DRUG:	BHV-3000 (PF-07899801) (rimegepant)
STUDY NUMBER(S):	BHV3000-309 (C4951021)
PROTOCOL TITLE:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects
IND NUMBER:	N/A
EudraCT NUMBER: (if applicable)	N/A
ClinicalTrials.gov ID:	NCT05399485
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	04-Apr-2022
VERSION NUMBER:	5.0
VERSION DATE:	04-Aug-2023
BRIEF TITLE:	Efficacy and Safety Study of Rimegepant for Migraine Prevention in Japanese Subjects

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 5.0 (04 August 2023)
Overall Rationale for the Amendment: Change in sponsorship from Biohaven to Pfizer

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Referenced study number BHV3000-309 to C4951021 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
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 #7i
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 and Devices #22
Removed tacrolimus from the Strong CYP3A4 inhibitors list. Removed grapefruit juice from the Moderate CYP3A4 inhibitors list.	Aligned with nonclinical and clinical drug to drug interaction (DDI) information available on rimegepant.	16.1 APPENDIX 1 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)
Changed the term Botox® to botulinum toxin injections.	Added broader drug class term.	5.5 Prophylactic and Rescue Medications 16.3 APPENDIX 3 – Categories of Migraine Prevention Medications
Changed term non-migraine to non-headache.	Clarified to include broader definition of headache which includes non-migraine and migraine headache.	5.4. Prohibited and Restricted Concomitant Medications #9
Updated potential drug-induced liver injury (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. Safety Laboratory Testing 8.4 Potential Drug Induced Liver Injury (DILI)
Clarified the requirement on the use of menstrual period paper log.	Clarified that menstrual period paper log is required only for women of childbearing potential (WOCBP).	4.3. Schedule of Assessments
Added appendix for ECG Findings of Potential Clinical Concern.	Aligned with Pfizer protocol template.	16.4. APPENDIX 4 – 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 the instruction for re-screening.	Clarified in accordance with the Dear Investigator Letter dated 17May2023.	4.3.1.1 Screening Visit 4.3.1.2 Pre-randomization Evaluation Visit
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
Clarified definition of analysis sets/Added analysis sets.	Aligned with Statistical Analysis Plan.	9.2 Analysis Set
Clarified/corrected statistical methods.	Provided updates, corrections or clarifications. Aligned with Statistical Analysis Plan.	9.1 Sample size 9.3.1 Primary Endpoint(s) 9.3.2 Secondary Endpoint(s) 9.3.3 Multiplicity Correction 9.3.4. Analysis of Safety
Clarified schedule of analyses.	Details on the schedule of analyses were added.	9.4 Schedule of Analyses
Updated text for Data Protection.	Aligned with Pfizer protocol template.	15. DATA PROTECTION
Added compliance aim for investigational product (IP) of 80%.	Defined compliance for clarity.	7.4 Treatment Compliance
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 Section 8.3. Overdose.	Overdose is reportable to Pfizer Safety only when associated with an SAE.	8.3. Overdose

Updated the publication policy.	Updated in alignment with the change in sponsorship.	13. Publications Policy
Added adverse event (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
Moved prior Protocol Amendment Summary of Changes to Appendix.	Editorial.	16.5 APPENDIX 5 – 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: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects

Brief Title: Efficacy and Safety Study of Rimegepant for Migraine Prevention in Japanese Subjects

Regulatory Agency Identification Number(s):

US IND Number:	NA
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05399485
Pediatric Investigational Plan Number:	NA
Protocol Number:	BHV3000-309 (C4951021) Version 5.0
Phase:	3

Rationale:

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 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.

Additionally, in a double-blind placebo-controlled study rimegepant at a dose of 75 mg dosed every other day (EOD) demonstrated superiority to placebo on the primary endpoint of mean change from the Observation Period (OP) in the number of migraine days per month on treatment in the last month (Weeks 9 to 12) of the Double-blind Treatment Phase.

This study is being conducted to evaluate the efficacy, safety, and tolerability of rimegepant in Japanese subjects for the prevention of migraine.

Primary Objectives:

To compare the efficacy of rimegepant relative to placebo as a preventive treatment for migraine.

Secondary Objectives:

- To compare the efficacy of rimegepant to placebo on the following endpoints:
    - Proportion of the subjects that have ≥50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks of the Double-blind Treatment Phase

- The mean reduction from baseline in the number of migraine days per month over the entire course of the Double-blind Treatment Phase.

- The mean reduction from baseline in the number of migraine days per month in the first 4 weeks of the Double-blind Treatment Phase.

- The mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month in the last 4 weeks of the Double-blind Treatment Phase.

- To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1) role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

- To compare the mean change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

- To compare the mean change from baseline in the EuroQol 5 dimensions 5-level (EQ-5D-5L) visual analog scale (VAS) score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

- To evaluate the frequencies of AEs by intensity, SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

- To evaluate the frequency of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN) concurrent with total bilirubin (T bili) >2 × ULN in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

- To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

Primary Endpoint:

Mean change from baseline in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.

Secondary Endpoints:

1. Proportion of subjects with ≥50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.

2. Mean change from baseline in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).

3. Mean change from baseline in the number of migraine days per month in the first 4 weeks (Weeks 1 through 4) of the Double-blind Treatment Phase.

4. Mean number of acute migraine-specific medication days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase. Acute migraine-specific medications are triptans and ergotamine.

5. Mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase.

6. Mean change from baseline in the MIDAS total score at Week 12 of the Double-blind Treatment Phase.

7. Mean change from baseline in the EQ-5D-5L VAS score at Week 12 of the Double-blind Treatment Phase.

8. Number and percentage of subjects with AEs by intensity, SAEs, AEs leading to study drug discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the Double-blind Treatment and Open-label Extension Phases.

9. Number and percentage of subjects with AST or ALT elevations > 3 x ULN concurrent (i.e., on the same laboratory collection date) with T bili > 2 x ULN on treatment during the Double-blind Treatment and Open-label Extension Phases.

10. Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment during the Double-blind Treatment and Open-label Extension Phases.

Overall Design:

This is a multicenter, randomized, double-blind, placebo-controlled bridging study to assess the efficacy and safety of rimegepant in migraine prevention in Japanese subjects with an Open-label Extension Phase.

The study will randomize approximately 490 subjects in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

The Screening Phase includes a Screening Visit and a 28-day OP. Upon completion of the Screening Visit, subjects will be provided an electronic diary (eDiary) to document migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication on each day of the 28-day OP. Subjects will record the standard of care migraine treatment received on a paper diary. For subjects to be eligible for the study, they must report

having had 4 to 18 migraine attacks of moderate to severe intensity per 4-week period within the 12 weeks prior to the Screening Visit, and at least 4 migraine days and no more than 18 headache days during the 28-day OP. After completing the 28-day OP, the subject will return to the clinical with both diaries for the Baseline Visit.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and before study drug is dispensed. Subjects will be instructed that they must take 1 orally disintegrating tablet (ODT) of blinded study drug (rimegepant 75 mg or placebo) every other calendar day. If subjects have a migraine attack during the Double-blind Treatment Phase, if needed, they may treat the migraine attack with their standard of care medication and continue to take study drug on their regular schedule (scheduled dosing days only).

At the completion of the 12-week Double-blind Treatment Phase, subjects may be entered into the 40-week Open-label Extension Phase following laboratory results within acceptable ranges. During the Open-label Extension Phase, subjects will be instructed that they must take 1 rimegepant 75 mg every other calendar day. If subjects have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the Open-label Extension Phase, subjects can take a maximum of 1 rimegepant 75 mg ODT per calendar day up to 40 weeks.

Subjects are required to record their migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary. Subjects are also required to record any rescue medication taken on a paper diary and WOCBP will record their menstrual period information on a paper log.

At select study visits, subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1), the Migraine Disability Assessment (MIDAS), EQ-5D-5L and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Additional assessments and visit schedule are outlined in the procedural table in Section 4.3.

Study visits will occur at Screening (Enrollment), Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12. At the completion of the 12-week Double-blind Treatment Phase, subjects may be entered into the 40-week Open-label Extension Phase following laboratory tests within normal ranges. Visits occur at Week 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/ End of Treatment (EOT). Subjects will return to the study site at the end of Week 52 (+/-3 days) for the EOT Visit. Any subject who discontinues early, at any time during the study, will return to the study site for the EOT Visit. There is a Follow-up Visit 14 days (+/-2 days) after the EOT Visit. Subjects who do not complete the Double-blind Treatment Phase and/or do not enter or complete the Open-label Extension Phase should complete the EOT and the Follow-up Week 2 Visits.

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

Number of Subjects:

Approximately 1064 subjects will be screened to randomize up to approximately 490 subjects (245 subjects to each of the rimegepant or placebo groups). It is estimated that approximately 400 subjects will be entered into the Open-label Extension Phase.

Study Population:

The study will recruit male and female subjects, 18 years of age or older with at least a 1-year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition. Per their own report, subjects must have migraine onset prior to age 50, migraine attacks that last 4 to 72 hours (if not treated) and have had, 4-18 ***migraine attacks*** of moderate to severe intensity per 4 week period within the 12 weeks prior to the Screening Visit.

Statistical Methods:

The study will randomize roughly 245 subjects per treatment arm to obtain roughly 225 evaluable subjects per treatment arm. With a sample size of roughly 490 subjects randomized, and 245 subjects per group, we expect roughly 225 evaluable subjects per group in the double-blind treatment migraine analysis set. Assuming rimegepant provides roughly a 1 day advantage over placebo on the primary endpoint, and a common standard deviation of 3.75 days, then the study will have roughly 80% power on the primary endpoint at a 2-sided alpha level of 0.05.

The primary endpoint, mean change from OP in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBP phase will be assessed using a linear mixed effects model with repeated measures.
The proportion of subjects with ≥50% reduction from baseline in the number of moderate or severe migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase will be analyzed using a Mantel-Haenszel risk estimation with stratification by randomization stratum.

The mean change from baseline in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed with the same model used for the primary endpoint.

The mean change from baseline in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the Double-blind Treatment Phase will be assessed with the same model used for the primary endpoint.

The mean number of acute migraine-specific medication days per month in the last 4 weeks (Weeks 9 to 12) of Double-blind Treatment Phase will be assessed using a linear mixed effects model with repeated measures.

The mean changes from baseline in MSQoL role function - restrictive domain score, MIDAS total score, and EQ-5D-5L VAS score at Week 12 will be assessed using linear models.

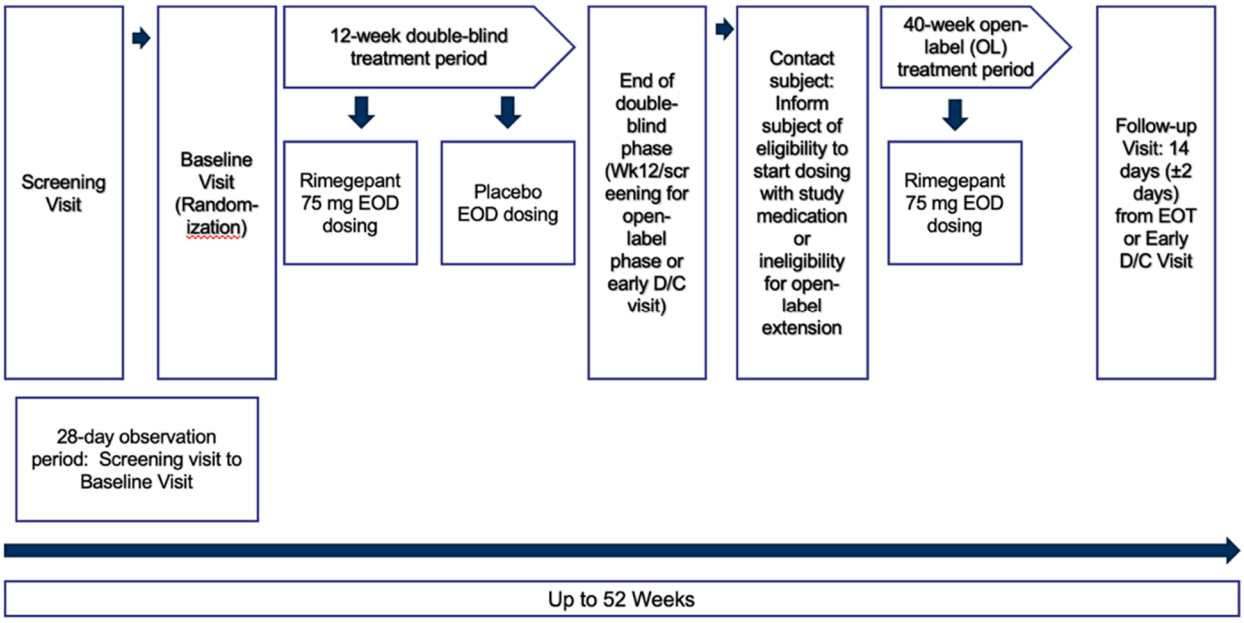
Safety endpoints will be assessed descriptively.

Ethical Considerations:

Broad and sustained efficacy of rimegepant 75 mg was demonstrated in 3 previously completed Phase 3 studies (BHV3000-301, BHV3000-302 and BHV3000-303). Statistically significant efficacy was demonstrated on the co-primary endpoints of freedom from pain, and freedom from most bothersome symptom at 2 hours post-dose. Also, in all 3 studies, significant results were achieved on photophobia freedom, phonophobia freedom and pain relief at 2 hours post-dose. Similar results were demonstrated in the BHV3000-310 study recently completed in China and Korea. In the Phase 2/3 placebo-controlled study (BHV3000-305) for the preventive treatment of migraine, rimegepant at a dose of 75 mg 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.

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

ADHD	Attention-Deficit Hyperactivity Disorder
ACE	Angiotensin converting enzyme
AE	Adverse Event
ALT	Alanine Aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate Aminotransferase
AV	Atrioventricular
BHV	Biohaven
bpm	beats per minute
BUN	Blood Urea Nitrogen
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence interval
CK	Creatine kinase
COVID-19	Coronavirus Disease of 2019
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
EOT	End of Treatment
EQ-5D-5L	EuroQol 5 dimensions 5-level
eTMF	electronic Trial Master File
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HbA1c	Hemoglobin A1c
HR	heart rate
HRT	hormone replacement therapy
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IHS	International Headache Society
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product

IRB	Institutional Review Board
ISF	investigator site file
IWRS	Interactive Web Response System
kg	Kilogram
L	Liters
LBBB	left bundle branch block
LFT	Liver Function Test
LSLV	last subject last visit
mg	Milligram
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MSQoL	Migraine-Specific Quality-of-Life Questionnaire
min	Minute
mmHg	Millimeters Mercury
MQI	medically qualified individual
NSAID	Nonsteroidal Anti-inflammatory Drugs
ODT	Orally disintegrating tablets
OP	Observation period
PACL	Protocol Administrative Clarification Letter
PCD	primary completion date
PCP	Phencyclidine
P-gp	P-glycoprotein
PK	Pharmacokinetic
PRN	Pro re nata, as needed
PSSA	Pfizer SAE Submission Assistant
PT	prothrombin
PVC	premature ventricular contraction
QTc	Interval between Q-wave and T-wave in the cardiac cycle
QTcF	QTc corrected using Fridericia's formula
QTL	Quality Tolerance Limits
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SE	Standard error
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
VAS	Visual Analog Scale
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 8,900 unique subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine; of these, approximately 6,036 unique subjects have received rimegepant at any dose. Overall, 1,857 unique subjects received rimegepant 75 mg in single dose studies: 1,771 unique subjects in the 3 pivotal Phase 3 single-dose, placebo-controlled, acute treatment studies (i.e., BHV3000-303[7], BHV3000-302[8], and BHV3000-301[9]), and 86 subjects in the Phase 2b dose-ranging study CN170003[10]. Safety data are also available for the 2,471 subjects who received rimegepant 75 mg in the Phase 2/3 multiple dose studies (BHV3000-201[11] and BHV3000-305[12]). In the pivotal migraine prophylaxis study (BHV3000-305), the Open-label Extension Phase remains ongoing, and a total of 527 subjects received rimegepant 75 mg (EOD or EOD + PRN up to once daily for at least 6 months, and 416 subjects received rimegepant for at least 1 year. In the supportive long-term safety study (BHV3000-201), a total of 1,154 subjects received rimegepant 75 mg for at least 6 months, and 368 subjects received rimegepant for at least 1 year.

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

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 two 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 drug-drug interactions; 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 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 electrocardiograms (ECGs). Safety data from the double-blind treatment and the open-label extension phases of the pivotal Phase 2/3, randomized, double-blind, placebo-controlled preventive treatment of migraine study (BHV3000-305) support a favorable safety profile of rimegepant 75 mg administered EOD for the preventive treatment of migraine. Rimegepant 75 mg administered EOD + PRN 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 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. WOCBP must have a negative pregnancy test and WOCBP and fertile men

must use two 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 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's Brochure, which is the single reference safety document (SRSD) for this study.

1.5. Study Rationale

The demonstrated efficacy of rimegepant in adults in the 3 pivotal Phase 3 registrational trials in the acute treatment of migraine and the safety profile observed to date in the Phase 2/3 BHV3000-201 long-term open-label safety study with up to daily dosing for as long as 1 year suggest that rimegepant may have an important role in the treatment of migraine.

Additionally, the U.S. trial BHV3000-305, a Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety in the preventive treatment of migraine, demonstrated efficacy of rimegepant in the preventing treatment of episodic migraine in adults.

The above package of studies supported the registration and approval of rimegepant in the US, UK and EU. for the acute treatment of migraine and for migraine prophylaxis. The purpose of the current study is to provide confirmatory evidence of the efficacy of rimegepant for migraine prophylaxis in Japanese subjects with migraine, thus permitting bridging to the results from the global rimegepant efficacy and safety program.

1.5.1. Study Design Rationale

This is a 12-week multicenter, randomized, double-blind, placebo controlled evaluation of the safety and efficacy of rimegepant 75 mg ODT taken every other day for the prevention of migraine with a 40-week Open-label Extension Phase. Up to approximately 490 subjects will be randomized and assigned treatment in the Double-blind Treatment Phase; it is estimated that approximately 400 subjects will enter the Open-label Extension Phase. During the Double-blind Treatment Phase, subjects will be instructed that they must take 1 ODT of blinded study drug every other calendar day. If subjects have a migraine during the Double-blind Treatment Phase, if needed, they may treat the migraine with their standard of care medication and continue to take study medication on their regular schedule (scheduled dosing days only).

During the Open-label Extension Phase, subjects will be required to take 1 ODT of rimegepant every other calendar day. However, if subjects have a migraine on a day that they are not

scheduled to dose with rimegepant, they may take 1 ODT of rimegepant on that calendar day to treat the migraine. Dosing with more than 1 ODT of study medication per calendar day is not permitted. Therefore, subjects can take a maximum of 1 ODT of study drug per calendar day for the 40 weeks of the Open-label Extension Phase.

The study will randomize approximately 490 subjects and it is expected that approximately 400 subjects will enter the Open-label Extension Phase. During the Double-blind Treatment Phase, the subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups, stratified by current use of prophylactic migraine medications (yes or no).

1.5.2. Dose Selection Rationale

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine. The 3 Phase 3 studies BHV3000-301, BHV3000-302, and BHV3000-303 confirmed this efficacy using the current registrational endpoints for acute treatment of migraine. Likewise, the adult prevention study, BHV3000-305, confirmed that 75 mg EOD is an effective dose for the preventive treatment of episodic migraine in adults.

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.

Thus, the 75 mg EOD dose is hypothesized to be effective in Japanese patients for the prevention of episodic migraine.

1.5.3. Research Hypothesis

Rimegepant is a safe and effective treatment for the prevention of migraine in Japanese subjects.

2. STUDY OBJECTIVES

2.1. Primary Objective(s)

To compare the efficacy of rimegepant relative to placebo as a preventive treatment for migraine as measured by the mean reduction from baseline in the number of migraine days per month in the last 4 weeks of the Double-blind Treatment Phase (A month is defined as 4 weeks for the purpose of this protocol).

2.2. Secondary Objective(s)

1. To compare the efficacy of rimegepant to placebo on the proportion of the subjects that have ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks of the Double-blind Treatment Phase.

2. To compare the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month over the entire course of the Double-blind Treatment Phase.

3. To compare the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month in the first 4 weeks of the Double-blind Treatment Phase.

4. To compare the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month in the last 4 weeks of the Double-blind Treatment Phase.

5. To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1) role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

6. To compare the mean change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

7. To compare the mean change from baseline in the EQ-5D-5L visual analog scale (VAS) score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

8. To evaluate the frequencies of AEs by intensity, SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

9. To evaluate the frequency of ALT or AST >3 x ULN concurrent with T bili >2 x ULN in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

10. To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

2.3. Exploratory Objective(s)

1. To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Double-blind Treatment Phase.

2. To evaluate the efficacy of rimegepant to placebo on the proportion of the subjects that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Double-blind Treatment Phase.

3. To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase.

4. To evaluate the mean reduction in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Open-label Extension Phase.

5. To evaluate the proportion of the subjects that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Open-label Extension Phase.

6. To evaluate the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month and acute migraine medication days per month in each month and the entire course of the Double-blind Treatment Phase.

7. To evaluate the mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the Open-label Extension Phase.

8. To evaluate the mean changes from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L VAS score over time during the Double-blind Treatment and Open-label Extension Phases.

3. STUDY ENDPOINTS

Migraine days per month, acute migraine-specific medication days per month, and acute migraine medication days per month are derived from eDiary data. For these endpoints, the Observation Period represents "baseline".

AEs are determined from case report forms (CRFs).

MSQoL domain scores, MIDAS scores, and EQ-5D-5L VAS score are derived from eDiary data.

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

3.1. Primary Endpoint(s)

Mean change from baseline in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.

3.2. Secondary Endpoint(s)

1. Proportion of subjects with ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.

2. Mean change from baseline in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).

3. Mean change from baseline in the number of migraine days per month in the first 4 weeks (Weeks 1 through 4) of the Double-blind Treatment Phase.

4. Mean number of acute migraine-specific medication days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase. Acute migraine-specific medications are triptans and ergotamine.

5. Mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase.

6. Mean change from baseline in the MIDAS total score at Week 12 of the Double-blind Treatment Phase.

7. Mean change from baseline in the EQ-5D-5L VAS score at Week 12 of the Double-blind Treatment Phase.

8. Number and percentage of subjects with AEs by intensity, SAEs, AEs leading to study drug discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the Double-blind Treatment and Open-label Extension Phases.

9. Number and percentage of subjects with of AST or ALT elevations > 3 x ULN concurrent (i.e., on the same laboratory collection date) with T bili > 2 x ULN on treatment during the Double-blind Treatment and Open-label Extension Phases.

10. Number and percentage of subjects with hepatic-related AEs and hepatic-related AEs leading to study drug discontinuation on treatment during the Double-blind Treatment and Open-label Extension Phases.

3.3. Exploratory Endpoint(s)

1. Mean change from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Double-blind Treatment Phase.

2. Proportion of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Double-blind Treatment Phase.

3. Mean change from baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks Double-blind Treatment Phase.

4. Mean change from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Open-label Extension Phase.

5. Proportion of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the Open-label Extension Phase.

6. Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the Double-blind Treatment Phase. Acute migraine medications are triptans, ergotamine, and other medications used to treat headache or aura.

7. Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the Open-label Extension Phase.

8. Mean change from baseline in MSQoL domain scores (restrictive role function, preventive role function, emotional function), MIDAS scores (total, absenteeism, presenteeism), EQ-5D-5L VAS score over time during the Double-blind Treatment Phase and Open-label Extension Phase.

3.4. Definition of Migraine Days

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

A) ≥ 2 of the following pain features:

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

B) ≥ 1 of the following associated symptoms:

- Nausea and/or Vomiting,
- Photophobia and phonophobia

During the Double-blind Treatment Phase, if the subject takes an acute migraine-specific medication (i.e., triptan or ergotamine) during aura or to treat a headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. The use of study medication on non-scheduled dosing days is only permitted during the Open-label Extension Phase. ***Dosing with study medication on non-scheduled dosing days is not permitted during the Double-blind Treatment Phase***.

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

For the full definition of Migraine Days, please refer to Section 16.2 APPENDIX 2.

3.5. Definition of Headache Days

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

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

4. STUDY PLAN

4.1. Study Design and Duration

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention in Japanese subjects.

The study will randomize approximately 490 subjects in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

The Screening Phase includes a Screening Visit and a 28-day Observation Period. Upon completion of the Screening Visit, subjects will be provided an electronic diary (eDiary) to document migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication on each day of the 28-day Observation Period. Subjects will record the standard of care migraine treatment taken on a paper diary. For subjects to be eligible for the study, they must report having had 4 to 18 migraine attacks of moderate to severe intensity per 4-week period within the 12 weeks prior to the Screening Visit, and at least 4 migraine days and no more than 18 headache days during the 28-day Observation Period. After completing the 28-day observation period, the subject will return to the clinical with both diaries for the Baseline Visit.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and before study drug is dispensed. Subjects will be instructed that they must take 1 orally disintegrating tablet (ODT) of blinded study drug (rimegepant 75 mg or placebo) every other calendar day. If subjects have a migraine attack during the Double-blind Treatment Phase, if needed, they may treat the migraine attack with their standard of care medication and continue to take study drug on their regular schedule (scheduled dosing days only).

At the completion of the 12-week Double-blind Treatment Phase, subjects may be entered into the 40-week Open-label Extension Phase following laboratory results within acceptable ranges. During the Open-label Extension Phase, subjects will be instructed that they must take 1 rimegepant 75 mg every other calendar day. If subjects have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the Open-label Extension Phase, subjects can take a maximum of 1 rimegepant 75 mg ODT per calendar day up to 40 weeks.

Subjects are required to record their migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary every day. Subjects are also required to record any rescue medication taken on a paper diary and WOCBP will record their menstrual period information on a paper log.

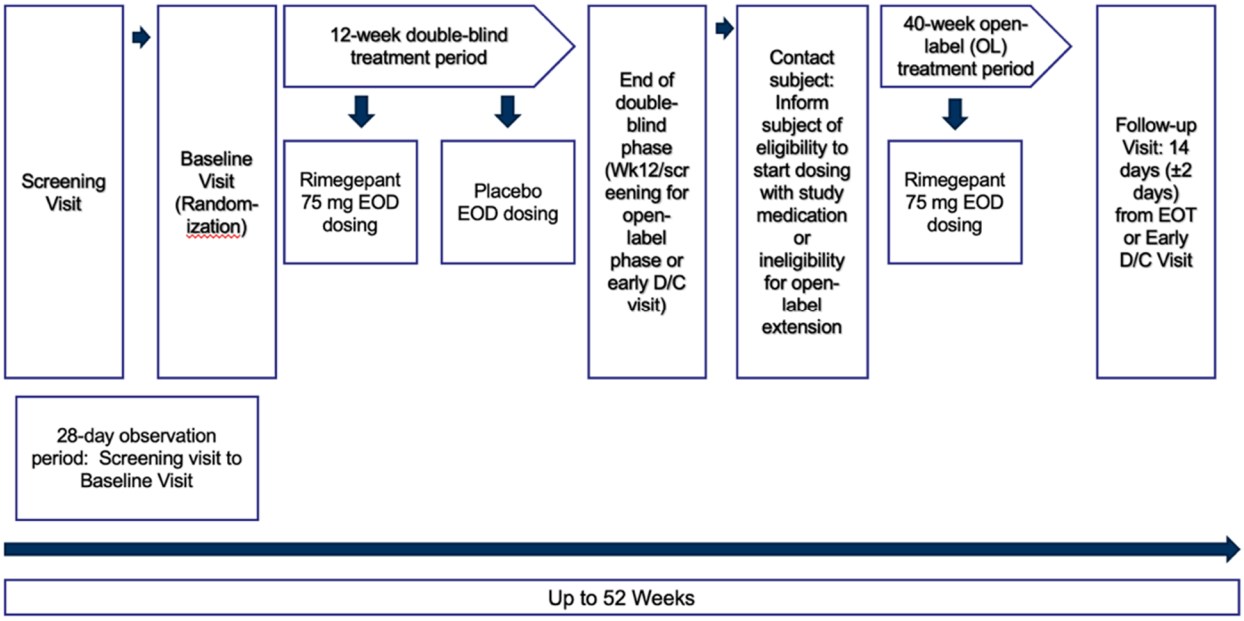
At select study visits, subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQoL v2.1), the Migraine Disability Assessment (MIDAS), EQ-5D-5L and the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects will use the eDiary to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

Study visits will occur at Screening (Enrollment), Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12. At the completion of the 12-week Double-blind Treatment Phase, subjects may be entered into the 40-week Open-label Extension Phase following laboratory tests within normal ranges. Visits occur at Week 14, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52/ End of Treatment (EOT). Subjects will return to the study site at the end of Week 52 (+/-3 days) for the EOT Visit. Any subject who discontinues early, at any time during the study, will return to the study site for the EOT Visit. There is a Follow-up Visit 14 days (+/-2 days) after the EOT Visit. Subjects who do not complete the Double-blind Treatment Phase and/or do not enter or complete the Open-label Extension Phase should complete the EOT and the Follow-up Week 2 Visits.

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

4.2. Study Schematic

Figure 1 Study Schematic



4.3. Schedule of Assessments

Table 1 Schedule of Assessments – Observation Period, Double-blind Treatment Phase

	Observation Period (28 days + 3 days)[9]		**Double-blind Treatment Phase[9] [10]**			
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit:** within 96 hours of Baseline (Randomization) Visit[11]	**Baseline** (Randomization) **Visit** (Day 0)	**Week 2** (Day14 +/- 2 days)	**Week 4** (Day 28 + 3 days)	**Weeks 8** (Day 56) **and 12** (Day 84) (all visits + 3 days)
Eligibility Assessments						
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X	X			
Medical History	X					
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X					
Rescue Medication paper diary, Concomitant Medication paper diary and Menstrual Period paper log (WOCBP)[1]	X	X	X	X	X	X
Enroll subject/IWRS	X					
Randomize subject / IWRS[2]			X			
Safety Assessments						
Physical Examination	X		X		X	X
Vital Signs / Physical Measurements[3]	X		X		X	X
Clinical Safety Laboratory Testing	X		X		X	X

	Observation Period (28 days + 3 days)[9]		**Double-blind Treatment Phase[9] [10]**			
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit:** within 96 hours of Baseline (Randomization) Visit[11]	**Baseline** (Randomization) **Visit** (Day 0)	**Week 2** (Day14 +/- 2 days)	**Week 4** (Day 28 + 3 days)	**Weeks 8 (**Day 56) **and 12** (Day 84) (all visits + 3 days)
Liver Function Test (LFTs)	X	X	X	X	X	X
Lipid Panel			X			X (week 12 only)
ECG	X		X		X	
Urinalysis			X			
Urine Drug Screen for drugs of abuse	X					
FSH, if applicable, to determine WOCBP status	X					
Pregnancy Test	X (urine)	X (serum)	X (urine)		X (urine)	X (urine)
AE, SAE, and Concomitant Procedure assessment[4]	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X		X	X	X	X
Clinical Drug Supplies / Study Supplies						
Dispense Study drug[5]			X		X	X
Administer study drug[6]				X	X	X
Electronic Diary (eDiary) dispensed[7]	X					
Enter use of study drug in paper diary			X	X	X	X

	Observation Period (28 days + 3 days)[9]		**Double-blind Treatment Phase[9] [10]**			
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit:** within 96 hours of Baseline (Randomization) Visit[11]	**Baseline** (Randomization) **Visit** (Day 0)	**Week 2** (Day14 +/- 2 days)	**Week 4** (Day 28 + 3 days)	**Weeks 8 (**Day 56) **and 12** (Day 84) (all visits + 3 days)
Return unused study drug to site for compliance check				X	X	X
eDiary returned / reviewed for completeness		X	X	X	X	X
Efficacy Assessments						
Daily report of migraine occurrence and pain intensity reported by subject in eDiary[8]		X	X	X	X	X
Other Assessments reported by subject in eDiary						
MSQoL v2.1[8]			X			X (week 12 only)
MIDAS[8]			X			X (week 12 only)
EQ-5D-5L[8]			X			X (week 12 only)

[1] Concomitant medications, including prophylactic and standard of care migraine medications, taken during Observation Period and rescue medication taken during the Treatment Phase should be recorded in the subject's paper diary and reviewed by study personnel at each visit. WOCBP will also record menstrual period information on the paper diary which should be reviewed by study personnel at each visit.

[2] The actual baseline visit date should be used for IWRS enrollment date and eligibility date.

[3] Height measured at Screening Visit only. Weight, body temperature, respiratory rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.

[4] SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the 2-week Follow up Safety Visit. Non-serious AEs should be reported from signing of consent through 2-Week Follow up Safety Visit.

[5] Subjects should finish a wallet of study drug before starting a new wallet. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study drug may be scheduled as needed. In cases the COVID-19 Pandemic impacts study visits, study medication may be delivered to a subject per local regulation, with up to a 4-week supply. When delivered by courier, site must select a courier that provides trackable delivery service and proper documentation must be maintained in the subject's source records including shipping vendor, tracking number, confirmation of receipt by

subject/family, and all other relevant information. Study medication at Baseline and Week 12 must not be shipped by the sites to subjects. At the Week 12 Visit, the open-label study drug will be dispensed and subjects will be instructed not to begin taking rimegepant until confirmation from site staff pending lab results.

[6] Subjects must take their study drug every other day, regardless of whether or not they have a migraine. Subjects must report each ODT they take in the paper diary. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits.

[7] The electronic subject diary (eDiary) will be dispensed at the Screening Visit, after all Screening Procedures are completed. The subject will be trained on the use of the eDiary.

[8] Subjects will use the eDiary every day during the Observation Period and Double-blind Treatment Phase to report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication. Subjects will use the eDiary at select visits to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

[9] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 14 or 28-day schedule if scheduling changes are made at any previous visit(s). In cases the COVID-19 Pandemic impacts study visits, visits between Week 2 and Week 8, inclusive, may be conducted remotely (e.g., telephone, telemedicine) with at least, but not limited to the following procedures completed: assessment of contraception, AE, SAE, and concomitant procedure assessment, and compliance check of study drug. The visits must be documented within the source records as being conducted remotely. At Week 4 and Week 8, these procedures conducted remotely must be completed before dispensing study drug. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation. In such cases, investigators should schedule a visit to perform all on-site procedures which cannot be completed remotely at their earliest convenience.

[10] Subjects who do not complete the Double-blind Treatment Phase or do not enter the Open-label Extension Phase should complete the End of Treatment Visit and 2-Week Follow-up Safety Visit.

[11] The duration between the Pre-randomization Evaluation Visit and the Baseline (Randomization) Visit is 4 days. The "+2" days window is included ***for scheduling purposes only***. Every effort should be made to collect the Pre-randomization Evaluation Visit samples as close to, and within, the 4 days prior to the Baseline Visit as possible. However, for scheduling convenience, this window may be up to 6 days (between the Pre-randomization Evaluation Visit and the Baseline Visit).

Table 2 Schedule of Assessments – Open-label Treatment Phase, Follow-up Visits

Procedure	**Phone visit**	**Week 14 (Day 98)[10]** (± 3 days)	**Week 16 (Day 112)[10]** (± 3 days)	**Week 20 (Day 140) to Week 52 (Day 364) / EOT Visits every 4 weeks[10]** (± 3 days)	**2-Week Follow-up Safety Visit[10]** (14 days after EOT visit ± 2 days)
Confirm eligibility based on Week 12 Laboratory Results[1]	X				
Rescue Medication paper diary, Concomitant Medication paper diary and Menstrual Period paper log (WOCBP)[2]		X	X	X	X[3]
Safety Assessments					
Physical Examinations			X	X (Week 24 and 52 / EOT only)	
Vital Signs / Physical Measurements[4]			X	X	X
Clinical Safety Laboratory Testing			X	X (Week 24 and 52 / EOT only)	
Liver function tests (LFTs)		X	X	X	X
Lipid Panel				X (Week 24 and 52 / EOT only)	
ECG			X	X (Week 24 and 52 / EOT only)	X
Urinalysis				X (Week 52 / EOT only)	
Pregnancy Test			X (urine)	X (urine)	X (serum)
AE, SAE, and Concomitant Procedure Assessment[5]		X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	X	X	X
Clinical Drug Supplies / Study Supplies					
Dispense Study drug [1, 6]			X	X all visits except Week 52 / EOT	
Administer Study drug[7]		X	X	X	

Procedure	**Phone visit**	**Week 14 (Day 98)[10]** (± 3 days)	**Week 16 (Day 112)[10]** (± 3 days)	**Week 20 (Day 140) to Week 52 (Day 364) / EOT Visits every 4 weeks[10]** (± 3 days)	**2-Week Follow-up Safety Visit[10]** (14 days after EOT visit ± 2 days)
Enter Use of Study drug in paper diary		X	X	X	
Return unused study drug to site for compliance check		X	X	X	
eDiary returned/reviewed for completeness[8]		X	X	X	
Efficacy Assessments					
Daily report of migraine occurrence and pain intensity reported by subject in eDiary[9]		X	X	X	
Other Assessments reported by subject in eDiary					
MSQoL v2.1[9]				X (Weeks 24 and 52 / EOT only)	
MIDAS[9]				X (Weeks 24 and 52 / EOT only)	
EQ-5D-5L[9]				X (Weeks 24 and 52 / EOT only)	

[1] Study eligibility must be confirmed by Week 12 laboratory results prior to first dose of study medication, which is dispensed at the Week 12 Visit. Sites must contact subject by phone to confirm study eligibility prior to subject taking first dose.

[2] Concomitant medications, including prophylactic and rescue medications, taken during the Open-label Extension Phase should be recorded in the subject's paper diary and reviewed by study personnel at each visit. WOCBP will also record menstrual period information on the paper log which should be reviewed by study personnel at each visit.

[3] Collect if treatment with concomitant medication is required for an AE or if concomitant medication is considered related to AE.

[4] Weight, body temperature, respiratory rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.

[5] SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the 2-week Follow up Safety Visit. Non-serious AEs should be reported from signing of consent through 2-Week Follow up Safety Visit.

[6] Subjects should finish a wallet of study drug before starting a new wallet. Study drug will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study drug may be scheduled as needed. In cases the COVID-19 Pandemic impacts study visits, study medication may be shipped to a subject per local regulation, with up to a 4-week supply. When delivered by courier, site must select a courier that provides trackable delivery service and proper documentation must be maintained in the subject's source records including shipping vendor, tracking number, confirmation of receipt by subject/family, and all other relevant information.

[7] Subjects must take their study drug every other day, regardless of whether or not they have a migraine. During the Open-label Extension Phase only, if subjects have a migraine on a day that they are not scheduled to take a study drug, if needed, they may take a study drug to treat a migraine on that calendar day.

Therefore, subjects can take a maximum of 1 ODT of study drug per calendar day. Subjects must report each ODT they take in the paper diary. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits.

[8] During the Open-label Extension Phase, subjects with 6 or more missed reports and 3 or more missed dosing entries per month for 2 months (sequential or non-sequential months) should be considered for discontinuation from the study for poor compliance, after discussion with Sponsor. Month is defined as 4 weeks for the purpose of this protocol.

[9] Subjects will be trained on the use of the eDiary. The subject will use the eDiary every day during the Open-label Extension Phase to report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication. Subjects will use the eDiary at select visits to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

[10] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 14 or 28-day schedule if scheduling changes are made at any previous visit(s). In cases the COVID-19 Pandemic impacts study visits, visits may be conducted remotely (e.g., telephone, telemedicine) with at least, but not limited to the following procedures completed: assessment of contraception, AE, SAE, and concomitant procedure assessment, and compliance check of study drug. The visits must be documented within the source records as being conducted remotely. These procedures conducted remotely must be completed before dispensing study drug. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation. In such cases, investigators should schedule a visit to perform all on-site procedures which cannot be completed remotely at their earliest convenience.

4.3.1. Observation Period

The Observation Period will be 28 days + 3 days. Note that the "+ 3 days" window is included for scheduling purposes only. The Observation Period will have 2 scheduled visits, Screening and Pre-randomization Evaluation, which should be completed in person.

4.3.1.1. Screening Visit

Before any study procedures are performed, subjects must provide documented informed consent. After informed consent, subjects will be enrolled in the IWRS system. The subject's migraine history and medical history will be collected at the Screening Visit, which starts at day 1 of the Observation Period. Subjects will undergo all screening procedures as detailed in Table 1. After completion of all screening procedures, subjects will be provided an eDiary.

Subjects will report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary every day during the Observation Period. All subjects will continue to use their acute standard of care migraine medications during the Observation Period. Subjects will record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the entire Observation Period in a concomitant medication paper diary. WOCBP will record their menstrual period information on a paper log.

If the subject meets study entry criteria (i.e., inclusion/exclusion criteria), the subject will return to the study site for the Pre-randomization Evaluation Visit. If the subject does not meet study entry criteria, the subject will be considered a screen failure and should be recorded as such in IWRS. The subject must return to the study site to return the eDiary. If a LFT abnormality is observed at the screening visit, the repeat sample can be obtained as part of an unscheduled assessment for confirmation, and, if within the protocol defined eligibility criterion, it would be obtained at the scheduled time at the Pre-randomization Evaluation Visit. If the result of that test meets the protocol defined eligibility criterion, the subject can be enrolled if otherwise eligible.

Subjects who resulted in screening failures at the Pre-randomization Evaluation Visit or earlier under one of the previous protocols and who are reasonably expected to be eligible provided the ineligibility was due to one of the eligibility items modified in the protocol amendment may be considered for re-screening. Subjects who were screen failures due to select circumstances and who are reasonably expected to be eligible (e.g., previously pregnant, screening window too long) may also be considered for re-screening. 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.

4.3.1.2. Pre-randomization Evaluation Visit

Within 96 hours +48 hours (4 days +2 days) of the Baseline (Randomization) Visit, subjects must return to the study site for the Pre-randomization Evaluation Visit. This visit occurs within the Observation Period. Safety labs and a serum pregnancy test for WOCBP will be obtained and compliance with the eDiary will be assessed. If the subject continues to meet study entry criteria

and laboratory test results are acceptable per protocol, the subject will be randomized at the Baseline Visit into the Double-blind Treatment Phase. If the laboratory results are not acceptable per protocol, the subject is determined to be a Screen Failure and must return to the study site to return the eDiary. Repeat testing because of LFT abnormalities will not be permitted. Subjects who do not meet eligibility criteria at the Pre-randomization Evaluation Visit may NOT be re-tested between this visit and the baseline (randomization) visit and must be screen failed. However, they may be able to be re-screened under a new subject number in select circumstances and after agreement by the Sponsor as described in Section 4.3.1.1.

4.3.2. Randomized, Double-Blind Treatment Phase (12 weeks)

The Double-blind Treatment Phase will be up to 12 weeks from the Baseline (Randomization) Visit through the Week 12 or EOT Visit.

During the Double-blind Treatment Phase, subjects will be instructed that they must take 1 ODT of blinded study drug every other calendar day, regardless of whether they have a migraine on that day or not. If subjects have a migraine during the Double-blind Treatment Phase, if needed, they may treat the migraine with their standard of care medication and continue to take study drug on their regular schedule (scheduled dosing days only).

NOTE: During the Double-blind Treatment Phase, if a dose of study drug for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the study drug wallet and should NOT take another dose of study medication until the next scheduled dosing day in accordance with the planned EOD dosing schedule.

Subjects will continue to report migraine occurrence, migraine pain features and associated symptoms and use of acute migraine medication in the eDiary every day during the Double-blind Treatment Phase.

The MSQoL v2.1, MIDAS, EQ-5D-5L and C-SSRS will be completed, or administered by the investigator, at specified study visits (Table 1). Subjects will use the eDiary to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

Subjects will continue to record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the entire Double-blind Treatment Phase in a concomitant medication paper diary.

After the Baseline Visit, study visits will be approximately every 2 weeks during the first month, and then every 4 weeks until the Week 12 or EOT Visit (Table 1). At each visit, the eDiary will be reviewed by site staff for completeness and compliance. Menstrual period information (WOCBP) will be also reviewed.

Study drug compliance will be reviewed at each visit using the returned study drug wallets. Unused, non-expired, partial wallets will be returned to the subjects for completion prior to starting a new wallet. Subjects will be dispensed additional study drug as needed, as per the IP

manual. Additional safety tests (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 1.

Subjects in the Double-blind Treatment Phase who demonstrate poor compliance will be discussed with the Sponsor, corrective training will be completed by the site with the subject and may not be considered for the Open-label Treatment Phase.

4.3.2.1. Baseline (Randomization) Visit

Once completing the Observation Period, subjects will return to the study site for the Baseline (Randomization) Visit, which should be completed in person. Subjects who continue to meet all study entry criteria and have had good compliance with the eDiary completion may enter the Double-blind Treatment Phase, pending review of additional laboratory test results.

Because laboratory results from the Baseline (Randomization) Visit will be available after the subject may have been determined to be otherwise eligible for the study, had been randomized, and started treatment, there is the possibility that exclusionary laboratory results from the Baseline Visit may result in early discontinuation from the study.

Subjects with fewer than 24 completed eDiary reports in the Observation Period will not be considered for participation due to non-compliance with the eDiary.

4.3.2.2. Week 12 or EOT Visit

Subjects will return to the study site at the Week 12 Visit (Day 85 +3 days), or at the EOT Visit for early discontinuation, for review of the eDiary, assessment of medication compliance and assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 1).

Subjects must return the unused study drug and eDiary to the study site. Subjects in the Double-blind Treatment Phase who demonstrate poor compliance will be discussed with the Sponsor, corrective training will be completed by the site with the subject and may not be considered for the Open-label Extension Phase.

All randomized subjects who discontinue early from the Double-blind Treatment Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 12 Visit.

In cases where the subject does not enter the Open-label Extension Phase, the subject should return to the site for the Follow-up Week 2 Visit (2 weeks ± 2 days after the Week 12 or EOT Visit), to complete all procedures.

4.3.3. Open-label Extension Phase (40 weeks)

It is estimated that approximately 400 subjects will be entered into the Open-label Extension Phase.

As indicated in Table 1, laboratory tests will be performed at the Week 12 Visit (final visit of the Double-blind Treatment Phase). Subjects who (1) complete the Double-blind Treatment Phase,

(2) continue to meet all inclusion/exclusion criteria, and (3) have been compliant with the eDiary may enter the Open-label Extension Phase, pending review of laboratory test results.

Subjects will be dispensed study drug (rimegepant 75 mg) and must be instructed that they cannot take study drug until laboratory results confirm study eligibility. Subjects may be contacted by telephone; an office study visit is not required.

Subjects will be instructed that they must take 1 ODT of rimegepant 75 mg every other calendar day, regardless of whether they have a migraine on that day. If subjects in this group have a migraine on a day that they are not scheduled to dose with study drug, they may take 1 study drug ODT on that calendar day to treat a migraine. Therefore, if needed, subjects can take a maximum of 1 ODT of study drug per calendar day for 40 weeks during the Open-label Treatment Phase.

NOTE: During the Open-label Extension Phase, if a dose of study drug for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the study drug wallet and should NOT take the scheduled dose of study medication until the next scheduled dosing day in accordance with the planned EOD dosing schedule.

Subjects will continue to report migraine occurrence, migraine pain features and associated symptoms and use of acute migraine medication in the eDiary every day during the Open-label Extension Phase.

The MSQoL v2.1, MIDAS, EQ-5D-5L and C-SSRS will be completed, or administered by the investigator, at specified study visits (Table 2). Subjects will use the eDiary to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

Subjects will continue to record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the entire Open-label Treatment Phase in a concomitant medication paper diary.

Study visits will be approximately every 2 weeks during the first month and then every 4 weeks, until Week 52 (Table 2). At each visit, the eDiary will be reviewed by site staff for completeness and compliance. Concomitant medication use will be reviewed and compared between the eDiary and concomitant medication paper diary entries, where applicable at each visit. Menstrual period information (WOCBP) will be also reviewed.

Study drug compliance will be reviewed at each visit using the returned study drug wallets, and subjects will be dispensed additional study drug as needed. Additional safety tests (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

4.3.3.1. Week 52 or EOT Visit

Subjects will return to the study at the end of Week 52 (± 3 days), or at end of treatment for early discontinuations, for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and

electrocardiography) (Table 2). Subjects must return the unused study drug and electronic subject diary to the study site.

All randomized subjects who discontinue early from the Open-label Extension Phase should complete the EOT Visit. Otherwise, subjects should complete the Week 52 Visit.

4.3.4. Follow-up Period

The Follow-up Period will have one scheduled visit, Follow-up Week 2. The visit should occur approximately 2 weeks after the last visit in the last treatment phase (i.e., Week 12/EOT Visit if the subject did not enter the Open-label Extension Phase; Week 52/EOT Visit if the subject entered the Open-label Extension Phase).

All randomized subjects should complete the Follow-up Week 2 Visit, regardless of completing either treatment phase. Subjects will continue to record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the entire Follow-up Period in a concomitant medication paper diary.

4.3.4.1. Follow-up Week 2 Visit

Subjects will return to the study site approximately 2 weeks (14 days +/- 2 days) after the last visit in the last treatment phase to collect vital signs, ECG, LFTs, assessment of AEs/SAEs, to have the C- SSRS performed, and to have a serum pregnancy test performed (WOCBP).

Subjects will return the prophylactic and rescue medication paper diary and menstrual period (WOCBP) paper logs which should be reviewed one final time by study staff. Subjects must continue to track any concomitant medications and therefore must maintain the concomitant medication paper diary through this visit.

Investigators should assess subjects for AEs consistent with drug dependency or withdrawal effects and report as appropriate (Section 7.4).

4.4. Post Study Access to Therapy (if applicable)

At the end of the study the sponsor will not continue to supply study drug to subjects or investigators. The investigator should ensure that the subject receives 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 1064 subjects will be screened to randomize up to approximately 490 subjects (245 subjects to each of the rimegepant or placebo groups). It is estimated that approximately 400 subjects will be entered into the Open-label Extension Phase.

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 center's institutional review board (IRB) or ethics committee, 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. Age of onset of migraines prior to 50 years of age.

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

    c. Per subject report, 4 to 18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit (month is defined as 4 weeks for the purpose of this protocol).

    d. 4 or more migraine days during Observation Period.

    e. Not more than 18 ***headache days*** during the Observation Period.

    f. Ability to distinguish migraine attacks from tension/cluster headaches.

    g. Subjects on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 3 months (12 weeks) prior to the Observation Period, and the dose is not expected to change during the course of the study.

        i. Subjects may remain on one (1) medication with possible migraine-prophylactic effects regardless of indication, excluding CGRP antagonists [biologic or small-molecule], during the Double-Blind Treatment Phase. See section 5.5.

        ii. Concomitant use of a CGRP antagonist, such as erenumab or fremanezumab, is prohibited.

iii. Subjects who previously discontinued prophylactic migraine medication must have done so at least 90 days 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. Male and female subjects ≥ 18 years.

b. Women of childbearing potential (WOCBP) and non-sterile men must be using two 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 to study participation.

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

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. Subjects with headaches occurring 19 or more days per month (migraine or non-migraine) in any of the 3 months prior to the Screening Visit.

c. 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. Subject with a history of human immunodeficiency virus (HIV) disease.

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 the 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 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, might 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. Subject 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 adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial.

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

l. History of use of opioid- or barbiturate- (e.g., butalbital) containing medication for 4 or more days per month during the 3 months (12 weeks) prior to Screening Visit.

m. Subjects should be excluded if they have a positive drug screen for drugs of abuse that in the investigator's judgment is medically significant, in that it would impact the safety of the subject or the interpretation of the study results. In addition:

    i. Detectable levels of cocaine, amphetamine, phencyclidine (PCP) and tetrahydrocannabinol (THC) in the drug screen are exclusionary. Subjects who have positive drug screen for amphetamines and who are on a prescribed amphetamine medication for an approved indication (e.g., ADHD) will be allowed into the study at the Investigator's discretion. The determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable from 3 months (12 weeks) prior to baseline until the End of Treatment Visit occurs.

n. Hematologic or solid malignancy diagnosis within 5 years prior to screening. Subjects with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the Screening Visit in this study.

o. Body mass index > 35.0 kg/m^2.

p. History of gallstones or cholecystitis within past year.

3. Allergies and Adverse Drug Reactions

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

4. Sex and Reproductive Status

    a. WOCBP who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for up to 60 days after last dose of study drug.

    b. Women with a positive pregnancy test at screening or prior to study drug administration.

5. ECG and Laboratory Test Findings

    a. Estimated glomerular filtration rate (eGFR) ≤ 40 ml/min/1.73m^2.

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

    c. Left Bundle Branch block.

    d. Right Bundle Branch Block with a QRS duration ≥ 150 msec.

    e. Intraventricular Conduction Defect with a QRS duration ≥ 150 msec.

f. T bili > 1.5 × ULN (may be repeated once for confirmation at Screening; refer to Sections 4.3.1.1 and 4.3.1.2; direct bilirubin >1.5 × ULN is exclusionary for Gilbert's syndrome).

g. AST or ALT > 1.5 × ULN (may be repeated once for confirmation at Screening; refer to Sections 4.3.1.1 and 4.3.1.2).

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

i. HbA1c > 7.5%.

6. Prohibited Medications

a. Subjects taking a prohibited medication (refer to Section 5.4).

7. Other Exclusion Criteria

a. Subjects are excluded if they have had no therapeutic response with > 2 of the medication categories for prophylactic treatment of migraine (see Section 16.3 APPENDIX 3) after an adequate therapeutic trial.

b. Non-compliance with or inability to complete eDiary during Observation Period. Subjects with less than 24 completed eDiary reports during the Observation Period will not be considered for participation due to non-compliance with the eDiary.

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

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

e. Exposure to biological investigational agents within the 90 days prior to Screening Visit.

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

g. 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).

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

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

5.4. Prohibited and Restricted Concomitant Medications

The medications listed below are prohibited starting at the Baseline Visit and during the course of this study or as specified.

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

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

6. History of use of ergotamine medications on $\geq$ 10 days per month on a regular basis for $\geq$ 3 months ($\geq$ 12 weeks).

7. Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone and hydrocodone) or barbiturates is prohibited starting from 2 days prior to the Baseline Visit and throughout the study.

8. Systemic use of analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on $\geq$ 15 days per month is prohibited during the study.

9. Use of acetaminophen or acetaminophen containing products for non-headache indications after the Baseline Visit is prohibited. Any use of acetaminophen or acetaminophen containing products for non-headache indications during the Observation Period must be stopped at least 2 days prior to Baseline Visit.

10. Use of triptans is prohibited during the Open-label Extension Phase.

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

12. The use of CGRP antagonists (biologic [e.g., Aimovig™ and Ajovy™ or Emgality®] or small molecule) other than rimegepant provided as study drug is prohibited during the study. CGRP antagonist biologics must be discontinued 6 months prior to screening and are prohibited throughout the study.

13. 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.

14. Use of marijuana and all forms of ingested or inhaled cannabidiol (CBD) and THC-containing products are prohibited during the study.

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 during the Open-label Extension Phase, 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 the moderate to strong CYP3A4 inhibitor. See Section 16.1 APPENDIX 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 during the Open-label Extension Phase, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the moderate to strong CYP3A4 inducer. See Section 16.1 APPENDIX 1.

17. Concomitant use of strong inhibitors of the P-glycoprotein (P-gp) transporter with rimegepant is prohibited during the study. See Section 16.1 APPENDIX 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. Concomitant use of LAMICTAL® (lamotrigine) is prohibited during the study.

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

21. Use of any investigational agent other than rimegepant from the Screening Visit through the 2-Week Follow-up Safety Visit.

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

5.5. Prophylactic and Rescue Medications

Subjects may not use more than 1 of the following medications with possible migraine-prophylactic effects if not otherwise prohibited by the protocol. Doses must be stable **within 3 months (12 weeks) prior to the start of the Observation Period** and throughout the study. Use of more than 1 of the following medications is prohibited within 3 months (12 weeks) prior to the start of the Observation Period and throughout the study.

Prophylactic migraine medications that are permitted during the study include:

- Topiramate, gabapentin
- Valproic acid/valproate (permitted if subject is on therapy for at least 6 months prior to the Screening Visit)
- Beta blockers (such as: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Tricyclic antidepressants (such as: amitriptyline, nortriptyline, protriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Flunarizine, lomerizine
- Lisinopril, candesartan
- Clonidine, guanfacine
- Cyproheptadine
- Methysergide
- Pizotifen
- Feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- Botulinum toxin injections (e.g., Botox®)
- The use of CGRP antagonists (biologic [e.g., Aimovig™, Ajovy™ or Emgality®] or small molecule) other than rimegepant as study drug is prohibited during the study.

The use of triptan medications is prohibited during the Open-label Extension Phase of the study, but is allowed as rescue medication during the Double-blind Treatment Phase.

Subjects may use their permitted standard of care medication if needed for acute treatment of a migraine and record any medications taken on the appropriate paper diary. Permitted medications include the following rescue medications:

- triptans (triptans are prohibited during the Open-label Extension Phase after Week 12)
- aspirin
- ibuprofen
- baclofen
- acetaminophen up to 2000 mg/day for a maximum of 2 consecutive days at a time (this includes Excedrin Migraine)
- naprosyn (or any other type of non-steroidal anti-inflammatory drug (NSAID))
- antiemetics (e.g., metoclopramide or promethazine)
- muscle relaxants for rescue during the study

These are the only medications allowed for rescue. Subjects should continue taking study drug on scheduled dosing days.

If a subject takes study drug and experiences a migraine later that day, after taking study drug for the day, the subject may take their ***rescue medication*** as described in this section of the protocol. ***During the Double-blind Treatment Phase, subjects are not allowed to take more than 1 ODT of study drug EVERY OTHER calendar day. During the Open-label Extension Phase, subjects are required to take 1 ODT of study drug every other day, but may also take 1 ODT of study drug on non-scheduled dosing days to treat a migraine. Subjects are not allowed to take more than 1 ODT of study drug per calendar day during the Open-label Extension Phase.***

Use of standard of care medication during Observation Period and use of rescue medication during the Double-blind Treatment Phase, Open-label Extension Phase, and standard of care medication through to the 2-Week Follow-up Safety Visit will be recorded by the subject on a paper diary and reported to the site.

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. Woman 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 1 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 two 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 IP 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 two methods of contraception for the duration of the study. The two 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.

WOCBP will complete a pregnancy test as outlined in Table 1 and Table 2. If a WOCBP suspects that she might be pregnant, she should immediately contact the study doctor.

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 following study materials will be provided at the study start:

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Investigator Brochure
- Interactive Web-based Response System (IWRS)
- Electronic Case Report Form (eCRF) instructions
- Electronic Diary: handheld electronic device (1 will be given to each subject)
- Electronic Diary for quality of life scales
- Paper copies of the C-SSRS
- Instructions for the eDiary device and access to the portal
- Paper diary to record study drug, standard of care migraine medications and rescue medications
- Paper diary to record menstrual period information (WOCBP)
- Laboratory Kits and Laboratory Manual
- Back-up forms for CT SAE report, Exposure During Pregnancy (EDP) and Pregnant Partner Release Information

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

The eDiary will be used daily to record migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication. The eDiary will be used at select visits to assess MSQoL v2.1, MIDAS, and EQ-5D-5L. 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 scales and assessments completed by the subject on the eDiary.

Safety laboratory, plasma, and serum 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 and Table 2. 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 during the Screening Visit and at all scheduled visits as outlined in Table 1 and Table 2. The investigator will determine if any ECG abnormalities are clinically significant or not (see Section 16.4 APPENDIX 4).

6.2.3. Physical Exam

Subjects will undergo a routine physical examination during the Screening Visit and at all scheduled visits as outlined in Table 1 and Table 2. Physical examination includes 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, Table 1 and Table 2.

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. Safety Laboratory Testing

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

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

Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin, creatine kinase (CK).

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

After Baseline Visit:

Elevations in CK (>5 x 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 gamma-glutamyltransferase (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

eGFR: eGFR will be calculated and reported by the central lab

Urinalysis: pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and blood. If blood, protein or leukocytes are positive and the result 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.

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

6.2.4.2. Pregnancy Testing

WOCBP will complete pregnancy tests (serum and / or urine) at specified study visits, prior to taking study drug, and as outlined in Table 1 and Table 2.

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

The eDiary will be used daily to record acute migraine medication dosing occurrences (i.e., with triptans, ergotamine, or other), and migraine occurrence, and migraine pain features and associated symptoms during the Observation Period, Double-blind Treatment Phase, and Open-label Extension Phase.

6.4. Other Assessments

The eDiary will be used at select visits to assess MSQoL v2.1, MIDAS, and EQ-5D-5L.

6.4.1. Migraine-Specific Quality-of-Life Questionnaire v 2.1

Impact of treatment on subject-reported quality of life will be assessed using the Migraine-Specific Qualify-of-Life Questionnaire version 2.1 (MSQoL v2.1). The MSQoL v2.1 is a 14-

item instrument that has been validated in 3 domains: role function - restrictive, role function - preventive, and emotional function[16].

6.4.2. Migraine Disability Assessment (MIDAS) Questionnaire

The Migraine Disability Assessment (MIDAS) is a retrospective, subject-reported, 5-item questionnaire that measures headache-related disability as lost days due to headache from paid work or school, household work and non-work activities over a 3-month period[17].

6.4.3. EQ-5D-5L

EQ-5D-5L is a standardised measure of health status. The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS)[18].

The descriptive system comprises the 5 dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

6.5. Early Discontinuation from the Study

Subjects MUST discontinue IP (and non-IP at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Exclusionary laboratory abnormality identified on the Randomization / Baseline Laboratory Report
- Pregnancy
- Termination of the study by Pfizer Inc.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Poor compliance with study procedures and visits, including poor completion compliance with reports in eDiary.
    - Subjects with less than 24 completed eDiary reports during the Observation Period will not be considered for participation due to non-compliance with the eDiary.

- Subjects in the Double-blind Treatment Phase will be monitored closely for compliance with the eDiary and may not be considered for the Open-label Extension Phase based on PI and / or Sponsor discretion if compliance is low. Subjects who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.

- During the Open-label Extension Phase, subjects with 6 or more missed reports in the eDiary and 3 or more missed dosing entries per month for 2 months (sequential or non-sequential months) should be considered for discontinuation from the study for poor compliance, after discussion with Sponsor. Month is defined as 4 weeks for the purpose of this protocol.

- Please see Section 6.2.5 for guidance on study discontinuation based on results from the C-SSRS.

All subjects who discontinue or who do not enter the Open-label Extension Phase should comply with protocol specified End of Treatment procedures as outlined in Table 2. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

In this protocol, IP is/are: rimegepant 75 mg and the matching placebo

7.1.2. Packaging, Shipment and Storage

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

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. The subject number must not be reused for any other subject in the study. Subjects will maintain their subject number assigned at screening throughout the study except in cases of re-screening, where permitted, in which case a new subject number must be assigned.

At the Baseline Visit, eligible subjects will be randomized in a 1:1 ratio to the rimegepant 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.**

After confirming subject eligibility, registering a subject for Baseline (Randomization) will trigger a container number for the study drug. The study drug will be dispensed at baseline and as needed at the study visits.

7.2.2. Selection and Timing of Dose and Administration

Study drug (rimegepant or matching placebo) will be assigned via the IWRS system. There are no dose adjustments in this study and subjects will receive rimegepant or placebo in wallets. Subjects will be dispensed study drug at the Baseline Visit, and the subjects will be instructed that they must take ***1 ODT every other calendar day, regardless of whether they have a migraine on that day or not.*** This is the scheduled dosing regimen for the Double-blind Treatment Phase and the Open-label Extension Phase. The ODT should be 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.

During the Open-label Extension Phase only, if a subject has a migraine on a non-scheduled dosing day, they may take 1 ODT of study drug as acute treatment for their migraine, if needed, with a maximum of 1 ODT of study drug per calendar day. This regimen of scheduled dosing on every other calendar day and as needed study drug dosing should be followed for up to 40 weeks in the Open-label Extension Phase. Subjects can take a maximum of 1 ODT of study drug per calendar day for 40 weeks during the Open-label Extension Phase.

Dosing should occur around the same time every other day for migraine prevention. It is preferred that subjects dose every other day in the morning; however, it is more important that the subject consistently dose at approximately the same time every other day. The time of dosing should be consistent throughout the study for the every other day dosing days. If the subject has a migraine on a day when they ***already took study drug***, the subject can take their rescue medication in accordance with protocol restrictions.

Subjects **must** be instructed that they CANNOT take more than 1 ODT of study drug every other day during the Double-blind Treatment Phase. Subjects **must** be instructed to continue taking study drug every other calendar day during the Open-label Extension Phase. As noted above, subjects may treat a migraine with study drug on a non-scheduled dosing day, but subjects **must** be instructed that during the Open-label Extension Phase, they **CANNOT** take more than 1 ODT of study drug per calendar day.

7.2.3. Dose Modifications

There will be no dose adjustments in this study.

7.2.4. Dose Interruptions

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

7.3. Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the IP 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 IP 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.

Sponsor, investigators and subjects will be blinded until the timing of PCD clinical study report (CSR), which will occur after the last subject completes the Week 12 visit (Section 9.4).

7.4. Treatment Compliance

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

Subjects must be counseled on the importance of taking the study drug as directed (see Section 7.2.2). Treatment compliance, review of study drug doses and through review of returned study drug, should be assessed by site staff at each study visit. Discrepancies between doses reported in the diary, review of study drug and information provided by subject must be documented in the source record. Incorrect or missing dosing data and migraine data that are reported in the diary will be corrected through either a Data Clarification Record or a Medication Reconciliation Form. Investigators should inform subjects that involuntary termination from the study will occur in cases where non-compliance is identified. Study staff should contact a subject in between the monthly study visits if the subject demonstrates non-compliance with the eDiary and document the contact in the source, to identify potential lost to follow up subjects as early as possible.

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

Cases of potential study drug abuse or overdose (including cases of non-compliance with study drug dosing instructions or subjects who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Dosing errors (e.g., accidentally taking 2 ODTs in one calendar day) should be reported as deviations.

Compliance with study intervention will be defined as:

- ≥80% (and ideally, up to 100%) of study-supplied intervention from Day 1 through the Treatment Phase are expected to be consumed.

- Post randomization, at each dispensation visit (refer to Table 1 and Table 2), subjects who are <80% compliant must be re-educated on the importance of daily self-administration of study intervention.

- Overall aim: maintain ≥80% compliance over the duration of dosing with randomized study intervention.

7.5. Destruction and Return of Study Drug

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

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

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 two types of adverse events, Serious Adverse Events (SAE) and Non-Serious Adverse Events (AEs). Subjects should be instructed to notify the Investigator when a Serious Adverse Event 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)
- Abuse or Overdose of medication
    - Potential study drug abuse (including cases of excessive non-compliance with study drug dosing instructions or subjects who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor subjects for possible cases of abuse of study drug (subjects taking study drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies
    - Potential study drug overdose is defined in Section 8.3

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

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

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

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

8.1.2. Collection and Reporting Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur from the time the ICF is signed throughout the course of the study up to and including the 2-Week Follow-up Safety 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 electronic data capture (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, and 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 form, 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 from signing the ICF through the 2-Weeks Follow up Safety Visit. Non-serious adverse events should be followed until conclusion or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

8.2.2. Laboratory Test Abnormalities

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

1. Any laboratory test result that is clinically significant or meets the definition of an SAE;
2. Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted;
3. Any laboratory abnormality that required the subject to receive specific corrective therapy.

8.3. Overdose

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

Asymptomatic dosing errors (e.g., accidentally taking two ODTs instead of prescribed dose of 1 ODT in one calendar day) should be reported as deviations.

8.4. Potential Drug Induced Liver Injury (DILI)

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

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

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

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

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

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

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

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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 is pregnant or may have been pregnant at the time of the IP exposure, including during at least 6 half-lives after the product administration, the IP will be permanently discontinued in an appropriate manner (i.e., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by the

pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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 by either using the CT SAE Report Form or via PSSA tool and by completing an Exposure During Pregnancy (EDP) Supplemental Form following the SAE reporting procedures as described in Section 8.1.2.

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

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 on an EDP Supplemental Form, as appropriate.

An EDP occurs if:

- A female subject is found to be pregnant while receiving or after discontinuing study intervention.
- A male subject who is receiving or has discontinued study intervention inseminates a female partner.
- A female non-subject is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then inseminates his female partner prior to or around the time of conception.

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

- If EDP occurs in a subject/subject's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form 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 non-subject is found to be breastfeeding while being exposed or having been exposed to study intervention (ie., environmental exposure). An example of

environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form or 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 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

The study will randomize roughly 245 subjects per treatment arm to obtain roughly 225 evaluable subjects per treatment arm.

With a sample size of roughly 490 subjects randomized, and 245 subjects per group, we expect roughly 225 evaluable subjects per group in the double-blind treatment migraine analysis set. Assuming rimegepant provides roughly a 1 day advantage over placebo on the primary endpoint, and a common standard deviation of 3.75 days, then the study will have roughly 80% power on the primary endpoint at a 2-sided alpha level of 0.05. The estimates for the change in migraine days per month and the standard deviation are consistent with publicly available information from another investigational oral CGRP antagonist for this indication.

9.2. Analysis Set

The following analysis sets will be used in this study:

- Enrolled: Subjects who sign the informed consent form and are assigned a subject identification number by the IWRS.
- Full: Subjects in the enrolled analysis set who were assigned a randomized treatment group by IWRS.
- Safety: subjects in the enrolled analysis set who take ≥ 1 dose of study drug (double-blind or open-label).
    - Double-blind treatment safety: Subjects in the safety analysis set who take ≥ 1 dose of double-blind study drug (rimegepant or placebo).
    - Open-label rimegepant safety: Subjects in the safety analysis set who take ≥ 1 dose of open-label rimegepant.
    - Double-blind or open-label rimegepant safety: Subjects in the safety analysis set who take ≥ 1 dose of double-blind or open-label rimegepant.
    - Follow-up safety: subjects in the safety analysis set whose last contact date is in the follow-up safety analysis period.
- Double-blind treatment efficacy: Subjects in the full analysis set who are randomized only once and take ≥ 1 dose of double-blind study drug.

- Double-blind treatment migraine: Subjects in the double-blind treatment efficacy analysis set with ≥ 14 days of eDiary data (not necessarily consecutive) in both the Observation Period and ≥ 1 month (4-week interval) during the Double-blind Treatment Phase.

- Double-blind treatment first month migraine: subjects in the double-blind treatment efficacy analysis set with ≥ 24 days of eDiary efficacy data (not necessarily consecutive) in both the OP and in first month (4-week interval) of the Double-blind Treatment Phase.

- Open-label rimegepant efficacy: subjects in the double-blind treatment efficacy analysis set who take ≥ 1 dose of open-label rimegepant.

9.3. Statistical Methods

The Observation Period represents "baseline" for endpoints based on migraine days.

9.3.1. Primary Endpoint(s)

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

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

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

9.3.2. Secondary Endpoint(s)

The proportion of subjects with ≥ 50% reduction from baseline in the number of moderate or severe migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase will be analyzed using a Mantel-Haenszel risk estimation with stratification by randomization stratum for the double-blind treatment migraine analysis set. Missing data are imputed as non-response (i.e., failure). The stratified difference estimate (rimegepant – placebo), SE, 95% CI, and p-value will be reported.

The mean change from baseline in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed for the double-blind treatment migraine analysis set with the same model used for the primary endpoint.

The mean change from baseline in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the Double-blind Treatment Phase will be assessed for the double-blind treatment migraine analysis set with the same model used for the primary endpoint.

The mean number of acute migraine-specific medication days per month in the last 4 weeks (Weeks 9 to 12) of Double-blind Treatment Phase will be assessed for the double-blind treatment migraine analysis set using a model that is similar in structure to that used for the primary endpoint, except that the number of acute migraine-specific medication days per month is the dependent variable and there is no covariate. Acute migraine-specific medications are triptans and ergotamine.

The mean changes from baseline in MSQoL role function - restrictive domain score, MIDAS total score, and EQ-5D-5L VAS score at Week 12 will be assessed for the double-blind treatment efficacy analysis set using linear models that will include the following variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; and fixed effects for treatment group and randomization stratum. The Week 12 difference estimate (rimegepant – placebo), SE, 95% CI, and p-value will be reported for each endpoint.

See Section 9.3.4 for safety endpoints.

9.3.3. Multiplicity Correction

Type I error will be controlled by using a hierarchical gate keeping procedure. First, the significance of the primary endpoint will be evaluated at a 2-sided alpha level of 0.05. If the primary endpoint is significant, then secondary endpoints 1 through 7 will be tested in the order in which they appear in the Section 3.2. Testing will stop at the first non-significant secondary endpoint. If the primary endpoint is not significant, then any further tests on secondary endpoints 1 through 7 will have p-values presented only for descriptive purposes.

9.3.4. Analysis of Safety

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

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

The frequencies of the following safety endpoints will be tabulated on treatment: AEs by intensity (mild, moderate, severe, total); AEs by relationship to study drug (related, possibly related, unlikely related, not related); SAEs; AEs leading to study drug discontinuation; hepatic-related AEs by intensity; hepatic-related AEs leading to study drug discontinuation; grade 3 to 4 laboratory test abnormalities; and LFT elevations based on fold changes above ULN, including ALT or AST >3 × ULN concurrent (on the same laboratory test collection date) with T bili >2 × ULN.

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

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).

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

9.4. Schedule of Analyses

There are 3 planned database locks: (1) primary completion date (PCD) database lock for the PCD clinical study report (CSR), which will occur after the last subject completes the Week 12 Visit; (2) Week 24 database lock for the Week 24 CSR, which will occur after the last subject completes the Week 24 Visit, if requested by a regulatory agency; and (3) last subject last visit (LSLV) database lock for the LSLV CSR, which will occur after the last subject completes the Follow-up Week 2 Visit. The content of the analyses in each CSR will be documented in the Statistical Analysis Plan (SAP).

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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

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

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

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

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 (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

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

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

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

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

10.5. 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 "bonafide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Subject level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.7. 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 non-study 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 IP (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 (or specified designee). A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately. Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Pfizer or specified designee will submit protocol amendments to the appropriate regulatory authorities for approval.

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

13. 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 inhibitorsis 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/DrugInteracti DrugInterac/ucm093664.htm#table3-2

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInterac DrugInteracti/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 – Definition of Migraine Days

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b)

a. ≥ 2 of the following pain features:

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

b. ≥ 1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

If the subject took a migraine-specific medication (i.e., study drug, triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. The use of study drug on non-scheduled dosing days is only permitted during the Open-label Extension Phase; **dosing with study drug on non-scheduled dosing days is not permitted during the Double-blind Treatment Phase**.

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

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

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

Acute Migraine-specific Medication Treatment Day: Any calendar day during which the subject took a migraine-specific medication (i.e., study drug, triptan or ergotamine). The use of study medication on non-scheduled dosing days is only permitted during the Open-label Extension Phase; **dosing with study drug on non-scheduled dosing days is not permitted during the Double-blind Treatment Phase**.

Monthly eDiary Data: Data collected by the eDiary based on the subject's monthly IP dosing schedule when at least 14 days of eDiary data are collected within that interval. Monthly frequency measurements will be prorated to 28-day equivalents.

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

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

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

16.3. APPENDIX 3 – Categories of Migraine Prevention Medications

No therapeutic response with > 2 of the following 8 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

- **Category 1**: Divalproex sodium, sodium valproate
- **Category 2**: Topiramate, carbamazepine, gabapentin
- **Category 3**: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- **Category 4**: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- **Category 5**: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- **Category 6**: Flunarizine, Lomerizine, verapamil
- **Category 7**: Angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB): (for example: lisinopril, candesartan)
- **Category 8**: Botulinum toxin injections: (for example: Botox®[onabotulinumtoxinA])

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) based on the investigator's assessment.

The following scenarios ***do not*** constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

16.4. APPENDIX 4 - ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie., rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

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

ECG Findings That Qualify as SAEs
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30-second duration). • Second- or third-degree AV block requiring pacemaker placement.

- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

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

16.5. APPENDIX 5 – 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 2.2, 2.3, Secondary Objectives and Exploratory Objectives: EQ-5D-5L related objectives modified. • Updated Section 3.2, 3.3, Secondary Endpoints and Exploratory Endpoints: EQ-5D-5L related endpoints modified. • 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 2.2, 2.3, Secondary Objectives and Exploratory Objectives: Reversed the order of secondary objectives 3 and 4 based on results from migraine-prevention study BHV3000-305. Modified language around objectives to align with more recent BHV3000 migraine prevention studies. Added efficacy exploratory objectives to align with more recent BHV3000 migraine prevention studies. • Updated Section 3, Study Endpoints: Provided clarifications where the endpoints data are derived from. • Updated Section 3.2, 3.3, Secondary Endpoints and Exploratory Endpoints: Modified language to align with changes to secondary and exploratory objectives. • Added Section 6.4 Other Assessments: Moved previous Sections 6.3.1 through 6.3.3 about MSQoL, MIDAS, and EQ-5D-5L) here. Specified the use of the eDiary. • Updated Section 9, Statistics: Modified language to align with more recent BHV3000 migraine prevention studies. • Provided clarifications throughout the protocol. • Corrected inconsistencies and typographical errors throughout the protocol.	29-Nov-2022
Version 4.0	• Updated Section 4.3, Schedule of Assessments: administrative letter 01 issued in Jan 2023 incorporated.	27-Feb-2023

	• Updated Section 4.3.1.1, Screening Visit: Provisions added which permit re-screening of those who were screen failures previously. • Updated Section 5.3, Exclusion Criteria: exclusion criteria 1a, 1c, 2i, 2o, 2p, 5f, 5g and 5i modified. • Updated Section 5.4, Prohibited and Restricted Concomitant Medications: #8 and 18 modified. • Updated Section 5.5, Prophylactic and Rescue Medications: valproic acid/valproate added as a prophylactic medication; revision to upper limit of acetaminophen dose from 1000 mg/day to 2000 mg/day. • Update Section 6.2.4.1, Safety Laboratory Testing: administrative letter 01 issued in Jan 2023 incorporated. • 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.	

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