Corrections to the statistical methodology Stated that there are 2 planned database locks and final CSRs, and no interim analysis is planned	

Version Number	Brief Description Summary of Changes	Date
	Re-screening policy updated 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 Minor grammatical and spelling corrections; Section renumbering Schedule of Activities DBT Phase Table 1 – added option for urine pregnancy test in addition to serum at EOT visit Clarification note added to Schedule of Activities DBT Phase Table -Under Physical Exam; If subject is eligible to enroll into the OLE Phase, a physical exam at DBT EOT is not required Clarification note added to Schedule of Activities DBT Phase Table under ECG; If subject is eligible to enroll into the OLE Phase, an ECG at DBT EOT is not required	
Version 5.0	Inclusion criterion #5 “Written informed consent” added Exclusion criteria #7.a and 7.b modified to include Germany Exclusion #7.m “Subjects detained for treatment of either a psychiatric or physical illness” added Appendix 7 modified to include Germany-specific country requirement	06 Feb 2024

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