DRUG:	BHV-3000 (PF-07899801) (rimegepant)
STUDY NUMBER(S):	BHV3000-313 (C4951022)
PROTOCOL TITLE:	Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Rimegepant for the Acute Treatment of Migraine in Japanese Subjects
IND NUMBER:	N/A
EudraCT NUMBER: (if applicable)	N/A
ClinicalTrials.gov ID:	NCT05399459
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	04-Apr-2022
VERSION NUMBER:	4.0
VERSION DATE:	03-Aug-2023
BRIEF TITLE:	Efficacy and Safety Study of Rimegepant for the Acute Treatment of Migraine in Japanese Subjects (Japan Only)

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).

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment Version 4.0 (03 August 2023)

Overall Rationale for the Amendment: Change in the statistical method; change in sponsorship from Biohaven to Pfizer

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Changed hypothesis testing strategy. Formal hypothesis testing will be conducted for rimegepant 75 mg at a 2-sided alpha level of 0.05. No formal hypothesis testing will be conducted for rimegepant 25 mg.	Considering the overall clinical development strategy on rimegepant in Japan, formal hypothesis testing for rimegepant 25 mg compared with placebo is confirmed not necessary in this study.	9.3.2 Primary Endpoint(s) 9.3.4 Multiplicity Correction
Referenced study number BHV3000-313 to C4951022 and compound name BHV-3000 to PF-07899801 to reflect identification changes by sponsor.	Reflects change in sponsorship protocol and compound identification numbers.	Headers Title page 1.1 Background
Changed sponsor name.	Reflects transfer of sponsorship from Biohaven Pharmaceuticals Holding Company Limited to Pfizer Inc.	Throughout the document
Removed the exclusion criterion for patients with HIV disease.	Aligned with rimegepant prescribing information where there is no exclusion for use in patients with HIV.	5.3 Exclusion Criteria #2a)
Changed exclusion criterion for liver enzymes (ALT and AST) to >2.0 × ULN.	Aligned with rimegepant prescribing information where there is no exclusion for subjects with mild hepatic disease.	5.3 Exclusion Criteria #5g)
Removed specific exclusionary ECG criteria	Allowed for investigator opinion on exclusionary ECG findings.	5.3 Exclusion Criteria #5d), 5e)
Changed GFR from 40 to 30 ml/min/1.73m^2.	Allowed for subjects with moderate renal impairment to be included in the trial consistent with the prescribing information.	5.3 Exclusion Criteria #5a)
Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members.	Aligned with Pfizer protocol template.	5.3 Exclusion Criteria #7h)
Removed exclusion criterion for “m. Hematologic or solid	Exclusion criterion already covered in another Exclusion criterion (#2j) and to align with	5.3 Exclusion Criteria #2m)

malignancy diagnosis within 5 years prior to screening".	rimegepant prescribing information where there is no contraindication for use.	
Updated exclusion criterion for illicit drug use. Updated prohibited and restricted concomitant medications accordingly.	Prohibited illicit drug use meeting DSM-V criteria for substance use disorder within 6 months of screening.	5.3 Exclusion Criteria #2l) 5.4 Prohibited and Restricted Concomitant Medications #13
Removed exclusion criterion for "l. positive drug screen for drugs of abuse".	Exclusion criterion already covered in another Exclusion criterion (#2k) and to align with rimegepant prescribing information where there is no contraindication for use.	5.3 Exclusion Criteria #2l)
Allowed for rescreening of subjects due to prior failed eligibility criteria.	Allowed for rescreening of subjects who previously were screen failed for an amended exclusionary criterion.	4.3.1 Screening Phase (3-28 days)
Allowed dose of aspirin up to 100 mg daily for cardiovascular prophylaxis.	Aligned with ex-US dosing for low dose aspirin prophylaxis.	5.4 Prohibited and Restricted Concomitant Medications #22
Removed tacrolimus from the Strong CYP3A4 inhibitors list. Removed grapefruit juice from the Moderate CYP3A4 inhibitors list.	Aligned with nonclinical and clinical drug-drug interaction (DDI) information available on rimegepant.	16.1 Appendix 1 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)
Updated potential DILI cases identification and management. Updated the requirement of laboratory testing accordingly.	Aligned with Pfizer protocol template and the latest exclusion criteria.	6.2.4.1. Laboratory Testing 8.4 Potential Drug Induced Liver Injury (DILI)
Added Appendix for ECG findings of Potential Clinical Concern.	Aligned with Pfizer protocol template.	16.2 Appendix 2 – ECG Findings of Potential Clinical Concern
Clarified definition of Sponsor's Medically Qualified Individual.	Aligned with Pfizer protocol template.	10.7 Sponsor's Medically Qualified Individual
Non-substantial Modification(s)		
Clarified definition of analysis sets.	Aligned with Statistical Analysis Plan.	9.2 Analysis Set
Clarified/corrected statistical methods.	Provided corrections or clarifications. Aligned with Statistical Analysis Plan.	9.3.1 Demographic and Baseline Characteristics 9.3.2 Primary Endpoint(s) 9.3.3 Secondary Endpoint(s)
Updated the analysis of safety.	Aligned with Statistical Analysis Plan.	9.3.5 Analysis of Safety
Clarified/corrected the objectives and endpoints.	Clarifications and corrections to provide more appropriate wordings. Aligned with Statistical Analysis Plan.	2. Study Objectives 3. Study Endpoints

Changed End of Treatment Visit window to +4 days.	Allowed flexibility.	4.3. Schedule of Assessments 4.3.4. End of Treatment
Updated Serious Adverse Event (SAE) reporting destination and electronic reporting system administrative changes and clarifications.	Incorporation of non-substantial changes described in previous PACL dated 28Apr2023.	8.1.2 Collection and Reporting Serious Adverse Events 8.5.1. Exposure During Pregnancy
Updated a summary of the clinical data.	Aligned with the most current Investigator Brochure.	1.3. Product Development Background
Added benefit risk assessment.	Aligned with Pfizer protocol template.	1.4 Benefit Risk Assessment
Updated text for Data Protection.	Aligned with Pfizer protocol template.	15 Data Protection
Deleted paper adverse event (AE) logs.	Clerical correction.	6.1. Study Materials
Updated study summary (Synopsis).	Aligned with Pfizer protocol template.	Study Summary (Synopsis)
Removed Clinical Protocol Approval Form.	Aligned with Pfizer protocol template.	Clinical Protocol Approval Form
Removed PI declaration page.	Aligned with Pfizer protocol template.	Confidentiality and Investigator Statement
Removed Phase I study exception. Removed statement regarding Principal Investigator and the Sponsor's representative signatory. Added Sponsor's regulatory and ethics responsibilities.	Aligned with Pfizer protocol template.	10.1 Good Clinical Practice
Added Pfizer standard text for Dissemination of Clinical Study Data.	Aligned with Pfizer protocol template.	10.6 Dissemination of Clinical Study Data
Updated the publication policy.	Updated in alignment with the change in sponsorship.	13. Publications Policy
Added AE information on lack of efficacy and medication errors.	Aligned with Pfizer protocol template.	8.6 Lack of Efficacy 8.7 Medication Errors
Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure.	Aligned with Pfizer protocol template.	8.5 Environmental exposure, Exposure during Pregnancy or Breastfeeding, and Occupational exposure
Updated Section 8.3. Overdose.	Overdose is reportable to Pfizer Safety only when associated with an SAE.	8.3. Overdose
Moved prior Protocol Amendment Summary of Changes to Appendix.	Editorial.	16.3 Appendix 3 Protocol Amendment History
Updated List of abbreviations.	Editorial.	List of Abbreviations

Removed Section 7.1.2 Concomitant Therapy.	Editorial changes.	7.1.2 Concomitant Therapy
Removed notified IRB/IEC within 5 days.	Amended to allow for immediate action to be implemented.	12 Amendments
Corrected inconsistencies and typographical errors throughout the protocol.	Corrections to provide clarity and consistency throughout the protocol.	Applicable sections of the protocol

STUDY SUMMARY (SYNOPSIS)

Protocol Title: Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Rimegepant for the Acute Treatment of Migraine in Japanese Subjects

Brief Title: Efficacy and Safety Study of Rimegepant for the Acute Treatment of Migraine in Japanese Subjects (Japan Only)

Regulatory Agency Identification Number(s):

US IND Number:	NA
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05399459
Pediatric Investigational Plan Number:	NA
Protocol Number:	BHV3000-313 (C4951022) Version 4.0
Phase:	2/3

Rationale: Rimegepant is being developed for the treatment of migraine. Effectiveness as an acute treatment for migraine was demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study that compared rimegepant at doses of 10, 25, 75, 150, 300 and 600 mg to placebo (CN170003 study). In this study, rimegepant at 75 mg showed efficacy on all 4 traditional endpoints: pain, nausea, photophobia and phonophobia. The primary endpoint was pain freedom at 2 hours post-dose. In this study the 10 and 25 mg doses did not separate from placebo. The 75, 150 and 300 mg doses were significantly better than placebo and showed similar efficacy. The efficacy of the 600 mg dose was somewhat less than that of the 75, 150 and 300 mg doses, but was still better than that of placebo.

In the United States, the 75 mg dose was selected as the optimal dose and tested against placebo in 3 pivotal studies for the acute treatment of migraine. The efficacy of the 75 mg dose was confirmed in all 3 studies.

This study is being conducted to determine the appropriate dose of rimegepant in Japanese subjects, as well as to evaluate the efficacy, safety, and tolerability of rimegepant in Japanese subjects for the acute treatment of migraine.

Since the optimal dose in the US has been demonstrated to be 75 mg and the 25 mg dose is included in the study to permit an assessment of the dose response for rimegepant in Japanese subjects, formal hypothesis testing compared with placebo will be restricted to rimegepant 75 mg arm.

Primary Objectives:

To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese subjects.

Secondary Objectives:

- To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese subjects on the following secondary endpoints:
  - Pain relief at 2 hours post-dose.
  - Freedom from the Most Bothersome Symptom (MBS) associated with migraine at 2 hours post-dose.
  - The ability to function normally at 2 hours post-dose
  - Sustained pain relief from 2 to 24 hours post-dose
  - Rescue medication use within 24 hours of initial treatment
  - Sustained pain relief from 2 to 48 hours post-dose
  - Freedom from photophobia at 2 hours post-dose
  - Sustained pain freedom from 2 to 24 hours post-dose
  - Freedom from phonophobia at 2 hours post-dose
  - Sustained pain freedom from 2 to 48 hours post-dose
  - Freedom from nausea at 2 hours post-dose
  - Pain relapse from 2 to 48 hours post-dose
- To compare the efficacy of rimegepant 25 mg with placebo in the acute treatment of migraine in Japanese subjects on the same efficacy endpoints
- To evaluate the tolerability and safety of rimegepant 75 mg and 25 mg in the acute treatment of migraine

Primary Endpoint:

Pain freedom at 2 hours post-dose will be assessed using the percentage of subjects that report no pain at 2 hours post-dose. Pain will be measured on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

Secondary Endpoints:

- Pain relief at 2 hours post-dose will be assessed using the percentage of subjects that report a pain intensity level of none or mild at 2 hours post-dose.

- Freedom from the most bothersome symptom (MBS) at 2 hours post-dose will be assessed using the percentage of subjects with an MBS reported before dosing that is absent at 2 hours post-dose. The MBS before dosing will be reported as nausea, phonophobia, or photophobia. Symptom status will be reported post-dose as present or absent for each symptom (nausea, phonophobia, and photophobia).

- Ability to function normally at 2 hours post-dose will be assessed using the percentage of subjects with a functional disability level of normal at 2 hours post-dose 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), and functional disability will be defined as mildly impaired, severely impaired, or requires bedrest.

- Sustained pain relief from 2 to 24 hours post-dose will be assessed using the percentage of subjects with pain intensities of none or mild from 2 to 24 hours post-dose.

- Rescue medication use within 24 hours post-dose will be assessed using the percentage of subjects that take rescue medication within 24 hours after administration of study medication (rimegepant or placebo).

- Sustained pain relief from 2 to 48 hours post-dose will be assessed using the percentage of subjects with pain intensities of none or mild at all time points from 2 to 48 hours post-dose.

- Freedom from photophobia at 2 hours post-dose will be assessed using the percentage of subjects with photophobia absent at 2 hours post-dose in the subset of subjects with photophobia present at the time of dosing.

- Sustained pain freedom from 2 to 24 hours post-dose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 24 hours post-dose.

- Freedom from phonophobia at 2 hours post-dose will be assessed using the percentage of subjects with phonophobia absent at 2 hours post-dose in the subset of subjects with phonophobia present at the time of dosing.

- Sustained pain freedom from 2 to 48 hours post-dose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 48 hours post-dose.

- Freedom from nausea at 2 hours post-dose will be assessed using the percentage of subjects with nausea absent at 2 hours post-dose in the subset of subjects with nausea present at the time of dosing.

- Pain relapse from 2 to 48 hours post-dose will be assessed using the percentage of subjects with a pain intensity of mild, moderate, or severe at any time point after 2 hours

through 48 hours post-dose in the subset of subjects with pain freedom at 2 hours post-dose.

- Tolerability and safety will be evaluated by the percentage of subjects with AEs by intensity, SAEs, and grade 3 to 4 laboratory test abnormalities.

Overall Design:

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant 75 mg as compared to placebo in the treatment of moderate or severe migraine in Japanese subjects. The investigational product will be rimegepant at a 25 mg or 75 mg dose level or a matching placebo. The 25 mg rimegepant dose is included in the study to permit an assessment of the dose response for rimegepant in Japanese subjects.

A subject whose usual migraine attack results in headache pain of moderate or severe intensity and who is otherwise found acceptable for entry into this trial based on inclusion and exclusion criteria will first participate in the screening phase (3 – 28 day period). Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.

After randomization, the subject will be dispensed a single dose of the double-blind study medication that will be taken at the time a migraine attack reaches moderate or severe pain intensity (described below) on the numeric rating scale (NRS) as indicated in the electronic diary (eDiary). The subject will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe pain intensity and only after they have identified their most bothersome migraine-associated symptom (phonophobia, photophobia or nausea). The subject will complete an eDiary for up to 48 hours after taking study medication. The subject will contact the study center immediately if they should experience any AEs. Subjects will record efficacy data in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to and at the time of taking study medication. The subject should record all headache intensity leading up to dosing, but should not dose with study medication until the headache reaches moderate or severe pain intensity. Headache severity will be recorded using a 4-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (4-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Subjects who experience reduction of headache pain to a mild intensity or pain free intensity level will be considered to have achieved pain relief. The subject who does not experience relief of their migraine headache at the end of 2 hours after dosing with study drug (and after the 2-hour assessments have been completed on the eDiary) will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen (up to 2000 mg/day), naproxen (or any other type of nonsteroidal anti-inflammatory drug (NSAID)), antiemetics (e.g., metoclopramide), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study drug. If at the end

of 48-hours after dosing with study drug (but before the End of Treatment Visit) subjects are in need of migraine relief, they may take their prescribed standard of care medications, including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed during this study. Similarly, if the migraine is relieved by study drug at 2 hours after dosing but then recurs to a moderate or severe intensity level between 2 and 48 hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete their eDiary for up to 48 hours after taking the study drug.

Number of Subjects:

Approximately 1220 subjects will be screened to randomize up to approximately 795 subjects (265 per arm). Subjects will be randomized in a 1:1:1 ratio to the rimegepant 25 mg, rimegepant 75 mg, or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

Study Population:

The study will recruit subjects 18 years of age and older with at least a 1-year history of migraines (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, including an age of onset prior to 50, migraine attacks that last about 4 - 72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.

Statistical Methods:

This study will randomize a total of 795 subjects in a 1:1:1 ratio to rimegepant 25 mg, rimegepant 75 mg, or placebo. It is anticipated that this will result in approximately 750 subjects in efficacy analysis set, with roughly 250 subjects in each treatment arm. The sample size for this study was initially designed to provide 80% power to test each of the 2 rimegepant doses against placebo at a Bonferroni corrected 2-sided alpha level of 0.025 using a chi-square test. Although testing strategy is changed in Protocol version 4.0 and formal hypothesis testing will no longer be conducted for rimegepant 25 mg, the original sample size will remain as it is. The sample size estimate was based on historical data from pivotal study BHV3000-303, in which the rates of pain freedom were 10.9% for placebo and 21.2% for Rimegepant.

The primary endpoint of pain freedom at 2 hours post-dose will be evaluated using Mantel-Haenszel risk estimation with stratification by the use of prophylactic migraine medication (yes or no). The same statistics for secondary endpoints will be presented as those for the primary endpoint.

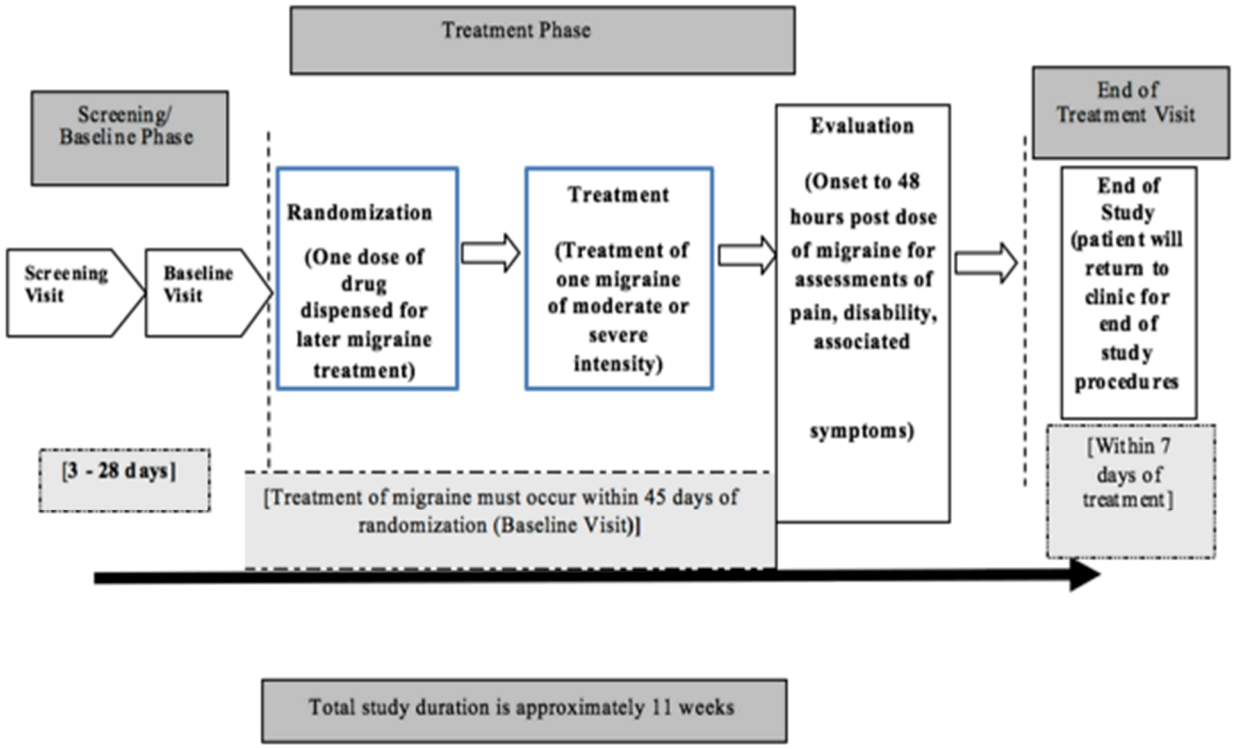
Safety endpoints will be assessed descriptively.

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 4 traditional endpoints: pain, nausea, photophobia and phonophobia. Efficacy was confirmed for the acute treatment of migraine in 3 pivotal Phase 3 trials using the current registrational co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2 hours after dosing. Effectiveness for the preventive treatment of episodic migraine was demonstrated in a Phase 2/3 double-blind, randomized, placebo-controlled study of rimegepant 75 mg dosed every other day (EOD). 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.

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.

STUDY SCHEMATIC



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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AV	Atrioventricular
BHV	Biohaven
bpm	beats per minute
BUN	Blood Urea Nitrogen
CGRP	Calcitonin Gene-Related Peptide
CI	confidence interval
CRF	Case Report Form
CRO	contract research organization
CRPS	Complex Regional Pain Syndrome
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CV	Cardiovascular
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-drug interaction
DILI	Drug-Induced Liver Injury
DSM-V	Diagnostic and Statistical manual of Mental Disorders Fifth edition
DSU	Drug Safety Unit
EC	Ethics committee
ECC	emergency contact card
ECG	Electrocardiogram
EDB	Exposure During Breastfeeding
EDC	Electronic Data Capture
eDiary	Electronic diary
EDP	Exposure During Pregnancy
eGFR	Estimated glomerular filtration rate

EOD	Every Other Day
eTMF	electronic Trial Master File
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HR	heart rate
HRT	hormone replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	investigator site file
IWRS	Interactive Web Response System
kg	Kilogram
L	Liters
LBBB	Left bundle branch block
LFTs	Liver Function Tests
MBS	most bothersome symptom
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
MQI	medically qualified individual
NC=F	Non-completer = Failure
NSAID	Nonsteroidal Anti-inflammatory Drugs
PACL	Protocol Administrative Change Letter
P-gp	P-glycoprotein
PK	Pharmacokinetic

PRN	Pro re nata, as needed
PSSA	Pfizer SAE Submission Assistant
PVC	Premature ventricular contraction
QTc	Interval between Q-wave and T-wave in the cardiac cycle
QTcF	QTc corrected using Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SRSD	Single Reference Safety Document
T bili	Total bilirubin
THC	Tetrahydrocannabinol
TMF	Trial Master File
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

1. INTRODUCTION AND RATIONALE

1.1. Background

Migraine is a common and debilitating neurological disorder that affects approximately 8.4% of the adult population in Japan[1]. 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 intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

BHV-3000 (PF-07899801) (Rimegepant) 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 causal 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. This new approach to the treatment of migraine 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™]).

1.2. CGRP

Rimegepant is a selective, high-affinity, orally administered, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist.

CGRP is an endogenous 37 amino acid peptide contained within pain-signaling nociceptive afferents, and is thought to play a causal role in migraine[2,3]. Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine[4;] 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief[4,5]; and 3) intravenous CGRP infusion produces lasting pain in non-migraineurs and migraineurs[3,6].

Rimegepant offers a novel therapeutic mechanism for the acute treatment of migraine with the potential to address important unmet needs (e.g., single-dose durable efficacy, efficacy without medication overuse headache, and no contraindications or warnings in patients with cardiovascular [CV] disease).

The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology. 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 following possible mechanisms:

- **Blocking Neurogenic Inflammation:** Binding of CGRP receptor antagonists to CGRP receptors located on mast cells would inhibit inflammation caused by trigeminal nerve release of CGRP onto mast cells within the tough outer covering of the brain, or the meninges.

- **Decreasing Artery Dilation:** By blocking the CGRP receptors located in smooth muscle cells within vessel walls, CGRP receptor antagonists would inhibit the pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.

- **Inhibiting Pain Transmission:** Binding of CGRP receptor antagonists to CGRP receptors would suppress the transmission of pain by inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.

1.3. Product Development Background

Details of the clinical and preclinical studies are provided in the most current Investigator Brochure. A summary of the relevant data is presented below.

As of 26-Aug-2022 more than 8900 unique subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine; of these, approximately 6036 unique subjects have received rimegepant at any dose. The clinical pharmacology of rimegepant has been well characterized in a comprehensive program based on 27 Phase 1 studies, including 7 studies that examined the biopharmaceutics of rimegepant. In the 4 Phase 3, placebo-controlled studies for the acute treatment, rimegepant administered as a single 75 mg dose (either as a tablet or ODT) was well tolerated in adult subjects experiencing migraine attacks with moderate to severe intensity and demonstrated a safety profile comparable to placebo (2439 rimegepant-treated subjects and 2456 placebo-treated subjects). In total, the current data suggests a favorable benefit-risk profile for rimegepant in the acute treatment of migraine attacks.

1.4. Benefit Risk Assessment

Rimegepant is approved in the US, EU, and UK for the treatment of migraine in adults, including both acute treatment of migraine and preventive treatment of episodic migraine. Rimegepant appears to be generally safe and well tolerated in humans when given as single oral doses from 75 mg up to the maximum dose of 1,500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. Rimegepant 75 mg represents an advancement in migraine therapeutics, providing the first CGRP antagonist to demonstrate benefit for both the acute treatment and prophylaxis of migraine. Dual action therapy for migraine with a single agent offers patients the potential for significant clinical advantages including: 1) a simplified medication regimen to treat migraine across the spectrum from acute episodes to the prevention

of future attacks, which are 2 manifestations of the same condition; 2) avoiding polypharmacy with concurrent use of multiple medications each with their own side effects; 3) reducing the risk of DDIs; and 4) cost-effectiveness of a single medication that provides both acute and preventive therapy.

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 (MBS) 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 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 1 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 + as needed (PRN) for up to 52 weeks in the open-label phase is well tolerated, with no new safety signals observed in the open-label-extension phase.

Across rimegepant clinical development program, low frequency of events of hypersensitivity (including urticaria, angioedema, anaphylactic reaction and rash) were observed. No AEs representing serious cutaneous manifestation of hypersensitivity (eg, 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 drug-induced liver injury (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. Women of childbearing potential (WOCBP) must have a negative pregnancy test and WOCBP and fertile men must use 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. 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 Food and Drug Administration (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.

1.5. Study Rationale

Rimegepant is being developed for comprehensive management of migraine. Efficacy of rimegepant as an acute treatment of migraine was shown by a phase 2b double-blind, randomized, placebo-control, dose-finding clinical study. In this study, rimegepant at 75 mg showed efficacy on all 4 traditional endpoints including pain, nausea, photophobia, and phonophobia[7]. Efficacy of rimegepant was confirmed by 3 pivotal phase 3 clinical studies in which freedom from pain and freedom from the MBS 2 hours post-dose were the co-primary endpoints[8,9,10].

Based on these data and long-term safety (for up to 52 weeks) observed in approximately 1,800 subjects in the open label Study BHV3000-201[11], once-daily administration of rimegepant 75 mg taken on an as-needed basis was approved as an acute treatment of migraine by the US FDA[12].

Study BHV3000-313 will be conducted to evaluate efficacy, safety, and tolerability of rimegepant for acute treatment of migraine in Japanese subjects. This clinical trial will be a bridging study to a U.S. dose-finding study (Study CN170003). In addition, efficacy of rimegepant in Japanese subjects will be evaluated in the context of the U.S. studies for acute treatment of migraine (Study CN170003, Study BHV3000-301, Study BHV3000-302, and Study BHV3000-303). Taken together, results of this trial (BHV3000-313) and the results of 4 U.S. Studies (3 pivotal phase 3 placebo-controlled clinical studies for acute treatment [Study BHV3000-303[8], Study BHV3000-302[9], and Study BHV3000-301[10]] and an open-label, long-term safety study [Study BHV3000-201[11]]) will enable the benefit/risk assessment of rimegepant 75 mg for acute treatment of migraine in Japanese subjects.

1.5.1. Study Design Rationale

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. The study is designed to provide data in Japanese subjects that will bridge to the existing comprehensive clinical trial data available for rimegepant at a 25 mg and 75 mg dose in the acute treatment of migraine.

Study BHV3000-313 will demonstrate that rimegepant for the acute treatment of migraine has a safety and efficacy profile in Japanese subjects with migraine that is consistent with the profile observed in the clinical program to date.

The study drug will be rimegepant formulated in a 25 mg or 75 mg ODT or a matching placebo. The subjects will be instructed to take their study drug, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity.

The study will screen approximately 1,220 subjects to allow approximately 795 subjects to be randomized. The subjects will be randomized in a 1:1:1 ratio to the rimegepant 25 mg, 75 mg or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

This study design is utilized to confirm the efficacy and safety profiles observed in the Phase 2b and 3 completed phase 3 studies with rimegepant. Incorporation of placebo and use of appropriate rescue medications will permit enrollment of subjects with a broad range of comorbidities, including cardiovascular conditions, representative of the potential treatment population.

1.5.2. Dose Selection Rationale

Effectiveness of rimegepant as an acute treatment for migraine was demonstrated in CN170003 study that compared rimegepant at doses of 10, 25, 75, 150, 300 and 600 mg to placebo[2]. The primary endpoint was pain freedom at 2 hours post-dose. In this study the 10 and 25 mg doses did not separate from placebo. The 75, 150 and 300 mg doses were significantly better than placebo and showed similar efficacy.

The 75 mg dose was selected as the optimal dose for evaluation in Phase 3 studies for the acute treatment of migraine. The efficacy of the 75 mg dose was confirmed in all 3 pivotal studies.

BHV3000-111 was a Phase 1, randomized, placebo-controlled, multiple-dose, double-blind study to evaluate and compare the PK and safety of rimegepant in healthy Caucasian and Japanese subjects. Rimegepant administered as multiple doses of 25 mg, 75 mg, and 150 mg is safe and well tolerated in healthy adult Caucasian and Japanese subjects. In addition, weight-normalized PK parameters were comparable between Caucasian and Japanese subjects and no dose or dose frequency adjustment is required in Japanese patients.

This study is being conducted to determine the appropriate dose of rimegepant in Japanese subjects, as well as to evaluate the efficacy, safety, and tolerability of rimegepant in Japanese subjects for the acute treatment of migraine.

Since increasing the dose of rimegepant above 75 mg was shown not to increase efficacy in study CN170003, this study tests the 75 mg dose of rimegepant against placebo in Japanese subjects. The 25 mg dose is being assessed to confirm the dose response in Japanese subjects is similar to that observed in the U.S. population in CN170003.

1.6. Research Hypothesis

Rimegepant 75 mg ODT will have efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile suitable for use by a broad subject population.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

- To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese subjects.

2.2. Secondary Objective(s)

- To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese subjects on the following secondary endpoints:
    - Pain relief at 2 hours post-dose
    - Freedom from the MBS associated with migraine at 2 hours post-dose
    - The ability to function normally at 2 hours post-dose
    - Sustained pain relief from 2 to 24 hours post-dose
    - Rescue medication use within 24 hours of initial treatment
    - Sustained pain relief from 2 to 48 hours post-dose
    - Freedom from photophobia at 2 hours post-dose
    - Sustained pain freedom from 2 to 24 hours post-dose
    - Freedom from phonophobia at 2 hours post-dose
    - Sustained pain freedom from 2 to 48 hours post-dose
    - Freedom from nausea at 2 hours post-dose
    - Pain relapse from 2 to 48 hours post-dose
- To compare the efficacy of rimegepant 25 mg with placebo in the acute treatment of migraine in Japanese subjects on the same efficacy endpoints
- To evaluate the tolerability and safety of rimegepant 75 mg and 25 mg in the acute treatment of migraine

2.3. Exploratory Objective(s) (if applicable)

Not Applicable.

3. STUDY ENDPOINTS

Subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. This method will apply to all endpoints listed below, except the secondary endpoint of rescue medication use within 24 hours post-dose.

3.1. Primary Endpoint(s)

- Pain freedom at 2 hours post-dose will be assessed using the percentage of subjects that report no pain at 2 hours post-dose. Pain will be measured on a 4-point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

3.2. Secondary Endpoint(s)

- Pain relief at 2 hours post-dose will be assessed using the percentage of subjects that report a pain intensity level of none or mild at 2 hours post-dose.

- Freedom from the MBS at 2 hours post-dose will be assessed using the percentage of subjects with an MBS reported before dosing that is absent at 2 hours post-dose. The MBS before dosing will be reported as nausea, phonophobia, or photophobia. Symptom status will be reported post-dose as present or absent for each symptom (nausea, phonophobia, and photophobia).

- Ability to function normally at 2 hours post-dose will be assessed using the percentage of subjects with a functional disability level of normal at 2 hours post-dose 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), and functional disability will be defined as mildly impaired, severely impaired, or requires bedrest.

- Sustained pain relief from 2 to 24 hours post-dose will be assessed using the percentage of subjects with pain intensities of none or mild from 2 to 24 hours post-dose.

- Rescue medication use within 24 hours post-dose will be assessed using the percentage of subjects that take rescue medication within 24 hours after administration of study medication (rimegepant or placebo).

- Sustained pain relief from 2 to 48 hours post-dose will be assessed using the percentage of subjects with pain intensities of none or mild at all time points from 2 to 48 hours post-dose.

- Freedom from photophobia at 2 hours post-dose will be assessed using the percentage of subjects with photophobia absent at 2 hours post-dose in the subset of subjects with photophobia present at the time of dosing.

- Sustained pain freedom from 2 to 24 hours post-dose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 24 hours post-dose.

- Freedom from phonophobia at 2 hours post-dose will be assessed using the percentage of subjects with phonophobia absent at 2 hours post-dose in the subset of subjects with phonophobia present at the time of dosing.

- Sustained pain freedom from 2 to 48 hours post-dose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 48 hours post-dose.

- Freedom from nausea at 2 hours post-dose will be assessed using the percentage of subjects with nausea absent at 2 hours post-dose in the subset of subjects with nausea present at the time of dosing.

- Pain relapse from 2 to 48 hours post-dose will be assessed using the percentage of subjects with a pain intensity of mild, moderate, or severe at any time point after 2 hours through 48 hours post-dose in the subset of subjects with pain freedom at 2 hours post-dose.

- Tolerability and safety will be evaluated by the percentage of subjects with AEs by intensity, SAEs, and grade 3 to 4 laboratory test abnormalities.

3.3. Exploratory Endpoint(s) (if applicable)

Not Applicable.

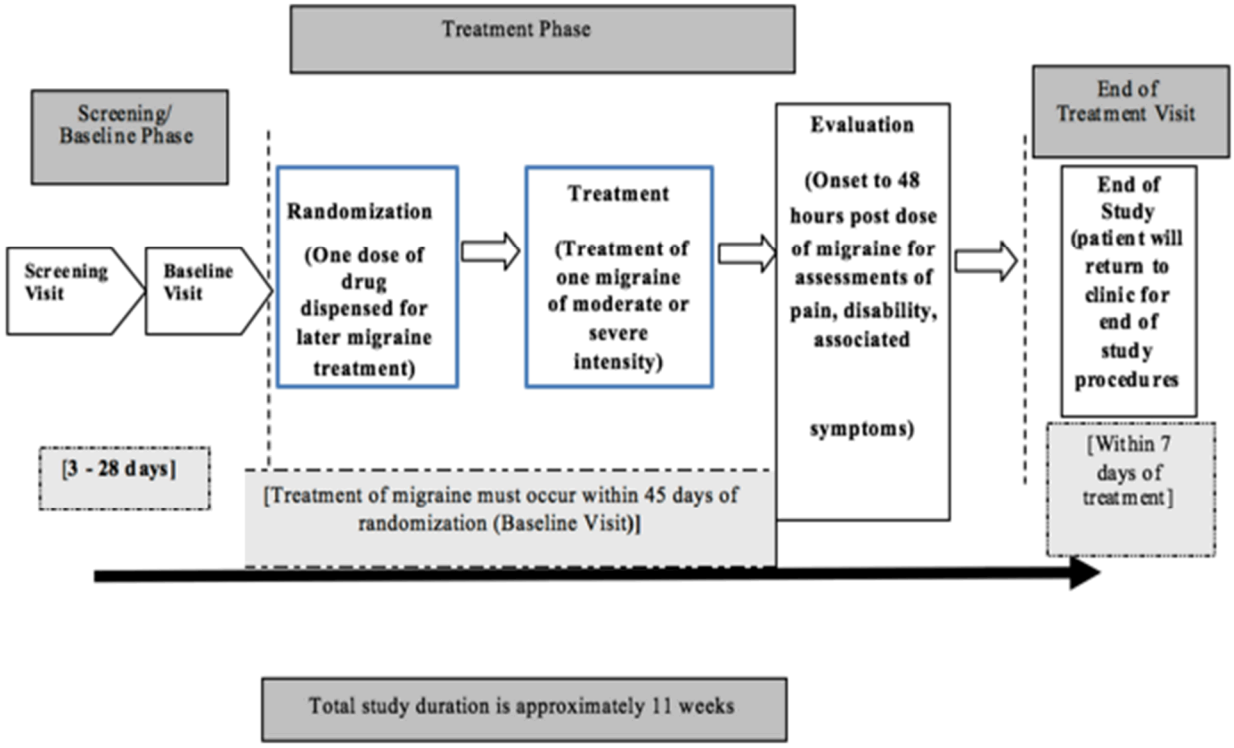
4. STUDY PLAN

4.1. Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant 75 mg as compared to placebo in the treatment of moderate or severe migraine. The investigational product is formulated as rimegepant 25 mg, rimegepant 75 mg or a matching placebo. The 25 mg rimegepant dose is included in the study to permit an assessment of the dose response for rimegepant in Japanese subjects. The total duration of the study will be approximately 11 weeks. This includes a 3 to 28 day Screening Period, a Treatment Phase that can last up to 45 days or until the subject has a migraine that reaches moderate or severe intensity, followed by an End of Treatment Visit within 7 days after the administration of the study drug. A month is defined as 4 weeks for the purpose of this protocol.

4.2. Study Schematic

Figure 1 Study Schematic



4.3. Schedule of Assessments

Table 1 Schedule of Assessments

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Treatment Phase					End of Treatment Visit (within 7 days of treatment)[15]
			Onset of moderate or severe migraine[2]	15, 30, 45, 60 and 90 minutes Post-Dose	2, 3, 4, 6, 8 hours Post-Dose	24 hours Post-Dose	48 hours Post- Dose	
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Prophylactic Migraine Medication/ Concomitant Medication[3]	X	X						X
Assessment of Migraine History (Signs and symptoms) paper source[4]	X							

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Treatment Phase					End of Treatment Visit (within 7 days of treatment)[15]
			Onset of moderate or severe migraine[2]	15, 30, 45, 60 and 90 minutes Post-Dose	2, 3, 4, 6, 8 hours Post-Dose	24 hours Post-Dose	48 hours Post- Dose	
Safety Assessments								
Physical Examination	X							X
Vital Signs/ Physical Measurements[5]	X	X						X
Clinical Safety Laboratory Testing	X[6]							X
Urine drug screen for drugs of abuse	X							X
ECG	X							X
Pregnancy Test[7]	X (serum)	X (urine)	X (urine)					X (serum)
Adverse Event and Serious Adverse Event Assessment[8]	X	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[9]	X	X						X

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Treatment Phase					End of Treatment Visit (within 7 days of treatment)[15]
			Onset of moderate or severe migraine[2]	15, 30, 45, 60 and 90 minutes Post-Dose	2, 3, 4, 6, 8 hours Post-Dose	24 hours Post-Dose	48 hours Post- Dose	
Clinical Drug Supplies/Study Supplies								
Randomization[10]		X						
eDiary provided		X						
Dispense Study Drug		X						
Administer 1 dose of study medication[11]			X					
Return unused study drug								X
eDiary returned/reviewed for completeness[12]								X

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Treatment Phase					End of Treatment Visit (within 7 days of treatment)[15]
			Onset of moderate or severe migraine[2]	15, 30, 45, 60 and 90 minutes Post-Dose	2, 3, 4, 6, 8 hours Post-Dose	24 hours Post-Dose	48 hours Post- Dose	
Efficacy Assessments[13]								
Assessment of migraine pain[14]			X	X	X	X	X	
Assessment of Migraine Symptoms (photophobia, phonophobia, and nausea – eDiary)[14]			X	X	X	X	X	
Functional Disability Scale[14]			X	X	X	X	X	

1 **Screening Phase** will be 3 – 28 days. The **Baseline Visit** may be scheduled but should only occur ***after*** all screening procedures are complete, subject meets inclusion/exclusion criteria, and lab test results have been received by the site. If the subject does not meet all eligibility requirements, the subject should be screen failed in the IWRS.

2 Subjects will use the eDiary before taking study drug to answer questions about their migraine symptoms upon experiencing a moderate or severe migraine headache. The subject will administer pre-dispensed study drug or matching placebo if the following criteria are met: 1) the headache remains moderate or severe; 2) the subject has completed all required migraine assessment questions in the eDiary, including their current most bothersome migraine symptom, and 3) the subject has not already taken prohibited medications (see protocol Section 5.4).

3 Subjects should keep track of their concomitant medications on the approved paper diary throughout the study. A concomitant medication paper diary will be provided to subjects at the Screening visit. These paper diaries should be returned to the investigational site at the End of Treatment Visit for review and electronic data capture (EDC) entry. Any medication taken for recurrent headache should be documented. Subjects should keep track of their rescue medications on the approved study paper diary provided throughout the study. A rescue medication paper diary will be provided to subjects at the Baseline visit (reference rescue medication Section 5.5 additional information). These paper diaries should be returned to the investigational site at the End of Treatment Visit for review and EDC entry. The paper diaries should be kept as source documents.

4 Migraine History, history of triptan use and CV risk factors will be recorded on paper source documents and entered into the EDC. Subjects will also be asked about their typical most bothersome symptom when having a migraine.

5 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 radial artery pulse rate will be measured.

[6] All screening visit laboratory test results must be received prior to Baseline (randomization) Visit. Refer to Section 6.2.4

[7] For WOCBP: A serum pregnancy test will be collected at the Screening and EOT Visit as part of the standard laboratory tests. Confirmatory urine pregnancy test for WOCBP will be completed on site at the Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion. Home pregnancy test will be provided to WOCBP after completion of Baseline Visit. WOCBP subjects must complete the urine pregnancy test at home **prior** to taking study drug.

[8] AE and SAEs must be reported from the time of informed consent. All ongoing non-serious AEs and SAEs will be followed to resolution or until investigator deems there will be no further status change. SAEs that occur during the treatment period should be reported to site according to local regulatory requirements. Non-serious AEs that occur during the treatment period should be reported to the site at the EOT.

[9] The C-SSRS will be clinician administered on site with a paper form.

[10] Subjects will be randomized in the IWRS system at the Baseline Visit (Randomization Day 01).

[11] Subjects should be instructed that the dose should be taken once the migraine attack reaches moderate or severe pain and after the subject has completed all required migraine assessments in the eDiary. The eDiary will prompt the subject when they should take study drug.

[12] Site staff to review and confirm entries with subjects and confirm all data points are transferred to the system and reset eDiary for future subject use, PRIOR to the subject leaving the clinic.

[13] **±** Windows for timeframe around efficacy assessments (15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 24 and 48 hours) will be automated and captured in the eDiary.

[14] These scales will be captured in the eDiary. Subjects will also be asked about their most bothersome symptom at the time of reporting and treating a qualifying migraine.

[15] Subjects should return to the site for their EOT visit within 7 (+4) days of study drug dosing.

4.3.1. Screening Phase (3-28 days)

It is estimated that approximately 1,220 subjects will be screened to allow approximately 795 subjects to be randomized at the Baseline visit. After obtaining informed consent, subjects will undergo all screening procedures as detailed in Table 1. All subjects who are screened into the study will be entered into the IWRS system. After all screening procedures are complete, subjects may return 3 to 28 days from signing informed consent to be randomized at the Baseline visit if they meet all eligibility criteria. Any subject who does not meet all eligibility criteria will be considered a Screen Failure.

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screening in select circumstances (e.g., previously pregnant, screening window too long). Subjects who were considered screen failures may also 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 may be discussed with the Sponsor prior to re-screening and a new subject number must be obtained from the appropriate study-related system. Re-screening will only be permitted one time.

4.3.2. Randomization Visit/Treatment Phase (Up to 45 days)

Subjects who meet all eligibility criteria will be randomized at the Baseline Visit via the IWRS. The subjects will be provided with an eDiary. The study personnel will instruct the subject on the proper use of the eDiary and ensure proper understanding and use of the tool, prior to the subject leaving the site.

After randomization via the IWRS, subjects will be dispensed the double-blind study drug to take home for up to 45 days. This study drug is to be taken when a migraine attack reaches moderate or severe intensity on the numeric rating scale (NRS) as indicated in the eDiary. Subjects will be instructed to take their study drug, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity **after they answer eDiary questions about their current pain and symptoms and identify their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea)**. The subject will complete an eDiary for 48 hours after taking study drug to record efficacy and other quality of life measures.

Subjects in this study may be randomized only once. Under no circumstances may a subject be re-randomized.

4.3.2.1. eDiary Data Collections

Subjects will record efficacy in their eDiary. A subject should not take study drug until the headache reaches moderate or severe intensity. Headache severity will be recorded using a 4-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (4-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Subjects will also identify their currently most bothersome symptom before taking study drug. Subjects will record the date and time study therapy was taken in their

eDiary. Subjects who have headache pain reduced to a mild intensity or pain free intensity level will be considered to have achieved pain relief.

After taking study drug, all other headache medication is prohibited during the 2 hours post dose. However, a subject who does not experience relief of their migraine headache at the end of 2 hours after dosing with study drug (and after the 2-hour assessments have been completed on the eDiary) will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen up to 2000 mg/day, naproxen (or any other type of nonsteroidal anti-inflammatory drug (NSAID)), antiemetics (e.g., metoclopramide), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study drug. However, if needed, after 48-hours of taking the single dose of study drug (and before returning for the End of Treatment Visit) subject may take their prescribed standard of care medications for treatment of migraine, including triptans if not contraindicated, **provided all of the assessments have been completed on the eDiary**. Exclusionary rescue medication such as, opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study drug at 2 hours after dosing but then recurs to a moderate or severe intensity level between 2 and 48 hours, the subject will be permitted to take the same rescue medication as outlined above.

Subjects should be encouraged to treat the first qualifying (moderate to severe) migraine that occurs during the treatment phase. If subjects are unable to treat their first qualifying migraine due to scheduling, etc. the same medication restrictions would still apply (i.e. aspirin, ibuprofen, naproxen (or any other type of nonsteroidal anti-inflammatory drug (NSAID)), antiemetics (e.g., metoclopramide) or baclofen.

Similarly, for treatment of non-qualifying migraines (i.e. mild migraines, or other headaches) that occur during the treatment phase before a qualifying migraine is reported, subject will only be permitted to use the medications listed above. Triptans and acetaminophen (over 2000 mg/day) are prohibited after randomization except as rescue medication as described in Section 5.5. In all circumstances, the subject will continue to complete the eDiary for up to 48 hours after taking the study drug.

4.3.3. Extension Phase

Not Applicable

4.3.4. End of Treatment

Subjects will return to the study site within 7 days of study drug dosing (+4 days) for review of the eDiary assessment of medication compliance and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a subject has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures. All subjects must return unused study drug and eDiary to the study site.

4.4. Post Study Access to Therapy

At the end of the study the sponsor will not continue to supply study drug to subjects/investigators. The investigator should ensure that the subject receives the appropriate standard of care to treat the condition under study.

5. POPULATION

Individuals entered in this trial will be subjects who suffer from migraines. The treatment setting for subjects may include headache clinics, hospitals or private practices, Subjects may be recruited from a variety of sources including referrals or professional recruitment agencies.

5.1. Number of Subjects

Approximately 1,220 subjects will be screened to randomize approximately 795 subjects (265 per arm). Subjects will be randomized in a 1:1:1 ratio to the rimegepant 25 mg, rimegepant 75 mg, or placebo treatment groups.

5.2. Inclusion Criteria

1. Signed Written Informed Consent

    a. Written informed consent must be obtained from the subject in accordance with requirements of the study site's institutional review board (IRB) or ethics committee (EC), prior to the initiation of any protocol-required procedures.

2. Target Population; Subject has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition[13] including the following:

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

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

    c. Not more than 8 attacks of moderate to severe intensity per month within the last 3 months (month is defined as 4 weeks for the purpose of this protocol).

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

    e. Consistent migraine headaches of at least 2 migraine attacks of moderate to severe intensity in each of the 3 months prior to Screening Visit and maintains this requirement during the Screening Period.

    f. Less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening visit and maintains this requirement during the Screening Period.

    g. Subjects on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 3 months prior to the Screening Visit, and if the dose is not expected to change during the course of the study. Valproic acid/valproate is permitted if subject is on therapy for at least 6 months prior to the Screening Visit.

    h. Subjects with contraindications for use of triptans may be included provided they meet all other study entry criteria.

3. Age and Reproductive Status

a. Subjects ≥ 18 years

b. Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential must be using 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months (24 weeks) prior the Screening Visit.

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).

d. Women must not be pregnant, lactating or breastfeeding

4. Other Inclusion Criteria

a. No clinically significant abnormality identified on the medical or laboratory evaluation. A subject with a clinical abnormality or laboratory parameters outside the reference range may be included only if the investigator considers the finding not clinically significant, that it will not introduce additional risk factors, nor interfere with the study procedures.

5.3. Exclusion Criteria

1. Target Disease Exclusion

a. Subject has a history of migraine with brainstem aura (basilar migraine), hemiplegic migraine or retinal migraine.

b. History of systemic use of analgesics (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit.

2. Medical History and Concurrent Diseases

a. (Deleted in a protocol amendment)

b. Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during 6 months (24 weeks) prior to screening.

c. Uncontrolled hypertension, or uncontrolled diabetes (however subjects can be included who have stable hypertension and/or diabetes for at least 3 months (12 weeks) prior to screening). Blood pressure greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary.

d. Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder.

Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening visit.

e. Active chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, complex regional pain syndrome (CRPS)).

f. Subjects with other pain syndromes (including trigeminal neuralgia), psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, interfere with study assessments.

g. Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder.

h. Subject has a history of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has a disease that causes malabsorption.

i. Patient has any active hepatic or biliary disorder.

j. The subject has a history or current evidence of any unstable medical conditions (e.g., history of congenital heart disease or arrhythmia, known or suspected infection, hepatitis B or C, or cancer) that, in the investigator's opinion, would expose them to undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the study.

k. History of alcohol abuse and/or illicit drug use meeting DSM-V criteria for substance use disorder within 6 months of screening. Note, non-dependent use of cannabis/marijuana is permitted.

l. (Deleted in a protocol amendment)

m. (Deleted in a protocol amendment)

n. Body mass index > 35 kg/m^2

3. Allergies and Adverse Drug Reactions

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

4. Sex and Reproductive Status

   a. Females of childbearing potential who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for 60 days after the study.

   b. Women with a positive pregnancy test on enrollment or prior to study drug administration.

5. Electrocardiogram (ECG) and Laboratory Test Findings

a. Estimated glomerular filtration rate (eGFR) ≤ 30 ml/min/1.73m^2

b. Corrected QT interval > 470 msec (QTc by method of Fridericia), at Screening

c. Left Bundle Branch block (LBBB)

d. (Deleted in a protocol amendment)

e. (Deleted in a protocol amendment)

f. Total bilirubin (T bili) > 1.5 × ULN (may be repeated once for confirmation during the screening period; direct bilirubin >1.5 × ULN is exclusionary for Gilbert's syndrome)

g. AST or ALT > 2.0 × ULN (may be repeated once for confirmation during screening period)

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

i. HbA1c > 7.5%

j. Other abnormal ECG that in the investigator's opinion makes the subject unsuitable for a clinical trial

6. Prohibited Medications

a. Subjects taking a prohibited medication (Refer to the Section 5.4)

7. Other Exclusion Criteria

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

b. Exposure to non-biological investigational agents or investigation interventional treatments within the 30 days prior to Screening visit.

c. Exposure to biological investigational agents within the 90 days prior to Screening visit.

d. Subjects who have previously participated in any study of rimegepant.

e. Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to the Screening Visit, OR subjects who endorse any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within the last 10 years prior to the Screening Visit, OR subjects who, in the opinion of the investigator, present a serious risk of suicide (See Section 6.2.5.)

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

g. Subjects must complete the Baseline/ Randomization visit within 3 to 28 days of the Screening visit.

h. 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.

5.4. Prohibited and Restricted Concomitant Medications

The below medications are prohibited prior to randomization ***and during the course of this study or as specified.***

1. Traditional Chinese Medicines should not be taken 14 days prior to randomization and throughout the study.

2. St. John's Wort should not be taken 14 days prior to randomization and throughout the study.

3. Barbiturate-containing products (e.g. Fioricet, Fiorinal, butalbital, phenobarbital) should not be taken 14 days prior to randomization and throughout the study.

4. Modafinil (PROVIGIL®) should not be taken 14 days prior to randomization and throughout the study.

5. Butterbur root or extracts should not be taken 14 days prior to randomization and throughout the study.

6. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for ≥ 3 months (≥ 12 weeks).

7. Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) for at least 2 days prior to randomization.

8. History of systemic non-narcotic analgesic intake on ≥ 15 days per month for ≥ 3 month (e.g. acetaminophen, NSAIDs, gabapentin etc.) for other pain indications. (Please refer to Section 5.5 for rescue medication).

9. Use of acetaminophen or acetaminophen containing products must be discontinued at least 2 days prior to randomization (acetaminophen up to 2000 mg/day is allowed as rescue medication, see Section 5.5). During the screening phase (3-28 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 2000 mg/day is prohibited.

10. The use of CGRP antagonist biologics [e.g. galcanezumab, erenumab, fremanezumab, eptinezumab-jjmr] is prohibited during the study. CGRP antagonist biologics must be discontinued 6 months prior to screening and are prohibited throughout the study.

11. The use of oral gepants must be discontinued 2 weeks prior to screening and are prohibited throughout the study (e.g. ubrogepant, atogepant). Any past exposure to rimegepant will be exclusionary.

12. Lasmiditan (Reyvow®) is prohibited 14 days prior to randomization and throughout the study.

13. Marijuana and all forms of ingested or inhaled cannabidiol and THC-containing products usage meeting DSM-V criteria for substance use disorder.

14. Muscle relaxants (baclofen is allowed as rescue medication, see Section 5.5).

15. Concomitant use of moderate to strong CYP3A4 inhibitors with rimegepant is prohibited during the study. If use of a moderate to strong CYP3A4 inhibitor is required, such as use of HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of a moderate to strong CYP3A4 inhibitor. Please see Section 16.1.

16. Concomitant use of moderate to strong CYP3A4 inducers with rimegepant is prohibited during the study. If use of a moderate to strong CYP3A4 inducer is required, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of a moderate to strong CYP3A4 inducer. Please see Section 16.1.

17. Concomitant use of strong inhibitors of the P-gp transporter with rimegepant is prohibited during the study. See Section 16.1.

18. Concomitant use of atypical antipsychotics such as Abilify® (aripiprazole), Zyprexa® (olanzapine), Seroquel® (quetiapine), Geodon® (ziprasidone), or Risperdal® (risperidone) is prohibited during the study.

19. Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.

20. Concomitant use of LAMICTAL® (lamotrigine) is prohibited during the study.

21. Use of Cefaly™ or any other device for migraine treatment is prohibited within 12 weeks of the Screening Visit and during the study.

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

5.5. Rescue Medications

After dosing with study drug, all headache medication is prohibited during the 2 hours post dose. However, a subject who does not experience relief of their migraine headache at the end of 2 hours after dosing with study drug (***and after the 2-hour assessments have been completed on the eDiary***), will be permitted to use ONLY the following rescue medication: ***aspirin, ibuprofen, acetaminophen up to 2000 mg/day, naproxen (or any other type of non-steroidal anti-inflammatory drug (NSAID)), antiemetics (e.g., metoclopramide), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study drug.***

However, if needed, after 48-hours of taking the one dose of study drug (and before coming in for the End of Treatment Visit) subject may take their prescribed standard of care

medications for treatment of migraine including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Similarly, if the migraine is relieved by study drug at 2 hours after dosing but then recurs to a moderate or severe intensity level between 2 and 48 hours, the subject will be permitted to take the same rescue medication as above. In all circumstances, the subject will always continue to complete the eDiary entries through the 48-hour assessment after taking the study drug. Use of concomitant medication after randomization, including rescue medication, will be recorded by the subject on a paper diary and reported to the site. The site will record medications that were taken within 14 days of taking study drug (or until the End of Treatment Visit).

During the 45 days the subject is participating in the study, if the subject has a nonqualifying migraine (mild migraine) or a migraine that they do not treat with study drug, the subject is permitted to use only the following medications: aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-inflammatory drug (NSAID)), antiemetics (e.g., metoclopramide), or baclofen.

After completing all assessments (through 48 hours and before End of Treatment Visit) in their eDiary, if subjects experience a migraine, they are allowed to take their standard of care medication (including triptans if not contraindicated and acetaminophen up to 2000 mg/day).

5.6. Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Menopause is defined as:

1. Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL at screening or

2. Woman with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL at screening or

3. Women on hormone replacement therapy (HRT) who no longer menstruate

NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year

NOTE: Women on HRT who still menstruate and women with irregular menses should be considered as WOCBP

Women of childbearing potential and all male subjects must be counseled on and understand the requirements to avoid pregnancy, as well as acceptable methods of contraception to use throughout the study.

WOCBP with male partners and men with women partners of childbearing potential must use 2 acceptable methods of contraception to avoid pregnancy throughout the study and for up to 60 days (for WOCBP) and 90 days (for men) after the last dose of investigational product in such a manner that risk of pregnancy is minimized (i.e., this study begins with signed consent

form through 60 days (for WOCBP) and 90 days (for men) after dosing with study drug). It is required that all WOCBP use 2 methods of contraception for the duration of the study. The 2 methods should include one barrier method (i.e., condom with spermicidal gel, non-hormonal intrauterine devices, cervical cap etc.) and one other method. The other method could include hormonal contraceptives (e.g., oral contraceptives, injectable contraceptives, patch, or contraceptive implant [e.g., hormonal intrauterine device]) used since at least 4 weeks prior to sexual intercourse or another barrier method (note, an intrauterine device is considered one method).

Subjects who report abstinence, or who report exclusively being in same-sex relationships are still required to understand the contraception requirements in this study to prevent pregnancy. If subjects who report abstinence, or who report exclusively being in a same-sex relationship engage in heterosexual activity, then the contraception requirements must be followed.

Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months (24) weeks prior to the screening visit. Vasectomy is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill the contraception requirements for the study. Male subjects must not donate sperm until 90 days following the last study drug administration.

All WOCBP must administer the home pregnancy test provided at home, prior to taking Investigational Study Drug. If the pregnancy test is positive, subjects should not take study drug and should immediately contact the Study Investigator.

5.7. Other Restrictions and Precautions (if applicable)

Not Applicable.

5.8. 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/IEC at the frequency required by your IRB/IEC. 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 study materials including, but not limited to the following will be provided at the study start:

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Paper Concomitant and Rescue Medication Logs (take home for subjects)
- Investigator Brochure
- Interactive Web-based Response System (IWRS) instructions
- Electronic Case Report Form (eCRF) completion instructions
- eDiary: one device will be given to each randomized subject
- Instructions for the eDiary and training materials for subjects
- Laboratory Kits (including home pregnancy test kit) and Laboratory Manual
- Back-up forms for CT SAE report, EDP and Pregnant Partner Release of Information
- Paper copies of the C-SSRS

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

Any assessment completed by the subject in the eDiary will be transferred from the site/subject to the vendor and from the vendor to the CRO and Sponsor. No additional source documents are required for the scales and assessments (See Section 6.3) which are completed by the subject in the eDiary.

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

6.2. Safety Assessments

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

Vital signs, weight will be recorded at the scheduled visits as outlined in Table 1. Height will be recorded at Screening visit only.

Vital signs will include body temperature, respiratory rate, sitting arterial systolic and diastolic blood pressure, pulse rate and heart rate.

6.2.2. Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded at the scheduled visits as outlined in Table 1. The investigator will determine if any ECG abnormalities are clinically significant or not. (see Section 16.2. Appendix 2)

6.2.3. Physical Exam

Subjects will undergo a routine physical examination at the scheduled visits as outlined in Table 1. Physical examinations to include at minimum examination of heart, abdomen, lungs, and neurologic system with review of any other system to be guided by symptoms.

6.2.4. Laboratory Assessments

The investigator must review all laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF (see guidance in Section 8.2.2). 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 laboratory tests with abnormal values considered to be clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a reasonable period of time as judged by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and Table 1.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in study management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

6.2.4.1. Laboratory Testing

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

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count (WBC) with differential, and platelets.

Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, T bili, direct bilirubin, indirect bilirubin, CK, HbA1c.

End of Treatment Visit:

- Elevations in CK (>5 × ULN) may have further CK fractionation tests performed through the central lab.

- Elevations in AST/ALT [≥3 × ULN in subjects with AST/ALT baseline value within normal range; AST or ALT ≥2 times the baseline values AND ≥3 × ULN, or ≥8× ULN (whichever is smaller) in subjects with AST or ALT baseline values above the normal range] or T bili [≥2 × ULN in subjects with T bili baseline value within normal range with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available; T bili level increased from baseline value by an amount of ≥1 × ULN or if the value reaches ≥3 × ULN (whichever is smaller) in subjects with T bili baseline values above the normal range] may have reflex to GGT, HAV antibody (HAVIgM), Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (HBcIgM) and Hepatitis C Antibody (HCVAb)

Lipid panel: Cholesterol, LDL, HDL, triglycerides.

Estimated glomerular filtration rate: eGFR will be calculated and reported by the central lab at each visit that clinical laboratory tests are collected as outlined in Table 1.

Urinalysis: pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose and blood. If blood, protein or leukocytes are positive and determined clinically significant by the investigator, then the subject should be asked to return for an unscheduled visit for microscopic examination.

Urine Drug Screen: For drugs of abuse.

FSH: For WOCBP at screening, to determine WOCBP status, if required.

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

6.2.4.2. Pregnancy Testing

Pregnancy tests will be conducted (serum, urine, home pregnancy) as outlined in Table 1. All WOCBP should use the home pregnancy test provided at Baseline Visit. Home pregnancy test should be administered prior to taking Investigational Study Drug. Subjects should not take Investigational Study Drug if the pregnancy test is positive, and subject should immediately contact Study Investigator.

A serum pregnancy test will be completed at Screening and End of Treatment Visits as part of the standard laboratory tests (if appropriate). Confirmatory urine pregnancy test for WOCBP should be completed on site at Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment[14]. The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[15] will be used at subsequent visits in this study.

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

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.

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

6.3. Efficacy Assessments

6.3.1. Pain

Subjects are given an eDiary to record their migraine pain score, on a 4-point numeric rating [no pain, mild pain, moderate pain, severe pain] at the time points indicated in Table 1.

6.3.2. Nausea, Phonophobia and Photophobia

The migraine associated symptoms of photophobia, phonophobia and nausea are measured on a 2 point scale (present or absent), using the eDiary, at the time points listed in Table 1. If a subject reports the presence of a symptom, the subject is then asked to rate the severity of the symptom on a 4-point scale (none, mild, moderate or serve). All assessments are done using the eDiary.

The subjects are also asked to identify their most bothersome symptom on the eDiary (nausea, phonophobia or photophobia) at the onset of the migraine to be treated. The most bothersome symptom must be identified before the subject takes study drug.

6.3.3. Rescue Medication

The subject's use of rescue medication is recorded by the subject in a paper diary.

6.3.4. Functional Disability

Impact of treatment on functional disability will be assessed using a single-question scale. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions. This is done in the eDiary, at the times indicated in Table 1, using a 4-point numeric rating scale: Normal Function, Mild Impairment, Severe Impairment, Required Bedrest.

6.4. Early Discontinuation from the Study

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 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 Sponsor.

- 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

All subjects who discontinue should comply with protocol specified End of Treatment 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 (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

6.4.1. Lost to Follow Up

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

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

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

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

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

7. STUDY DRUG MANAGEMENT

7.1. Description of Study Drug

7.1.1. Investigational Product

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

- A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized

form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

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

In this protocol, investigational product is/are: rimegepant and the matching placebo

7.1.2. Packaging, Shipment and Storage

Study drug will be packaged in blister packaging, which is heat sealed into a wallet. Study drug is a double-blind double dummy design to maintain the blind, as the different rimegepant strength ODTs have different flavours.

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

7.2. Dose and Administration

7.2.1. Method of Assigning Subject Identification

Immediately after written informed consent is obtained and before performing any study-related procedures, the site staff must obtain a subject identification by adding a new subject in the appropriate study-related system. In this study, an IWRS system will be utilized for obtaining subject identification. Each subject will be assigned a unique subject number through the appropriate study-related system. The subject number must not be reused for any other study subjects.

After completion of all screening evaluations all eligible subjects will be randomized in a 1:1:1 ratio to the rimegepant 25 mg, 75 mg or placebo treatment groups. **The randomization will be stratified by the use of prophylactic migraine medications (yes or no). It is important to correctly enter subjects who are using prophylactic migraine medication in the IWRS system. Once a subject is stratified in the IWRS, this cannot be changed and will be considered a protocol deviation if later found to be entered incorrectly.**

Randomization schedules will be generated and kept by the IWRS vendor in a secure network folder with access limited to only unblinded team members. Each subject who is qualified for treatment will be randomized via the IWRS randomization option. Subjects will maintain their subject number assigned at screening throughout the trial. The IWRS will provide the double-blind treatment assignments.

The randomization will trigger a blister card number for the randomized treatment type. The study drug will be dispensed at the time of randomization.

7.2.2. Selection and Timing of Dose and Administration

Two ODTs will be dispensed to each subject as shown in Table 2. There are no dose adjustments in this study and subjects will receive 2 ODTs to treat one migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit). Subjects will be dispensed the study drug at randomization (Baseline Visit) and will take 2 ODTs at the time of moderate or severe migraine headache onset ***ONLY after answering questions regarding their migraine symptoms in the eDiary*** device. The 2 ODTs should be taken together (at the same time) placed on top of or under the tongue until fully dissolved then swallowed. Subjects should be instructed to use dry hands when handling the study drug.

Table 2 Treatment Assignment to each group

	25 mg or matching placebo	75 mg or matching placebo
Rimegepant 25 mg group	25 mg	Matching placebo (matches rimegepant 75 mg)
Rimegepant 75 mg group	Matching placebo (matches rimegepant 25 mg)	75 mg
Placebo group	Matching placebo (matches rimegepant 25 mg)	Matching placebo (matches rimegepant 75 mg)

7.2.3. Dose Modifications

There will be no dose adjustments in this study.

7.3. Blinding and Unblinding

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

Before breaking the blind of an individual subject's treatment, the Investigator should have determined that the information is necessary, (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.
In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind for remaining site personnel.

7.4. Treatment Compliance

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

Subjects will be counseled on the importance of taking the study drug as directed when a migraine occurs and reaches moderate or severe intensity. If the subject does not have a

migraine or take their study drug within 45 days of the Baseline Visit, they should return to the clinic for their End of Study Visit and return their unused study drug.

Subjects who take study drug will be asked to return all empty blister packaging and wallets to the study site at the End of Study Visit.

7.5. Destruction and Return of Study Drug

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

AEs 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.

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

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

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

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

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

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

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

Assessment for Determining Relationship of AE to Study Drug:

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

Related: This category applies to AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered related when it follows a temporal

sequence from the administration of study drug, it cannot reasonably be explained by the known characteristics of the subject's clinical state, environment, or toxic factors, or other modes of therapy administered to the subject. An AE may be considered related when it follows a known pattern of response to the study drug, or if the AE reappears upon re-challenge.

Possibly related (non-serious AEs only): This category applies to AEs that are considered to have an unlikely connection to study drug, but a 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 2 types of AEs, SAEs and Non-Serious AEs. Subjects should be instructed to notify the Investigator when a SAE occurs.

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)

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

The following hospitalizations are not considered SAEs in this study (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 that occur from the time the informed consent form (ICF) is signed and throughout the course of the study up to and including the End of Treatment Visit. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study drug, overdose (see Section 8.3), potential drug induced liver injury (see Section 8.4) and pregnancies (see Section 8.5.1) must be reported within 24 hours of the Investigator becoming aware of the event. For this study, SAEs will be captured through EDC and on the SAE report.

The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) and/or the head of the institutional site 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 safety reporting system (i.e.: event term, start stop dates, causality, severity).

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to the Pfizer Drug Safety Unit (DSU) within 24 hours of learning of the event.

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, that must be sent by facsimile (fax or eFax) or email to the Pfizer DSU on 0120-442-370 or 03-5309-9061.

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

The minimum information required for an initial SAE report is:

Sender of report (Site number, Investigator name)

Subject identification (subject number)

Protocol number

SAE term (if an SAE is being reported)

8.2. Non-serious Adverse Events

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

8.2.1. Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the Baseline Visit through the End of Treatment Visit.

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

8.2.2. Laboratory Test Abnormalities

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

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

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

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

8.3. Overdose

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

Overdose is reportable to Pfizer Safety only when associated with an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

Asymptomatic dosing errors should be reported as deviations.

8.4. Potential Drug Induced Liver Injury (DILI)

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

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

should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

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

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

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

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

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

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

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

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, or the female partner of a male study subject, is pregnant or may have been pregnant at the time of the investigational product 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's safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the subject unless contraindicated by the pregnancy (ie, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Sites should instruct subjects to contact the Investigator if they become pregnant during the course of the study. The investigator must immediately notify the Pfizer Medical Monitor (or designee) and report the event to the Pfizer DSU by either using the PSSA tool or by completing an EDP Supplemental Form and 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 also be reported as described above.

Any pregnancy that occurs in a female partner of a male study subject should be reported to the Pfizer DSU. Information on this pregnancy will be collected as described above.

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 nonsubject 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 or via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 66 hours after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form or via PSSA. Since the exposure information does not pertain to the 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 follow-up 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 nonsubject 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 via 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 via 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.

8.6. Lack of Efficacy

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

8.7. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

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

8.8. Adverse Events of Special Interest

Not applicable for this study.

9. STATISTICS

Complete details on the statistical methods for this study may be found in the Statistical Analysis Plan (SAP).

9.1. Sample Size

This study will randomize a total of 795 subjects in a 1:1:1 ratio to rimegepant 25 mg, rimegepant 75 mg, or placebo. It is anticipated that this will result in approximately 750 subjects in efficacy analysis set, with roughly 250 subjects in each treatment arm.

Although testing strategy is changed in Protocol version 4.0 and formal hypothesis testing will no longer be conducted for rimegepant 25 mg, the original sample size will remain as it is. The sample size for this study was designed to provide 80% power to test each of the 2 rimegepant doses against placebo at a Bonferroni corrected 2-sided alpha level of 0.025 using a chi-square test. The sample size estimate is based on historical data from pivotal study BHV3000-303, in which the rates of pain freedom were 10.9% for placebo and 21.2% for Rimegepant.

9.2. Analysis Set

The following analysis sets will be used for statistical analyses, as applicable:

- Enrolled: Subjects who sign an ICF and are assigned a subject identification number.
- Full: Subjects in the enrolled analysis set who receive a randomization treatment assignment from the IWRS (rimegepant 25 mg, 75 mg or placebo).
- Safety: Subjects in the enrolled analysis set who take study therapy (rimegepant 25 mg, rimegepant 75 mg, or placebo).
- Efficacy: Subjects in the full analysis set who are randomized only once, take study therapy, have a migraine of moderate or severe pain intensity at the time of treatment, and provide at least one post-dose efficacy data point.

9.3. Statistical Methods

9.3.1. Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be produced for the efficacy and safety analysis sets.

9.3.2. Primary Endpoint(s)

BHV-3000 (rimegepant) 75 mg is tested for superiority to placebo, at a 2-sided alpha level of 0.05, on the primary endpoint of pain freedom at 2 hours post-dose. For rimegepant 25 mg, formal hypothesis testing will not be conducted, and the nominal p-value will be provided only for descriptive purposes.

The endpoint will be evaluated using Mantel-Haenszel risk estimation with stratification by the use of prophylactic migraine medication (yes or no) for the efficacy analysis set. The difference estimate (rimegepant – placebo), 95% CI, and p-value will be reported for each rimegepant treatment group versus placebo. Subjects with missing data at 2 hours post-dose will be imputed to be failure (i.e., Non-completer = Failure; NC=F).

Subjects who use rescue medication at or before the assessment of their primary endpoint will be classified as failures. Sensitivity analyses are described in the Statistical Analysis Plan (SAP).

9.3.3. Secondary Endpoint(s)

The same statistics for secondary endpoints (as listed in Section 3.2) will be presented as those for the primary endpoint.

For endpoints based on a single time point, such as pain freedom at 2 hours post-dose, subjects with missing data at a single time point will be classified as failures (NC=F). For endpoints based on multiple time points, such as sustained pain relief from 2 to 48 hours post-dose, subjects with missing data at (1) 2, 24, or 48 hours post-dose, or (2) more than 1 time point from 3 to 8 hours post-dose will also be classified as failures.

For all secondary endpoints except the rescue medication use within 24 hours post-dose, subjects who use rescue medication at or before the assessment of their endpoint will be classified as failures.

See section 9.3.5 for safety endpoints.

9.3.4. Multiplicity Correction

For rimegepant 75 mg, if the primary endpoint test is significant, then the secondary endpoints will be evaluated using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha=0.05. Testing will stop at the first non-significant endpoint. Nominal p-value will still be reported but will not be used for inference purpose.

These secondary endpoints will be tested in the order shown in the Study Objectives section of this protocol.

For rimegepant 25 mg, formal hypothesis testing will not be conducted, and the nominal p-values will be presented only for descriptive purposes as described in Section 9.3.2.

9.3.5. Analysis of Safety

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

Deaths will be listed for the enrolled analysis set without regard to onset.

The frequencies of the following on-treatment safety events and findings will be summarized by treatment group for the safety analysis set: SAEs; AEs by intensity; AEs by relationship to study drug; laboratory test abnormalities by toxicity grade; and liver function test elevations based on fold changes above the upper limit of normal.

Laboratory test results will be graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017), if available. Otherwise, if CTCAE grades are not available, then results will be graded according to numeric laboratory test criteria in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017). If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported.

Further safety analyses will be described in the SAP.

9.4. Schedule of Analyses

There is a final analysis after the last subject has his/her last visit. No interim analyses are anticipated.

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 Institutional Review Board/Independent Ethics Committee (IRB/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 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 IECs 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

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

This study will not make use of a Data and Safety Monitoring Committee. Rimegepant has been found to be well tolerated in previous clinical studies and post-marketing in the U.S. Safety will be closely monitored via the sites and procedures for unblinding in cases of emergency will be followed.

10.3. Institutional Review Board/Independent Ethics Committee

The Investigators or the head of institutional sites 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.

10.4. 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 regarding clinical studies in which they volunteer to participate.

Pfizer (or designee) will provide the investigator with an appropriate sample ICF which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample ICF 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 read, sign and date an IRB/IEC approved written ICF 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 ICF versions and a copy of each version of the IRB/IEC approved protocol and ICF 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 ICF must also include a statement that Pfizer and its representatives and regulatory authorities may have direct access to subject records.

10.5. 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.

10.6. 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.

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.

10.6.1. Data sharing

Pfizer provides researchers secure access to subject-level data or full CSRs for the purposes of “bona-fide 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.

10.7. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the principal investigator ISF.

To facilitate access to their investigator and the sponsor's MQI for study related medical questions or problems from nonstudy healthcare professionals, subjects are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) subject's study identification number, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

The ECC is intended to augment, not replace, the established communication pathways between the subject and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a subject. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the subject directly; if a subject calls that number directly, they will be directed back to the investigator site.

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 and/or the head of institutional site 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 and/or the head of institutional site must contact the Sponsor prior to destroying any records associated with this study.

Pfizer will notify the investigators and/or the head of institutional site 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 or designee to ensure that the current disposition record of investigational product (may be supplied by the sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount of study drug received and placed in storage area
- label ID number or batch number or Kit number as specified for the protocol
- amount dispensed to and returned from each subject
- amount transferred to another area or site for dispensing or storage if applicable
- amount of drug lost or wasted
- amount destroyed at the site if applicable
- amount returned to sponsor, if applicable
- retain samples for bioavailability/bioequivalence, if applicable
- record of dates and initials of personnel responsible for IM dispensing and accountability

11.1. Source Documentation

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

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

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

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

11.2. Study Files and Record Retention

The Sponsor does not require original documents that have already been scanned and entered into the eTMF system to be forwarded to the Sponsor. Any original documents (e.g. 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. training materials) should be maintained by the CRO. The Sponsor will be contacted to determine whether the study documents/materials that are retained outside of the TMF will be forwarded to the Sponsor, destroyed or kept at the CRO or at another facility for a longer period of time at the Sponsor's expense.

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

12. AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Pfizer. 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 will submit protocol amendments to the appropriate regulatory authorities for approval.

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

13. PUBLICATIONS POLICY

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

14. STUDY DISCONTINUATION

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

15. DATA PROTECTION

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of 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 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)

The following medications and medication combinations are moderate to strong inhibitors of CYP3A4. This list should not be considered all-inclusive. As described in the study protocol, concomitant use of moderate to strong CYP3A4 inhibitors is prohibited. Individual drug labels should be reviewed for specific information on propensity to cause moderate to strong inhibition of the CYP3A4 enzyme for a specific compound.

Strong CYP3A4 inhibitors
Boceprevir, cobicistat, conivaptan, 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.

Moderate CYP3A4 inhibitors
Amprenavir, aprepitant, casopitant, cimetidine, ciprofloxacin, diltiazem, dronedarone, erythromycin, fluconazole, Seville orange, isavuconazole, lefamulin, letermovir, netupitant, ravuconazole, verapamil

The following medications and supplements are moderate to strong inducers of CYP3A4. As described in the study protocol, concomitant use of moderate to strong CYP3A4 inducers is prohibited. This list should not be considered all-inclusive. Individual product labels should be reviewed for specific information on propensity to cause moderate to strong induction of the CYP3A4 enzyme for a specific compound.

Strong CYP3A4 inducers
Carbamazepine, phenytoin, rifampin, St. John's Wort, rifapentine, phenobarbital, apalutamide

Moderate CYP3A4 inducers
Bosentan, rifabutin, modafinil, nafcillin, efavirenz, etravirine, lopinavir

The following medications are strong P-glycoprotein (P-gp) inhibitors. As described in the study protocol, concomitant use of strong P-gp inhibitors is prohibited. This list should not be considered all-inclusive. Individual product labels should be reviewed for specific information on propensity to strongly inhibit P-gp for a specific compound.

Strong P-gp Inhibitors
Amiodarone, clarithromycin, cyclosporine, dronedarone, itraconazole, lapatinib, propafenone, quinidine, ritonavir, verapamil

Resources:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3

Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010 Oct;5(1):61-72

University of Washington Metabolism and Transport Drug Interaction Database accessible at https://www.druginteractioninfo.org/

16.2. APPENDIX 2 – ECG Findings of Potential Clinical Concern

ECG Findings That May 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 May Qualify as SAEs

- QTcF prolongation >500 ms.
- Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms.
- New ST-T changes suggestive of myocardial ischemia.
- New-onset LBBB (QRS complex >120 ms).
- New-onset right bundle branch block (QRS complex >120 ms).
- Symptomatic bradycardia.
- Asystole
  - In awake, symptom-free subjects in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  - In awake, symptom-free subjects with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
- Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) (“sustained” = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

16.3. APPENDIX 3 – Protocol Amendment History

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	04-Apr-2022
Version 2.0	• Updated Section 4.3, Schedule of Assessments: history of triptan use and CV risk factors added • Updated Section 5.2, Inclusion Criteria: inclusion criteria 2g clarified. • Updated Section 5.3, Exclusion Criteria: exclusion criteria 1a reworded. • Updated Section 5.4, Prohibited and Restricted Concomitant Medications: Traditional Chinese Medicines and Lasmiditan added. • Corrected inconsistencies and typographical errors throughout the protocol.	30-Aug-2022
Version 3.0	• Updated Section 5.2, Inclusion Criteria: inclusion criteria 2g modified. • Updated Section 5.3, Exclusion Criteria: exclusion criteria 1a, 1b, 2i, 2n, 5f, 5g and 5i modified. • Updated Section 5.4, Prohibited and Restricted Concomitant Medications: #8,9 and 18 modified. • Updated Section 5.5, Rescue Medications: Revision to upper limit of acetaminophen dose from 1000 mg/day to 2000 mg/day. • Updated Section 8.1.2, Collection and Reporting Serious Adverse Events: immediate notification to the Medical Monitor no longer required. • Provided clarifications throughout the protocol. • Corrected inconsistencies and typographical errors throughout the protocol.	27-Feb-2023

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Document Approval Record

Document Name:	BHV3000-313_C4951022_Protocol_V.4.0
Document Title:	BHV3000-313_C4951022_Protocol_V.4.0

Signed By:	Date(GMT)	Signing Capacity
PPD	03-Aug-2023 07:07:18	Final Approval
PPD	03-Aug-2023 08:27:19	Final Approval