DRUG:	BHV-3000 (PF-07899801) (rimegepant)
STUDY NUMBER(S):	BHV3000-404 (C4951010)
PROTOCOL(S) TITLE:	A Phase 4 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Episodic Migraine Prevention with Multiple Dosing Regimens
IND NUMBER:	109886
EudraCT NUMBER:	2021-005239-22
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	22 November 2021
VERSION NUMBER:	5.0
VERSION DATE:	26 June 2023

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

Overall Rationale for the Amendment: Change in sponsorship from Biohaven to Pfizer with alignment of the protocol template.

Description of change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Referenced study number BHV3000-404 to C4951010 and compound name BHV-3000 to PF-07899801 to reflect identification changes by sponsor.	Reflects change in sponsorship protocol and compound identification numbers	1.1 Background 7.1.1 Investigational Product Headers Title page
Removed the exclusion criterion for patients with HIV disease.	Aligned with rimegepant prescribing information where there is no exclusion for use in patients with HIV	5.3. #2a)Exclusion Criteria
Updated the exclusion criterion for patients with biliary disorder.	Aligned with rimegepant prescribing information where there is no exclusion for use in subjects with biliary disorder	5.3. #2f) Exclusion Criteria
Removed Gilbert's Syndrome from the exclusionary criteria.	Aligned with rimegepant prescribing information where there is no exclusion for use in Gilbert's Syndrome	5.3. #2h) Exclusion Criteria
Amended the exclusion criterion for body mass index to > 35.0 kg/m2 from 33.0 kg/m2.	Aligned definition to be inclusive of all Class 1 Obesity subjects	5.3. #2o) Exclusion Criteria
Amended exclusion criterion for HbA1c to > 7.5 %.	Allowed inclusion of well controlled diabetics aligned with rimegepant prescribing information where there is no exclusion for subjects with diabetes	5.3. #5g) Exclusion Criteria
Amended the hepatic exclusion criteria to allow subjects with 1.5xULN of ALT, AST and Total Bilirubin.	Allowed for inclusion of subjects with mild LFT elevations consistent with the prescribing information where there is no exclusion for subjects with mild hepatic disease	4.3.1.1 Screening Visit 4.3.1.2 Pre-randomization Evaluation Visit 5.3. #5c) & 5d) Exclusion Criteria
Removed specific exclusionary ECG criteria	Allowed for investigator opinion on exclusionary ECG findings	5.3. #5b) Exclusion Criteria

Changed GFR from 40 to 30 ml/min/1.73m^2.	Allowed for subjects with moderate renal impairment to be included in the trial consistent with the prescribing information	5.3. #5a) Exclusion Criteria
Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members.	Aligned with Pfizer protocol template	5.3. #7l) Exclusion Criteria
Allowed for rescreening of subjects due to prior failed eligibility criteria.	Allowed for rescreening of subjects who previously were screen failed for an amended exclusionary criterion	4.3.1.1 Screening visit
Allowed dose of aspirin up to 100 mg daily for cardiovascular prophylaxis.	Aligned with ex-US dosing for low dose aspirin prophylaxis	5.3. #6c) bullet Prohibited Medications 5.4. #14) Prohibited and Restricted Concomitant Medications and Devices
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	16.2 Appendix 2 – Inhibitors and Inducers of CYP3A4
Changed the term onabotulinumtoxinA to botulinum toxin injections.	Added broader drug class term	5.4 #1 & #3 Prohibited and Restricted Concomitant Medications and Devices
Changed neuromuscular blocker to Botulinum toxin injections.	Maintained consistency of nomenclature with section 5.4	16.4 Appendix 4 Category #8. 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. #7 and 5.4. #14 Prohibited and Restricted Concomitant Medications and Devices
Clarified that in case of DILI the PI should determine if the patient can safely continue in the study and expanded DILI definition to include subjects with abnormal hepatic function at study entry.	Aligned with country specific amendment and updated definition to align with revised exclusion criteria	8.4 Potential Drug Induced Liver Injury (DILI)
Added Appendix for ECG findings of Potential Clinical Concern.	Aligned with Pfizer protocol template	16.6 Appendix 6 ECG Findings of Potential Clinical Concern
Clarified definition of Sponsor's Medically Qualified Individual.	Aligned with Pfizer protocol template	10.6 Sponsor's Medically Qualified Individual
Added benefit risk assessment	Aligned with ex-US country specific amendment requirements	1.4 Benefit Risk Assessment

Defined end of study	Aligned with country specific amendment	4.1 Study Design and Duration
Non-substantial Modification(s)		
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
Clarified Section 8.2.1	Aligned with Pfizer protocol template	8.2.1 Collection and Reporting of Non-serious Adverse Events
Updated text for Data Protection.	Aligned with Pfizer protocol template	15 Data Protection
Added compliance aim for IP of 80%	Defined compliance for clarity	7.4 Treatment Compliance
Added contraception requirement	Aligned with Italy country specific amendment	16.1 Appendix 1 Country Specific Requirements
Clarified the disbursement of unused, non-expired partial wallets	Aligned with details of IP Manual	4.3.2 Double-blind Treatment Phase
Updated to include US, UK, EU reference and IB reference.	Additional safety reference	1.3 Product Development Background
Clarified study drug destruction	Updated destination for study drug destruction	7.5 Destruction and Return of Study Drug
Updated study summary (Synopsis)	Synopsis was changed to include all relevant sections of the EU CTR	Study summary (Synopsis)
Removed Clinical Protocol Approval Form	Aligned with Pfizer protocol template	Protocol approval form
Removed PI declaration page	Aligned with Pfizer protocol template	PI declaration page
Clarified definition of analysis sets	Aligned with Statistical Analysis Plan	9.2 Analysis Sets
Added reference to quality tolerance limits	Aligned with Pfizer protocol template	9.3.2 Safety Analyses
Clarified/corrected statistical methods	Aligned with Statistical Analysis Plan and FDA Guidance for Industry Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products	9.3.1.1 Primary Efficacy Endpoint 9.3.1.2 Secondary Efficacy Endpoint 9.3.1.3 Multiplicity Correction
Removed Phase I study exception. Removed statement regarding Principal Investigator and the Sponsor's representative signatory. Added Sponsor's	Aligned with Pfizer protocol template	10.1 Good Clinical Practice

regulatory and ethics responsibilities.		
Added Pfizer standard text for Dissemination of Clinical Study Data.	Aligned with Pfizer protocol template	10.5 Dissemination of Clinical Study Data
Added AE information on lack of efficacy and medication errors	Aligned with Pfizer protocol template	8.6 Lack of Efficacy 8.7 Medication Errors
Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure	Aligned with Pfizer protocol template	8.5 Environmental exposure, Exposure during Pregnancy, and Occupational exposure
Moved prior Protocol Amendment Summary of Changes to Appendix	Editorial	16.7 Appendix 7 Protocol Amendment History
Updated List of abbreviations.	Editorial	List of Abbreviations
Changed term Non-Investigational Product, to Concomitant Therapy	Editorial changes	7.1.2 Concomitant Therapy
Stated that there is 1 planned database lock and no interim analysis is planned	Clarification	9.4 Schedule of Analyses
Removed notified IRB/IEC within 5 days	Amended to allow for immediate action to be implemented	12 Amendments
Removed the sub header other inclusion criteria #6.	Editorial/formatting change	5.2 Inclusion Criteria
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 4 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Rimegepant in Episodic Migraine Prevention with Multiple Dosing Regimens

Brief Title: The purpose of this study is to compare the efficacy and safety of daily and every other day dosing of rimegepant to placebo as a preventive treatment for episodic migraine.

Regulatory Agency Identification Number(s):

US IND Number:	109886
EudraCT Number:	2021-005239-22
ClinicalTrials.gov ID:	NCT05217927
Protocol Number:	BHV3000-404 (C4951010) Version 5.0
Phase:	4

Rationale: This study is being conducted to evaluate the efficacy, safety, and tolerability of EOD and daily rimegepant dosing regimens for the prevention of episodic migraine.

Primary Objectives:
To evaluate the efficacy of EOD and daily rimegepant dosing regimens relative to placebo as a preventive treatment for episodic migraine, as measured by the mean reduction from the Observation Phase in the number of migraine days per month over the entire Double-blind Treatment Phase.

Secondary Objectives:

1. To evaluate the proportion of subjects with ≥50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.
2. To evaluate the mean reduction from the Observation Phase in the number of migraine days per month in the last 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.
3. To evaluate the mean reduction from the Observation Phase in the number of migraine days per month in the first 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.
4. To evaluate the mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.
5. To evaluate the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

6. To evaluate the safety and tolerability of rimegepant during the Double-blind Treatment and Open-label Extension Phases.
7. To evaluate the frequency of ALT or AST > 3x upper limit of normal (ULN) concurrent with total bilirubin > 2x ULN in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases
8. To evaluate the frequencies of hepatic-related adverse events (AEs) and hepatic-related AEs leading to study drug discontinuation in subjects treated with rimegepant during the Double-blind Treatment and Open-label

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

Secondary Endpoints:
1. Proportion of subjects with ≥50% reduction the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).
2. Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.
3. Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the Double-blind Treatment Phase.
4. Mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12). Acute migraine-specific medications are triptans and ergotamine.
5. Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the Double-blind Treatment Phase.
6. Number and percentage of subjects with AEs by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities during the Double-blind Treatment and Open-label Extension Phases.
7. Number and percentage of subjects treated with rimegepant with AST or ALT elevations > 3x ULN concurrent (i.e., on the same laboratory collection date) with total bilirubin > 2x ULN during the Double-blind Treatment and Open-label Extension Phases.
8. Number and percentage of subjects treated with rimegepant with hepatic related AEs by intensity, and hepatic-related AEs leading to study drug discontinuation during the Double-blind Treatment and Open-label Extension Phases.

Overall Design:
This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in episodic migraine prevention. During the Double-blind Treatment Phase, subjects will be randomized to daily dosing (rimegepant 75 mg ODT daily, rimegepant 75 mg ODT dosed every other day (EOD) alternating with placebo for matching rimegepant 75 mg ODT dosed EOD, or placebo).

All subjects will participate in a 28-day Observation Phase. During the Observation Phase, subjects will treat migraines with acute standard of care migraine medications. Subjects will

report migraine occurrence, migraine pain features and associated symptoms (e.g., pain intensity, nausea, photophobia and phonophobia), and use of acute migraine medication in an electronic diary (eDiary).

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 randomized 1:1:1 across 3 treatment groups in the Double-blind Treatment Phase: rimegepant 75 mg ODT dosed EOD alternating with matching placebo (n = 220); rimegepant 75 mg ODT dosed daily dosing (n =220); or placebo for matching rimegepant 75 mg ODT dosed daily (n = 220). During the Double-blind Treatment Phase, subjects will be instructed that they must take 1 tablet of blinded study drug daily. If subjects have a migraine during the Double-blind Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed while continuing to take the study drug. Subjects will take the assigned study drug for 12 weeks. Subjects will record migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary during the Double-blind Treatment Phase.

At the completion of the 12-week Double-blind Treatment Phase, subjects will be evaluated for entry into the 12-week Open-label Extension Phase following laboratory results within acceptable ranges per protocol. During the Open-label Extension Phase, subjects will be instructed that they must take 1 tablet of rimegepant 75 mg ODT medication every day, regardless of whether they have a migraine that day.

All randomized subjects will have follow-up visits at approximately 2 weeks and 8 weeks after the last visit in the last treatment phase. Subjects will also record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken throughout the entire study in the concomitant medication paper diary.

Number of Subjects:
Approximately 2000 subjects will be screened to randomize up to approximately 660 subjects with a history of episodic migraine that is confirmed in the Observation Phase. Subjects will be randomized 1:1:1 across 3 treatment groups in the Double-blind Treatment Phase: rimegepant 75 mg ODT dosed EOD alternating with matching placebo (n = 220) rimegepant 75 mg ODT dosed daily (n = 220); or placebo for matching rimegepant 75 mg ODT dosed daily (n = 220). Up to 660 subjects (including up 220 subjects in the daily dosing cohort) may enter the Open-label Extension Phase for an additional 12 weeks with daily dosing.

Study Population:
The study will recruit male and female subjects, 18 years of age or older with at least a one-year history of episodic migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition.4 Per their own report, subjects must have migraine onset prior to age 50, migraine attacks that last 4-72 hours (if not treated), and have had 4-14 migraine attacks per 4 week period within the 12 weeks prior to the Screening Visit. Subjects must also have at least 4 Migraine Days and no more than 14 Headache Days during 28 days in the Observation Phase.

WOCBP who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study and for 60 days after the last dose of study drug, women who are pregnant or breastfeeding, and women with a positive pregnancy test at screening or prior to study drug administration will be excluded.
Use of prophylactic migraine medication within 30 days prior to the Screening Visit is prohibited. Subjects with a history of use of analgesics (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) or use of medication accepted for treatment of acute migraine for a nonmigraine indication on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit are excluded. Subjects who previously discontinued biologic migraine medications (such as CGRP monoclonal antibodies) must have done so at least 6 months (24 weeks) prior to the Screening Visit.

Statistical Methods:
The study will randomize approximately 220 subjects with confirmed episodic migraine per treatment group. Based on data from study BHV3000-305, we estimate that this will result in roughly 200 subjects per treatment group in the migraine analysis set. Assuming rimegepant provides roughly a 1.1 day advantage over placebo on the primary endpoint, and assuming a common standard deviation of 3.5 days, then the study will have roughly 80% power on the primary endpoint at a 2-sided alpha level of 0.025.

The primary endpoint, mean change from the Observation Phase in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12), will be assessed using a linear mixed effects model with repeated measures.

The proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate or severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed using Mantel-Haenszel risk estimation.

The mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) and the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase will be assessed from the same model used for the primary efficacy endpoint.

The mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed using a linear mixed effects model with repeated measures.

The mean change from baseline in the MSQ restrictive role function domain score at Week 12 will be assessed using a linear model.

Safety endpoints will be assessed descriptively.

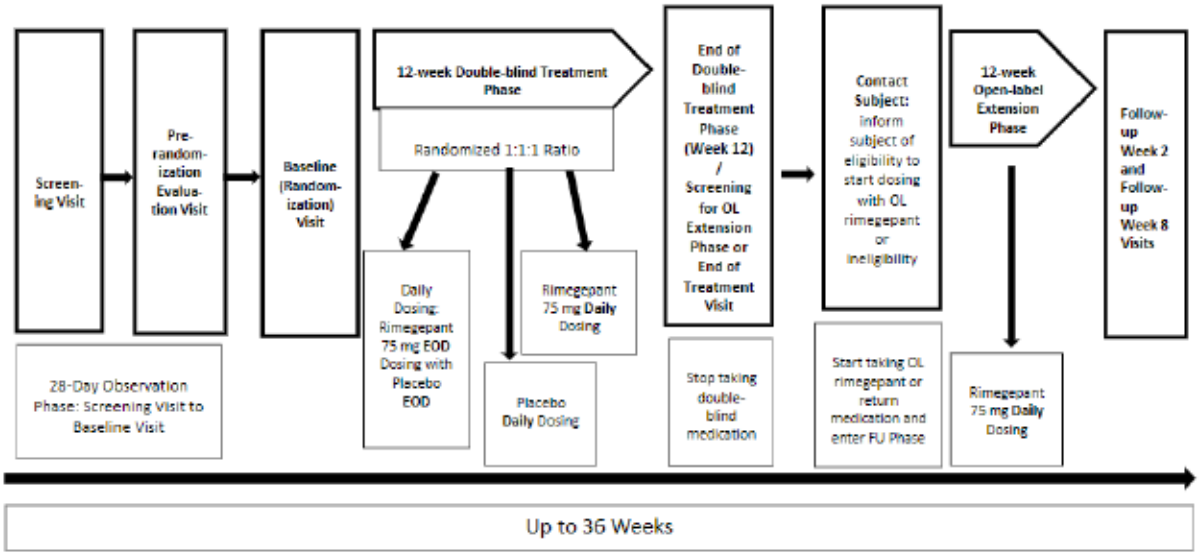
Risk/Benefit Assessment:
Rimegepant is being developed for the treatment of migraine. Effectiveness for the acute treatment of migraine was initially demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia.1 Efficacy was confirmed for

the acute treatment of migraine in three pivotal Phase 3 trials using the current registrational co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2 hours after dosing. Effectiveness for the preventive treatment of episodic migraine was demonstrated in a Phase 2/3 double-blind, randomized, placebo-controlled study of rimegepant 75 mg dosed every other day (EOD).2 Every other day dosing was also well tolerated with no signals of hypersensitivity, cardiovascular events, or hepatotoxicity. Every other day scheduled dosing with as needed dosing was shown to be well tolerated with a favorable safety profile

The results of previous studies of rimegepant support the investigation of rimegepant in episodic migraine prevention with multiple dosing regimens, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to subjects, the potential risks associated with rimegepant are justified by the anticipated benefits that may be afforded to subjects with episodic migraine.

STUDY SCHEMATIC

Figure 1 **12 Weeks of Double-blind Treatment with Daily Dosing, Followed by 12 Weeks of Open-label Treatment with Daily Dosing**



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LIST OF ABBREVIATIONS

AE	Adverse Event
ACE	Angiotensin-converting enzyme
ALT	Alanine Aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV	Atrioventricular
BHV	Biohaven
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGI-c	Clinical Global Impressions- change scale
CGRP	Calcitonin Gene-Related Peptide
CI	Confidence interval
CK	Creatine Kinase
C_{max}	Maximum Plasma Concentration
COVID-19	Coronavirus Disease 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
CTS	Clinical Trial Subject
CV	Coefficient of Variation
CYP	cytochrome P450
DAIDS	Division of AIDS
DILI	Drug-Induced Liver Injury
DDI	drug-drug interaction
DSMC	Data and Safety Monitoring Committee
DSM-V	Diagnostic and Statistical manual of Mental Disorders Fifth edition
DSU	Drug Safety Unit
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDB	Exposure During Breastfeeding

EDC	Electronic Data Capture
eDiary	Electronic diary
EDP	Exposure During Pregnancy
EOD	Every Other Day
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practices
HDL	High-density Lipoprotein
HbA1c	Hemoglobin A1C
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHS	International Headache Society
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
kBq	Kilobecquerel
kg	Kilogram
L	Liters
LBBB	left bundle branch block
LDH	Lactate Dehydrogenase
LDL	Low-density Lipoprotein
LFT	Liver Function Test
MBq	Megabecquerel
MDZ	Midazolam
mg	Milligram
MSQ	Migraine-Specific Quality-of-Life Questionnaire
min	Minute

mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
NSAID	Non-steroidal anti-inflammatory drug
ODT	Orally Disintegrating Tablet
OTC	Over the Counter
PACL	Protocol Administrative Clarification Letter
PO	By Mouth, Orally
PSSA	Pfizer SAE Submission Assistant
PVC	premature ventricular contraction
QD	Once Daily
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
SE	Standard error
SM	Satisfaction with Medication
SRSD	single Reference Safety Document
T bili	total bilirubin
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Background

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

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. There is widespread agreement that this new approach avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists (e.g., sumatriptan [Imitrex™])).

1.2 CGRP's Role in Migraine

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.[5,6] Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine;[7] 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief;[7,8] and 3) intravenous CGRP infusion produces lasting pain in non-migraineurs and migraineurs.[6,9]

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 in the meninges, 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.

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).

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 to the study are presented below. Rimegepant is

approved for the treatment of acute treatment and prevention of episodic migraine in the US, UK and EU and is well tolerated in humans when given as single oral dose of 75 mg to treat acute migraine and at a dose of 75 mg EOD for the prevention of episodic migraine. Every other day dosing was well tolerated with no signals of hypersensitivity, cardiovascular events, or hepatotoxicity.[2]

Rimegepant has been studied up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days.

The BHV3000-201 study is a completed Phase 2/3, 52-week, open-label, safety study in 1800 subjects (up to one year in duration) with rimegepant 75 mg dosed as needed or scheduled EOD plus as needed. Rimegepant 75 mg administered in multiple doses for up to 52 weeks in subjects with migraine was well tolerated. No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow-up.

The BHV3000-305 study is a completed Phase 2/3, 64-week (12 weeks of a double-blind, placebo-controlled phase followed by 52 weeks of open-label treatment) study with rimegepant 75 mg or matching placebo dosed every other day (EOD) for the prevention of migraine. During the open-label phase, subjects were able to dose on non-scheduled dosing days and therefore were able to dose up to once daily.

The primary identified adverse event (AE) of interest is the potential elevation of liver function tests. Investigators must carefully monitor routine liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin, and ALP) and potentially liver related symptoms and signs. Clinicians should also monitor changes in hematology and other laboratory measures.

1.4 Benefit Risk Assessment

Rimegepant is approved in the US, EU, and UK for the treatment of migraine in adults, including both acute treatment of migraine and preventive treatment of episodic migraine. Rimegepant appears to be generally safe and well tolerated in humans when given as single oral doses from 75 mg up to the maximum dose of 1,500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. Rimegepant 75 mg represents an advancement in migraine therapeutics, providing the first CGRP antagonist to demonstrate benefit for both the acute treatment and prophylaxis of migraine. Dual action therapy for migraine with a single agent offers patients the potential for significant clinical advantages including: 1) a simplified medication regimen to treat migraine across the spectrum from acute episodes to the prevention of future attacks, which are 2 manifestations of the same condition; 2) avoiding polypharmacy with concurrent use of multiple medications each with their own side effects; 3) reducing the risk of 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 every other day (EOD) demonstrated statistically significant superiority to placebo on the primary endpoint of change from the observation period in the mean number of migraine days per month on treatment in the last month of the double-blind treatment phase.

A multicenter open-label, long-term study (BHV3000-201) was conducted to evaluate the safety and tolerability of rimegepant 75 mg tablet taken as needed (up to 1 tablet per day upon onset of a migraine of mild, moderate, or severe intensity) for the acute treatment of migraine for up to 52 weeks. This multiple-dose, long-term study of rimegepant 75 mg administered for up to 52 weeks confirmed the favorable safety profile across a variety of safety endpoints, including AE assessments, clinical laboratory testing including LFTs, vital signs and ECGs. Safety data from the double-blind treatment and the open-label extension phases of the pivotal Phase 2/3, randomized, double-blind, placebo-controlled preventive treatment of migraine study (BHV3000-305) support a favorable safety profile of rimegepant 75 mg administered EOD for the preventive treatment of migraine. Rimegepant 75 mg administered EOD + 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.

There are no adequate data on the developmental risk associated with the use of rimegepant in pregnant women. Women of childbearing potential (WOCBP) must have a negative pregnancy test and WOCBP and fertile men must use 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. Subjects undergo regular pregnancy testing throughout the duration of the study. Although no safety issues in clinical trials of rimegepant were observed, cardiovascular events, cerebrovascular events, hypertensive events, and serious gastrointestinal events associated with constipation are reviewed in each aggregate report per 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 SRSD for this study.

1.5 Study Rationale

The goal of this study is to assess the efficacy and safety of every other day (EOD) and daily (QD) dosing vs. placebo.

This study is being conducted to evaluate the efficacy, safety, and tolerability of a QD dosing regimen of rimegepant, as well as to further evaluate an EOD regimen, for the prevention of episodic migraine. It will also further define the safety profile of rimegepant administration for up to 24 weeks. Approximately 660 subjects will dose with double-blind study drug every day for a period of approximately 12 weeks, followed by an additional 12 weeks with open-label rimegepant dosed daily.

1.5.1 Study Design Rationale

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of rimegepant 75 mg taken every other day (EOD) ***or*** daily for the prevention of episodic migraine with a 12-week Open-label Extension Phase.

Approximately 660 subjects will be randomized and assigned treatment in the Double-blind Treatment Phase of the study. Subjects will be randomized in a 1:1:1 ratio across 3 treatment groups: rimegepant 75 mg dosed EOD alternating with matching placebo (n = 220); rimegepant 75 mg dosed daily (n = 220); or placebo matching rimegepant 75 mg dosed daily (n = 220). Randomization will be stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no; see Section 7.2.1). In addition, randomization of prophylactic migraine treatment-naïve subjects ("no" category) will be capped at 30% in order to allow ≥ 70% of randomized subjects to be prophylactic migraine treatment-experienced ("yes" category).

During the Double-blind Treatment Phase, subjects will be instructed to take one (1) ODT of blinded study drug **every day**. Depending on the randomization, blinded study drug will alternate EOD between rimegepant and matching placebo, will be entirely rimegepant 75 mg or will be entirely matching placebo.

During the Open-label Extension Phase, subjects will be required to take 1 tablet of rimegepant 75 mg ODT **every day**.

If subjects have a migraine, they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.1) while continuing with the study drug.

1.5.2 Dose Selection

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine. The three Phase 3 studies BHV3000-301, BHV3000-302, and BHV3000-303 confirmed this efficacy using the current registrational endpoints for acute treatment of migraine. The pivotal Phase 3 Study BHV3000-305 demonstrated that rimegepant 75 mg EOD is effective and has a favorable safety profile for the prevention of migraine headache. The current study will evaluate the efficacy and safety of more frequent daily dosing relative to the EOD regimen in episodic migraine prevention.

1.6 Research Hypothesis

Rimegepant 75 mg ODT is effective and well tolerated when taken daily for the prevention of episodic migraine.

2 STUDY OBJECTIVES

A month is defined as 4 weeks (28 days) for the purpose of this protocol.

2.1 Primary

To evaluate the efficacy of EOD and daily rimegepant dosing regimens relative to placebo as a preventive treatment for episodic migraine, as measured by the mean reduction from the Observation Phase in the number of migraine days per month over the entire Double-blind Treatment Phase.

2.2 Secondary

1. To evaluate the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

2. To evaluate the mean reduction from the Observation Phase in the number of migraine days per month in the last 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

3. To evaluate the mean reduction from the Observation Phase in the number of migraine days per month in the first 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

4. To evaluate the mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

5. To evaluate the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

6. To evaluate the safety and tolerability of rimegepant during the Double-blind Treatment and Open-label Extension Phases.

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

8. To evaluate the frequencies of hepatic-related adverse events (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 Objectives

1. To evaluate the mean reductions from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

2. To evaluate the proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

3. To evaluate the mean reductions from the Observation Phase in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

4. To evaluate the proportions of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

5. To evaluate the proportions of subjects with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

6. To evaluate the mean number of acute migraine-specific medication days per month in each month and over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

7. To evaluate the mean number of acute migraine medication days per month in each month and over the entire Double-blind Treatment Phase for the EOD and daily rimegepant dosing regimens relative to placebo.

8. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or total bilirubin) based on fold changes above ULN in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

9. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

10. To evaluate the mean changes from baseline in MSQ domain scores during the Double-blind Treatment and Open-label Extension Phases.

11. To evaluate the Satisfaction with Medication (SM) scale during the Double-blind Treatment and Open-label Extension Phases.

12. To evaluate the Clinical Global Impression – change (CGI-c) scale during the Double-blind Treatment and Open-label Extension Phases.

3 STUDY ENDPOINTS

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

AEs are determined from case report forms (CRFs).

MSQ domain scores are derived from CRFs.

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

3.1 Primary

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

3.2 Secondary

1. Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).

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

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

4. Mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12). Acute migraine-specific medications are triptans and ergotamine (see Section 3.3).

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

6. Number and percentage of subjects with AEs by intensity, serious adverse events (SAEs), AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities during the Double-blind Treatment and Open-label Extension Phases.

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

8. Number and percentage of subjects treated with rimegepant with hepatic-related AEs by intensity, and hepatic-related AEs leading to study drug discontinuation during the Double-blind Treatment and Open-label Extension Phases.

3.3 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 either Criteria A or B below:

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 a migraine-specific medication (i.e. triptan) 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 ergotamine medication is prohibited throughout the entire duration of this study. However, use of this medication, if taken for migraine treatment, must be documented for the purposes of assessing migraine days and must be captured as a protocol deviation.

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 day, please refer to Section 16.3 Appendix 3.

3.4 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.

For the full definition of headache days, please refer to Section 16.3 Appendix 3.

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 two different dosing regimens of rimegepant 75 mg ODT in episodic migraine prevention with an open-label extension phase.

The 28-day Observation Phase includes the Screening Visit and Pre-randomization Evaluation Visit. To be eligible for the study, subjects must have reported having had 1). ***4-14 migraine attacks*** per month in the 3 months (12 weeks) prior to the Screening Visit, and 2). at least ***4 migraine days*** and no more than ***14 headache days*** during 28 days in the Observation Phase, which will be documented in the eDiary.

Upon the completion of the Screening Visit, subjects will be provided an electronic diary (eDiary) to document the following on each day of the Observation Phase: migraine occurrence; migraine pain features and associated symptoms (see Section 3.3); and use of acute migraine medication (i.e., triptans; see Section 5.5.1). In addition, subjects will record all concomitant medications, including acute standard of care migraine medications taken in the concomitant medication paper diary (see Section 5.5.1). After completing the Observation Phase, the subject will return to the clinic with the eDiary and concomitant medication paper diary for the Baseline (Randomization) Visit.

Subjects will have blood drawn and a urinalysis performed for baseline profiles, an ECG performed, and other procedures as noted in Table 1 at the Pre-randomization Evaluation Visit. Subjects will then return for the Baseline (Randomization) 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 randomized 1:1:1

across 3 treatment groups in the Double-blind Treatment Phase: rimegepant 75 mg ODT dosed EOD alternating with matching placebo (n = 220); rimegepant 75 mg ODT dosed daily (n = 220); or placebo for matching rimegepant 75 mg ODT dosed daily (n = 220). Randomization will be stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no; see Section 7.2.1). In addition, randomization of prophylactic migraine treatment-naïve subjects ("no" category) will be capped at 30% in order to allow ≥ 70% of randomized subjects to be prophylactic migraine treatment-experienced ("yes" category).

During the Double-blind Treatment Phase, subjects will be instructed that they must take 1 tablet of blinded study drug daily. If subjects have a migraine during the Double-blind Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.1) while continuing to take the study drug. 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 following day's assigned dose until the next calendar day at the specified time.

At the completion of the 12-week Double-blind Treatment Phase, subjects will be evaluated for entry into the 12-week Open-label Extension Phase following laboratory test results within acceptable ranges per protocol (Sections 5.2 and 5.3). During the Open-label Extension Phase, subjects will be instructed that they must take 1 tablet of rimegepant 75 mg ODT daily.

During the Double-blind Treatment Phase, subjects will record their migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication on each day in the eDiary.

Subjects will also record all concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the entire study in the concomitant medication paper diary.

At select study visits, subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ v 2.1), Clinical Global Impression – change (CGI-c) scale, the Satisfaction with Medication (SM) scale, and the Columbia-Suicide Severity Rating Scale (C-SSRS) on paper forms.

Additional assessments and visit schedule are outlined in the procedural tables in Section 4.3. Procedures include study personnel review of the eDiary (during the Double-blind Treatment Phase) and concomitant medication paper diary with the subject, assessment of study drug compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography).

During the Observation Phase, study visits will occur at Screening (Enrollment) and Pre-randomization Evaluation.

During the Double-blind Treatment Phase, study visits will occur at Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12 or End of Treatment (EOT) for early discontinuation.

At the completion of the 12-week Double-blind Treatment Phase, subjects may enter the 12-week Open-label Extension Phase if they continue to meet study entry criteria and laboratory test results are acceptable per protocol (Sections 5.2 and 5.3). Study visits will occur at Week 14, Week 16, Week 20, and Week 24 or EOT for early discontinuation.

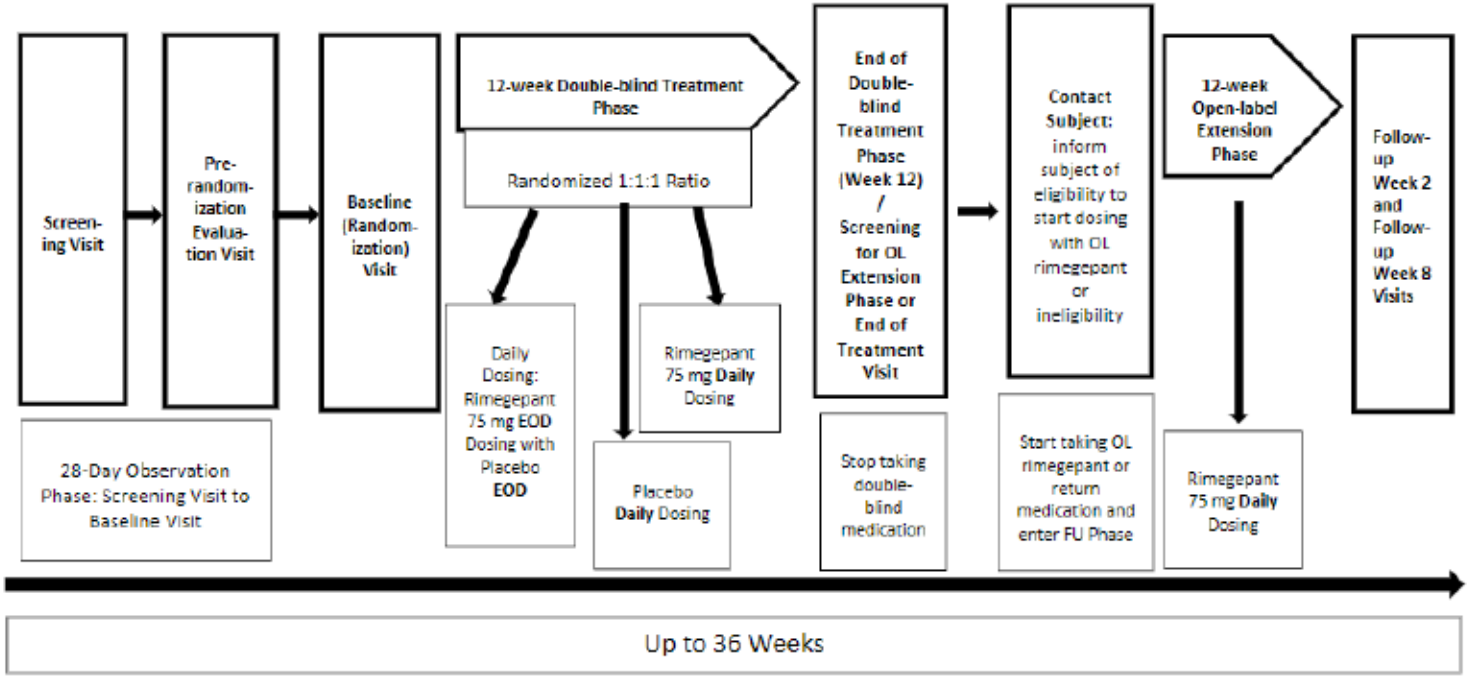
During the Follow-up Phase, study visits will occur at Follow-up Week 2 and Follow-up Week 8 for assessment of AEs and laboratory assessments. All randomized subjects should complete the Follow-up Week 2 and Follow-up Week 8 Visits.

The end of the study is defined as the last visit of the last subject.

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

4.2 Study Schematic

Figure 2 12 Weeks of Double-blind Treatment with Daily Dosing, Followed by 12 Weeks of Open-label Treatment with Daily Dosing



4.3 Schedule of Assessments

Every effort should be made to conduct the study visits as planned. Concerns related to the Coronavirus disease 2019 (COVID-19) pandemic, other natural catastrophes (e.g., hurricane), and any additional case-by-case situations may be discussed for approval with the Sponsor. Following approval, provisions may be implemented to minimize potential hazards to study subjects and to maintain compliance with local government and institutional guidance (e.g., study center has a policy that a clinical research visit must be delayed). These provisions may allow alternatives to in-person study visits and include, but are not limited to, the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, or performing safety labs via local laboratory or professional in-home phlebotomy vendors. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. The Screening, Pre-Baseline Evaluation, Baseline, and Follow-up Week 8 Safety visits must be done in person. Other visits may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.).

Table 1 Schedule of Assessments – Observation Phase, Double-blind Treatment Phase, EOT, & Follow-up Phase

	Observation Phase (28 days + 3 days) 1		Double-blind Treatment Phase2, 3, 4				Follow-up Phase3, 4
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit**	**Baseline (Randomization) Visit** (Day 1)	**Week 2 Visit** (Day 14 +/- 2 days)	**Week 4** (Day 28) **and Week 8** (Day 56) **Visits** (both visits +/- 2 days)	**Week 12** (Day 86 +3 days) **or EOT Visit** for early discontinuation	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects4
Eligibility Assessments							
Informed Consent	X						
Duplicate Subject Check (in CTSdatabase)	X						
Inclusion/Exclusion Criteria	X		X				
Medical History	X						
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X						
Concomitant medication paper diary[5]	X	X	X	X	X	X	X
Randomize subject / IWRS[6]			X				
Safety Assessments							
Physical Examination[7]	X	X				X	
Vital Signs / Physical Measurements[8]	X	X	X	X	X	X	X
Clinical Safety Laboratory Testing[9]	X	X		X	X	X	
Liver Function Test (LFTs)[9]	X	X	X	X	X	X	X

	Observation Phase (28 days + 3 days) 1		Double-blind Treatment Phase2, 3, 4				Follow-up Phase3, 4
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit**	**Baseline (Randomization) Visit** (Day 1)	**Week 2 Visit** (Day 14 +/- 2 days)	**Week 4** (Day 28) **and Week 8** (Day 56) **Visits** (both visits +/- 2 days)	**Week 12** (Day 86 +3 days) **or EOT Visit** for early discontinuation	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects4
Lipid Panel[9]		X				X	
ECG	X	X		X	X	X	
Urinalysis		X				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)	X: FU W2 (urine) & FU W8 (serum)
AE, SAE, and Concomitant Procedure assessment[10]	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X		X	X	X	X	X (FU W2 only)
Clinical Drug Supplies / Study Supplies							
Dispense study drug[11]			X		X	X (OL drug dispensed for subjects planning to enter OL Phase)	

	Observation Phase (28 days + 3 days) 1		Double-blind Treatment Phase2, 3, 4				Follow-up Phase3, 4
Procedure	**Screening Visit**	**Pre-randomization Evaluation Visit**	**Baseline (Randomization) Visit** (Day 1)	**Week 2 Visit** (Day 14 +/- 2 days)	**Week 4** (Day 28) **and Week 8** (Day 56) **Visits** (both visits +/- 2 days)	**Week 12** (Day 86 +3 days) **or EOT Visit** for early discontinuation	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects4
Administer study drug[11, 12]				X	X	X	
Dispense / Collect Electronic Diary (eDiary)[13]	X (Dispense eDiary)					X (Collect eDiary)	
Return used and unused study drug to site for compliance check				X	X	X	
eDiary returned / reviewed for completness[13]		X	X	X	X	X	
Other Assessments							
Daily report of migraine occurrence and pain intensity reported by subject in eDiary[13]		X	X	X	X	X	
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1			X			X	
Satisfaction with Medication (SM)						X	
Clinical Global Impression-Change (CGI-c)						X	

1.The Observation Phase to determine eligibility is 28 days + 3 days. The "+ 3" days window is included for scheduling purposes only. Subjects with less than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary. 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.
2.While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to their original visit schedule by calculating the visit window interval from the Baseline/Randomization Visit.
3. All randomized subjects ***who discontinue early from the Double-blind Treatment Phase*** should complete the EOT Visit and enter the Follow-up Phase (they should not enter the Open-label Extension Phase). All randomized subjects should complete the Follow-up Week 2 and Follow-up Week 8 Visits.
4. For subjects who do not enter the Open-label Extension Phase, the follow-up visits should be scheduled based on date of the Week 12 or EOT Visit. The visit window for the Follow-up Week 2 Visit is 14 days +/- 2 days. The visit window for the Follow-up Week 8 Visit is 56 days +/- 2 days; however, in cases of a delayed visit due to restrictions resulting from the COVID-19 pandemic, + 14 days may be utilized instead of + 2 days in order to ensure this final visit is completed in person.
5. Concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the Observation, Double-blind Treatment, and Follow-up Phase should be recorded in the subject's concomitant medication paper diary, reviewed by study personnel at each visit, and a copy made at each study visit to be maintained in source records. At end of study, the concomitant medication paper diary should be collected at the Follow-up Week 8 Visit.
6. The actual Baseline Visit date should be used for IWRS enrollment date and eligibility date.
7. Per Section 6.2.3, a full Physical Exam (PE) is required at screening ONLY and brief symptom-directed PEs are required at all other visits.
8 Height will be measured at the 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.
9 If possible, subjects should be fasting for a minimum of 8 hours before laboratory tests. However, if a subject is not fasting, the blood draw should still be performed, and the non-fasting status should be documented. HbA1c is only collected at Screening, Repeat or Unscheduled Visit.
10 SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs and Concomitant Procedures should be reported from signing of consent through the Follow-up Week 8 Visit. Non-serious AEs should be reported from signing of consent through the Follow-up Week 2 Visit.
11 Subjects must 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. Site staff should mark each wallet with the scheduled date of each dose to be taken when dispensing the study drug. At the Week 12 / EOT Visit, all double-blind study drug should be collected, open-label study drug should be dispensed, and subjects must be instructed that dosing with open-label study drug cannot initiate until eligibility has been confirmed via lab results (telephone visit).
12 Subjects must take study drug daily regardless of whether they have a migraine. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits. 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 the following day's assigned dose until the next calendar day at the specified time.
13 The 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. The subject will use the eDiary every day during the Observation and Double-blind Treatment Phases to report migraine occurrence, migraine intensity and use of acute migraine medication. The eDiary must be collected at the Week 12 or EOT Visit.

Table 2 Schedule of Assessments – Open-label Extension Phase, EOT, & Follow-up Phase

	Phone visit to confirm eligibility based on laboratory criteria[1]	**Open-label Extension Phase**[2,3]			**Follow-up Phase**[3,4]
Procedure		**Week 14 Visit** (Day 98 +/- 3 days)	**Week 16** (Day 112) **and Week 20** (Day 140) **Visits** (both visits +/- 2 days)	**Week 24** (Day 168 +/- 2 days) **or EOT Visit** for early discontinuation	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]
Confirm Week 12 Laboratory Results	X				
Concomitant Medication paper diary[5]		X	X	X	X
Safety Assessments					
Physical Examination[6]			X (Week 16 only)	X	
Vital Signs / Physical Measurements[7]		X	X	X	X
Clinical Safety Laboratory Testing[8]		X		X	
Liver Function Test (LFTs)[8]		X	X	X	X
Lipid Panel[8]				X	
ECG		X		X	
Urinalysis				X	
Pregnancy Test		X (urine)	X (urine)	X (urine)	X: FU W2 (urine) & FU W8 (serum)
AE, SAE, and Concomitant Procedure assessment[9]		X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	X	X	X (FU W2 only)

	Phone visit to confirm eligibility based on laboratory criteria[1]	**Open-label Extension Phase**[2,3]			**Follow-up Phase**[3,4]
Procedure		**Week 14 Visit** (Day 98 +/- 3 days)	**Week 16** (Day 112) **and Week 20** (Day 140) **Visits** (both visits +/- 2 days)	**Week 24** (Day 168 +/- 2 days) **or EOT Visit** for early discontinuation	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]
Clinical Drug Supplies / Study Supplies					
Dispense study drug[10]			X		
Administer study drug[10, 11]		X	X	X	
Return used and unused study drug to site for compliance check		X	X	X	
Other Assessments					
Migraine-Specific Quality-of-Life Questionnaire (MSQ) v 2.1				X	
Satisfaction with Medication (SM)				X	
Clinical Global Impression-Change (CGI-c)				X	

1. Study eligibility must be confirmed by Week 12 laboratory results prior to first dose of open-label study drug, 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. While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to their original visit schedule by calculating the visit window interval from the Baseline/Randomization Visit.
3. All randomized subjects ***who discontinue early from the Open-label Extension Phase*** should complete the EOT Visit. All randomized subjects should complete the Follow-up Week 2 and Follow-up Week 8 Visits.

4. For subjects who enter the Open-label Extension Phase, the follow-up visits should be scheduled based on date of the Week 24 or EOT Visit. The visit window for the Follow-up Week 2 Visit is 14 days +/- 2 days. The visit window for the Follow-up Week 8 Visit is 56 days +/- 2 days; however, in cases of a delayed visit due to restrictions resulting from the COVID-19 pandemic, + 14 days may be utilized instead of + 2 days in order to ensure this final visit is completed in person.
5. Concomitant medications, including acute standard of care migraine medications (both prescribed and OTC), taken during the Open-label Extension Phase and Follow-up Phase should be recorded in the subject's concomitant medication paper diary, reviewed by study personnel at each visit, and a copy made at each study visit to be maintained in source records. At end of study, the concomitant medication paper diary should be collected at the Follow-up Week 8 Visit.
6. Per Section 6.2.3, a full Physical Exam (PE) is required at screening ONLY and brief symptom-directed PEs are required at all other visits.
7. Height will be measured at the 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.
8. If possible, subjects should be fasting for a minimum of 8 hours before laboratory tests. However, if a subject is not fasting, the blood draw should still be performed, and the non-fasting status should be documented. HbA1c is only collected at Screening, Repeat or Unscheduled Visit.
9. SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs and Concomitant Procedures should be reported from signing of consent through the Follow-up Week 8 Visit. Non-serious AEs should be reported from signing of consent through the Follow-up Week 2 Visit.
10. 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. Site staff should mark each wallet with the scheduled date of each dose to be taken when dispensing the study drug.
11. Subjects must take study drug daily regardless of whether they have a migraine. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits. 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.

4.3.1 Observation *Phase*

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

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

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 Phase.

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

After completing the Observation Phase, subjects will return to the study site for the Baseline (Randomization) Visit, and both their eDiary and paper diary will be reviewed for completeness.

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 Phase.

Subjects will undergo all screening procedures as detailed in Table 1. After completion of all screening procedures, subjects will be provided an eDiary.

If the subject meets study entry criteria (i.e., inclusion/exclusion criteria), then the subject will return to the study site for the Pre-randomization Evaluation Visit.

If the subject does not meet study entry criteria, then the subject will be considered a screen failure and should be recorded as such in IWRS. The subject must return to the study site to return the eDiary.

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screening in select circumstances (e.g., previously pregnant, screening window too long). Subjects who were considered screen failures may also be considered for re-screening provided the ineligibility was due to 1 of the eligibility criteria that may have changed due to medical intervention or 1 of the eligibility criteria modified in a protocol amendment. Adequate documentation in source records must support the previously failed criteria. In all possible re-screening circumstances, the situation must be discussed with the Sponsor prior to re-screening, with approval in writing from the Sponsor prior to re-screening. If a subject is approved for re-screening, a new subject number must be obtained from the appropriate study-related system. Re-screening will only be permitted one time.

4.3.1.2 Pre-randomization Evaluation Visit

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

Safety labs, and an assessment of how the subject is feeling will be performed, a urinalysis will be completed, a serum pregnancy test, where applicable, will be obtained, an ECG will be performed, a brief physical exam (PE) will be performed unless a full PE is clinically warranted, vital signs and physical measurements will be performed according to Table 1, and compliance with the concomitant mediation paper diary and eDiary will be assessed.

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

If the laboratory results are not acceptable per protocol, then the subject is determined to be a screen failure and should be recorded as such in IWRS. The subject must return to the study site to return the eDiary.

4.3.2 Double-blind Treatment Phase

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 tablet of blinded study drug daily. If subjects have a migraine during the Double-blind Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.1) while continuing to take the study drug.

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 MSQ, SM, CGI-c, and C-SSRS will be completed, or administered by the investigator, on paper at specified study visits (Table 1).

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. Concomitant medication use will be reviewed and compared between the eDiary and concomitant medication paper diary entries, where applicable at each visit. 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 Extension Phase.

Certain provisions may be implemented, in order to minimize potential hazards to study subjectss due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in-home phlebotomy vendors, and shipping of study drug directly to study subjects if needed. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.

4.3.2.1 Baseline (Randomization) Visit

Once completing the Observation Phase, subjects will return to the study site for the Baseline (Randomization) Visit, which should be completed in person. Subjects who continue to meet all study entry criteria and have been compliant with the eDiary may enter the Double-blind Treatment Phase, pending review of additional laboratory test results; see Section 4.3.1.2. Subjects with fewer than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary. Because laboratory results from the Baseline 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.

At the Baseline Visit, subjects will be randomized 1:1:1 across 3 treatment groups: rimegepant 75 mg ODT dosed EOD alternating with matching placebo (n = 220); rimegepant 75 mg ODT dosed daily (n = 220); or placebo for matching rimegepant 75 mg ODT dosed daily (n = 220). Randomization will be stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no; see Section 7.2.1). In addition, randomization of prophylactic migraine treatment-naïve subjects ("no" category) will be capped at 30% in order to allow ≥ 70% of randomized subjects to be prophylactic migraine treatment-experienced ("yes" category).

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 the following day's assigned dose until the next calendar day at the specified time.

4.3.2.2 Week 12 or EOT Visit

Subjects will return to the study site at the Week 12 Visit (Day 86 +3 days), or at the EOT Visit for early discontinuation, 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 a (1) Week 12 or EOT Visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 pandemic and (2) 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 after the Week 12 or EOT Visit, -2 to +14 days), to complete all procedures that were not able to be completed remotely. Procedures completed at the Week 12 or EOT Visit occurring remotely do not need to be repeated.

4.3.3 *Open-label Extension Phase*

Up to 660 subjects (including up to 220 subjects in the daily dosing cohort) may be entered into the Open-label Extension Phase for an additional 12 weeks with daily dosing.

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 ODT) medication 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 tablet of rimegepant 75 mg ODT every day, regardless of whether they have a migraine on that day. If subjects have a migraine during the Open-label Extension Phase, then they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.1) while continuing to take the study drug.

Study visits will be approximately every 2 weeks during the first month and then every 4 weeks, until Week 24 (Table 2). Study drug compliance and concomitant medication use will be reviewed, and subjects will be dispensed additional study drug as needed. Additional safety (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

Certain provisions may be implemented in order to minimize potential hazards to study subjects due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in-home phlebotomy vendors, and shipping of study drug directly to study subjects if needed. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.

4.3.3.1 Week 24 or EOT Visit

Subjects will return to the study site at the Week 24 Visit (Day 168 +/- 3 days), or at the EOT Visit for early discontinuation, for 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 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 24 Visit.

In cases where a Week 24 or EOT Visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 pandemic, the subject should return to the site for the Follow-up Week 2 Visit (2 weeks after the Week 24 or EOT Visit, -2 to +14 days), to complete all procedures that were not able to be completed remotely. Procedures completed at the Week 24 or EOT Visit occurring remotely do not need to be repeated.

4.3.4 Follow-up Phase

The Follow-up Phase will have 2 scheduled visits, Follow-up Week 2 and Follow-up Week 8. These visits should occur approximately 2 weeks and 8 weeks, respectively, 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 24/EOT Visit if the subject entered the Open-label Extension Phase). All randomized subjects should complete both follow-up visits, 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 Phase 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, LFTs, assessment of AEs/SAEs, to have the C-SSRS performed, and to have a urine pregnancy test performed (WOCBP).

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

4.3.4.2 Follow-up Week 8 Visit

Subjects will return to the study site approximately 8 weeks (56 days +/- 2 days) after the last visit in the last treatment phase to collect vital signs, LFTs, assessment of SAEs, and to have a serum pregnancy test performed (WOCBP). Subjects will return the concomitant medication paper diary for documenting concomitant medications.

The visit window for the Follow-up Week 8 Visit is 56 days +/- 2 days; however, in cases of a delayed visit due to restrictions resulting from the COVID-19 pandemic, + 14 days may be utilized instead of + 2 days in order to ensure this final visit is completed in person.

4.4 Post Study Access to Therapy (if applicable)

At the conclusion of this study, subjects or investigators will not have access to the study drug. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

5 POPULATION

5.1 Number of Subjects

It is anticipated that up to approximately 2000 subjects may be screened in order to randomize up to approximately 660 subjects to study drug (rimegepant or placebo). Subjects will be randomized 1:1:1 across 3 treatment groups in the Double-blind Treatment Phase: rimegepant 75 mg ODT dosed EOD alternating with matching placebo (n = 220); rimegepant 75 mg ODT dosed daily (n = 220); or placebo for matching rimegepant 75 mg ODT dosed daily (n = 220). Randomization will be stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no; see Section 7.2.1). In addition, randomization of prophylactic migraine treatment-naïve subjects ("no" category) will be capped at 30% in order to allow ≥ 70% of randomized subjects to be prophylactic migraine treatment-experienced ("yes" category).

Up to 660 subjects (including up to 220 subjects in the daily dosing cohort) may be entered into the Open-label Extension Phase for an additional 12 weeks with daily dosing.

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 episodic migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition[4], including the following:

   a) Age of onset of migraines prior to 50 years of age.

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

   c) Per subject report, 4-14 migraine attacks 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 28 days in the Observation Phase.

   e) Not more than 14 ***headache days*** during 28 days in the Observation Phase.

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

g) 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. See Section 5.6 for the definition of WOCBP. 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.

4. 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 (not including exclusion criteria listed in Section 5.3).

5.3 Exclusion Criteria

1. Target Disease Exclusion

   a) Subject has a history of basilar migraine, hemiplegic migraine, retinal migraine or migraine accompanied by diplopia or decreased level of consciousness as defined by International Classification of Headache Disorders, 3rd Edition.[4]

   b) Subjects with headaches occurring 15 or more days per month (migraine or non-migraine) in any of the 3 months prior to the Screening Visit.

2. Medical History and Concurrent Diseases

   a) 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 the Screening Visit.

   b) Uncontrolled hypertension (high blood pressure) or uncontrolled diabetes. However, subjects can be included who have stable hypertension and/or diabetes for 3 months (12 weeks) prior to the Screening Visit. Blood pressure greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest is exclusionary. This may be repeated once at screening once during visit to confirm reproducibility.

   c) Subjects with major depressive (MDD) or any anxiety disorder (AD) which require more than 1 daily medication for each disorder or subjects with major depressive episode (MDE) within last 12 months. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months (12 weeks) prior to the Screening Visit.

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

   e) 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 of safety or efficacy.

   f) Diagnosis of active biliary disorder (eg., gallstones).

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

   h) Subject has a history or diagnosis of any active hepatic disorder.

i) 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 study.

j) 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[10] for any significant substance use disorder within the past 12 months (48 weeks) from the Screening Visit according to PI assessment.

k) History of use of narcotics, such as opioids (e.g., morphine, codeine, oxycodone, hydrocodone) or barbiturates (e.g., butalbital) for ≥ 4 days per month during the 3 months (12 weeks) prior to the Screening Visit.

l) 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 and phencyclidine (PCP) in the drug screen are **exclusionary**. Retesting is not allowed.

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

   iii. Detectable levels of marijuana in the drug screen are **not exclusionary**, if in the investigator's documented opinion the subject does not meet DSM-V criteria [10] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results. Subject must agree to refrain from marijuana use during the study.

m) Hematologic or solid malignancy diagnosis within 5 years prior to the Screening Visit. 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.

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

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

3. History of anaphylaxis to any substance or a clinically important reaction to any drug.

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 and for 60 days after the last dose of study drug.

   b) Women who are pregnant or breastfeeding.

   c) 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) according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 30 ml/min/1.73m^2.

   b) Abnormal ECG that in the investigator's opinion makes the subject unsuitable for a clinical trial (e.g. Corrected QT interval > 470 msec, Left Bundle Branch block)

   c) Total serum bilirubin > 1.5 x ULN.

   d) AST or ALT > 1.5 x ULN.

   e) Serum albumin < 2.8 g/dL.

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

   g) HbA1c > 7.5%

6. Prohibited Medications

   a) Medication for migraine prophylaxis generally considered to have efficacy, regardless of indication, taken within 30 days prior the Screening Visit (see Section 16.5 Appendix 5).

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

   c) Medication accepted for treatment of acute migraine (Section 5.5.1) for a non-migraine indication taken ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit.

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

d) Biologic migraine medication (such as CGRP monoclonal antibodies listed in Section 16.5 Appendix 5) taken during the 6 months (24 weeks) prior to the Screening Visit.

e) Prohibited medication or device used during the Observation Phase (see Section 5.4).

7. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

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

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

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

f) Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to 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).

g) Previous enrollment in any multiple dose BHV3000 (rimegepant) study, such as BHV3000-201, BHV3000-305, BHV3000-405, BHV3000-406, or BHV3000-407, regardless of the number of doses taken. Subjects may be considered for BHV3000-404 if the subject participated in any of the following single dose studies: BHV3000-301, BHV3000-302, BHV3000-303, but did not participate in any multiple dose rimegepant study. Note that subjects who were considered screen failures in a past BHV3000 study may be considered after discussion with the Sponsor and written approval is received.

h) Subjects are excluded if they have had no therapeutic response with > 2 of the 8 medication **categories** for prophylactic treatment of migraine listed in Appendix 4 after an adequate therapeutic trial. Additional details can be found in Section 16.4 Appendix 4.

i) Participation in any other investigational clinical study while participating in this clinical study. Participation in a COVID-19 mRNA vaccine study (vaccine must be authorized

under FDA emergency use authorization or approval) ***who are at least 30 days post last dose*** of the vaccine are permitted to be screened for this study.

j) Past participation in a clinical study within 30 days prior to the Screening Visit. Note: Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screening in select circumstances (e.g., previously pregnant, screening window too long, ineligibility was due to 1 of the eligibility criteria that may have changed due to medical intervention or 1 of the eligibility criteria modified in a protocol amendment). In all possible re-screening circumstances, the situation must be discussed with the Sponsor prior to re-screening, with approval in writing from the Sponsor prior to re-screening.

k) The subject is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason (including any known, suspected, or confirmed infections in the subject that may put the subject or study staff at risk).

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

5.4 Prohibited and Restricted Concomitant Medications and Devices

All medications taken by subjects at the Screening Visit until the last study day will be documented as concomitant medications including vaccinations.

The medications and devices listed below are prohibited or restricted **during the entire study**, i.e., starting at the Screening Visit and through the Follow-up Week 8 Visit, unless otherwise specified.

1. Medication for migraine prophylaxis generally considered to have efficacy, regardless of indication (see Section 16.5 Appendix 5). Note these are also prohibited 30 days prior to the Screening Visit (see Section 5.3), with exceptions noted for CGRP monoclonal antibodies in item 2 below and botulinum toxin injections in item 3 below.

2. CGRP antagonists (monoclonal antibodies [e.g., Aimovig® or Ajovy®] or small molecule [e.g., Nurtec® ODT or Ubrelvy™]) other than rimegepant provided for this clinical study. Note that CGRP monoclonal antibodies listed in Section 16.5 Appendix 5 are also prohibited within 6 months (24 weeks) prior to the Screening Visit (see Section 5.3).

3. Botulinum toxin injections (eg, Botox®) used for the prevention of migraine, listed in Section 16.5 Appendix 5. Note that this is also prohibited within 3 months (12 weeks) prior to the Screening Visit.

4. St. John's Wort

5. Ergotamine. Note the following:
   a. Reporting of ergotamine use is required for the purpose of defining migraine days.
   b. Use of ergotamine on ≥ 10 days per month on a regular basis for ≥ 3 months (≥ 12 weeks) in the year prior to the Screening Visit is also prohibited.

6. Narcotics, such as opioids (e.g., morphine, codeine, oxycodone, hydrocodone) or barbiturates (e.g., butalbital). Note that use of narcotics for ≥ 4 days per month during the 3 months (12 weeks) prior to the Screening Visit is also prohibited.

7. Acetaminophen or acetaminophen-containing products for non-headache indications. Note that acetaminophen as acute migraine medication as described in Section 5.5.1 is allowed during the study.

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

9. Moderate to strong CYP3A4 inhibitors. If use of a moderate or strong CYP3A4 inhibitor is required, then dosing with study drug should be stopped and should not start again until 14 days after the last dose of the moderate or strong CYP3A4 inhibitor. Please see Section 16.2 Appendix 2.

10. Moderate to strong CYP3A4 inducers. If use of a moderate or strong CYP3A4 inducer is required, then dosing with study drug should be stopped and should not start again until 14 days after the last dose of the moderate or strong CYP3A4 inducer. Please see Section 16.2 Appendix 2.

11. Strong inhibitors of the P-gp transporter. If use of a strong inhibitor of the P-gp transporter is required, then dosing with study drug should be stopped and should not start again until 14 days after the last dose of the strong inhibitor of the P-gp transporter. Please see Section 16.2 Appendix 2.

12. Atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate).

13. LAMICTAL (lamotrigine)

14. Analgesics other than acetaminophen for non-headache use (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs]) on ≥ 15 days per month. Acetaminophen and acetaminophen containing products for non-headache indications are prohibited (see item 7 above). Low dose aspirin (up to 00 mg daily) for documented cardiovascular prophylaxis is allowed.

15. Cefaly™ or any other device for migraine prevention or treatment. Note that these devices are also prohibited within 12 weeks prior to the Screening Visit.

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

5.5 Standard of Care Migraine Medications

Use of acute standard of care migraine medication during the Observation Phase through the Follow-up Week 8 Visit will be recorded by the subject in the concomitant medication paper diary and reported to the site. Migraine medications include both prescribed and OTC, acute migraine medications.

5.5.1 Acute Migraine Medications

Subjects may use their permitted standard of care medication if needed for acute treatment of a migraine throughout the study. **Acute migraine medications that are permitted during the study include the following:**

- triptans,
- aspirin,
- ibuprofen,
- baclofen,
- acetaminophen up to 1000 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 (NSAID)),
- antiemetics (e.g. metoclopramide or promethazine),
- muscle relaxants

The above listed medications are the only acute migraine medications allowed

If a subject takes a tablet of study drug and experiences a migraine later that day, after dosing with study drug for the day, the subject may take their ***permitted acute migraine medication*** as described in this section of the protocol. ***During the study, subjects are not allowed to take more than 1 tablet of study drug per day***.

5.6 Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Tubal ligation is considered

one form of contraception; therefore, one additional form of contraception must be used to fulfill contraception requirements for the study. Essure, tubal occlusion and endometrial ablation are not acceptable methods of contraception. Menopause is defined as:

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

  OR

- Woman on hormone replacement therapy (HRT) who no longer menstruate.

Women of childbearing potential (WOCBP) and all men must understand the following requirements and use an acceptable method of contraception to avoid pregnancy throughout the study and for up to 60 days (for WOCBP) and 90 days (for men) after the last dose of investigational product in such a manner that risk of pregnancy is minimized.

It is required that all WOCBP use 2 methods of contraception to prevent pregnancy, for the duration of the study (i.e., this study begins with signed consent form through 60 days (for WOCBP) and 90 days (for men) after dosing with study drug). The 2 methods should include 1 barrier method (e.g., Condom with spermicidal gel, non-hormonal intrauterine devices, cervical cap etc.) and 1 other method. The other method could include another barrier method or 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.

WOCBP and all male subjects must be counseled on the requirements to avoid pregnancy throughout the study and for 60 days (for WOCBP) and 90 days (for men) after the last dose of study drug, as well as acceptable methods of contraception to use during the study. Subjects who report abstinence, or who report exclusively being in same-sex relationships are still required to understand the contraception requirements in this study to prevent pregnancy. If subjects who report abstinence, or who report exclusively being in a same-sex relationship engage in heterosexual activity, then the contraception requirements must be followed.

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

All WOCBP must complete the pregnancy test schedule in Table 1 and Table 2.

5.7 Other Restrictions and Precautions (if applicable)

Not Applicable

5.8 Deviation from Inclusion/Exclusion Criteria and Study Procedures

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 study. Deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant medication paper diary (take home for subject)
- Investigator Brochure
- Interactive Web-based Response System (IWRS)
- Electronic Case Report Form (eCRF) instructions
    - Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields
    - All sites will use an Electronic Data Capture (EDC) tool to submit study data to the CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including queries) will be submitted to the CRO using eCRFs.
- Electronic Diary (eDiary): hand-held electronic device (1 will be given to each subject)
    - Instructions for the eDiary device and access to the portal

- During the Double-blind Treatment Phase, the eDiary will be used daily to record migraine occurrence, migraine pain features and associated symptoms and use of acute migraine medication (i.e., triptans, ergotamine, or other). Use of ergotamine medication is prohibited throughout the entire duration of the study, however reporting of any use of ergotamine medication is required for the purpose of defining migraine days.

- Laboratory Kits and Laboratory Manual
  - Safety laboratory, plasma, and serum instructions for all specimens collected will be provided by a designated central laboratory.
- ECG Machine and Instructions
  - ECG equipment, supplies, instructions and training materials will be supplied by a centralized ECG vendor.
- Back-up forms for CT SAE report, Exposure During Pregnancy and Pregnant Partner Release of Information
- Columbia-Suicide Severity Rating Scale (C-SSRS) forms
- Satisfaction with Medication (SM) forms
- MSQ v 2.1 forms
- CGI-c forms
- Study system access:
  - Electronic Data Capture (EDC) tool to submit study data to Sponsor / CRO
  - IWRS
  - Central Laboratory vendor portal
  - Central ECG vendor portal
  - eDiary vendor portal

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

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

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at all scheduled visits as outlined in Table 1 and Table 2. A central ECG service will be utilized for reading all ECGs. The over read from the central ECG vendor should be used to determine eligibility for the study. The investigator will determine if any ECG abnormalities are clinically significant or not (see Section 16.6 Appendix 6)

6.2.3 Physical Exam

Subjects will undergo a routine physical examination during the Screening Phase and brief and symptom-directed physical exam at all scheduled visits as outlined in Table 1 and Table 2. Physical examinations to include at minimum examination of heart, abdomen and lungs, and neurologic system with review of any other system to be guided by symptoms.

6.2.4 Laboratory Assessments

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

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.

17. Clinical safety labs:

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

    Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c (only collected at Screening, Repeat or Unscheduled Visit), BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin, CK

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

18. **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

19. **Lipid Panel:** Cholesterol, LDL, HDL, triglycerides

20. **Urinalysis:** pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and blood. If blood, protein or leukocytes are positive, reflex to microscopic examination.

21. **Urine Drug Screen:** For drugs of abuse

22. **FSH:** At screening in female subjects to confirm postmenopausal status, if applicable

23. **Reflex/add-on tests:**

    If ALT or AST $\geq$ 3 x ULN *OR* total bilirubin $\geq$ 2 x ULN at any visit after the Baseline Visit, additional reflex or add-on tests may be performed that may include: CK, GGT, and anti-viral serologies. Subjects may have to return to the study site to provide additional blood samples for these laboratory tests. See section on potential Drug Induced Liver Injury (Section 8.4).

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

6.2.4.2 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.[11] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[12] will be used at subsequent visits in this study.

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

At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit (reference Table 1 and Table 2).

Any "Yes" responses must be immediately evaluated by the investigator. If the Investigator determines that a subject is at risk of suicide, self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. In such circumstances, the subject must immediately be discontinued from the study. The event 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 medication dosing occurrences (i.e., with triptans, ergotamine, or other), and migraine pain features and associated symptoms during the Observation Phase and the Double-blind Treatment Phase.

Efficacy assessments will be derived from eDiary data and will include the number of migraine days per month by pain intensity (total; moderate or severe), and number of acute migraine-specific medication days per month, in each month by study period. Please refer to Table 1.

6.4 Other Assessments

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

Impact of treatment on subject-reported quality of life will be assessed using the Migraine-Specific Qualify-of-Life Questionnaire version 2.1 (MSQ v 2.1). The MSQ v 2.1 is a 14-item instrument that has been validated in 3 domains: role function - restrictive, role function - preventive, and emotional function.[13] The MSQ will be completed on a paper form at the site.

6.4.2 Clinical Global Impression – Change (CGI-c) Scale

The Clinical Global Impression-change (CGI-c) scale is an observer-rated, 7-point scale that measures subject total improvement relative to the investigator's past experience with other subjects with the same diagnosis, with or without collateral information.[14] The CGI-c will be administered by the investigator or designee and will be completed on a paper form at the site.

6.4.3 Satisfaction with Medication (SM) Scale

The Satisfaction with Medication (SM) scale is a subject-rated, 7-point scale that measures satisfaction with the study medication to treat migraine headaches. The SM will be completed on a paper form at the site.

6.5 Early Discontinuation from the Study

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

- Subjects who discontinue early from the Double-blind Treatment Phase are not eligible to enter the Open-label Extension Phase.
- Withdrawal of informed consent (subject's decision to withdraw for any reason)

- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- 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 evening reports in eDiary.
    i. Subjects with less than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary.
    ii. 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.
- Please see Section 6.2.5 for guidance on study discontinuation based on results from the C-SSRS.
- All subjects who discontinue should comply with protocol-specified Week 12/EOT or Week 24/EOT Visit procedures as outlined in Table 1 or 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.

6.6 Clinical Trial Subject Database (CTSdatabase)

CTSdatabase is a clinical trial subject registry that maintains the privacy and security of research subjects while providing sponsors and investigators with crucial information about subjects' current and/or previous study participation.

CTSdatabase has been shown to reduce the number of duplicate and professional subjects entering clinical trials.

The use of this database must be presented to all subjects participating in this protocol, where approved locally. If subjects refuse to provide authorization, the study team should be notified. At the time of providing the Informed Consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

During screening, site staff that have received training and login information should access www.ctsdatabase.com and enter the last 7 digits of the subject study ID and authorized subject identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days or (3) the subject matches with a subject who has *pre*-screened at another site.

At the last subject contact, CTSdatabase staff will automatically close out subjects (SF, ET, or Completer) based on IWRS information.

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

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

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

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

- During the Double-blind Treatment Phase, investigational product (study drug) is rimegepant (BHV-3000) (PF-07899801) 75 mg ODT dosed EOD alternating with matching placebo, 75 mg ODT dosed daily, or matching placebo dosed daily.

- During the Open-label Extension Phase, investigational product (study drug) is open-label rimegepant (BHV-3000) (PF-07899801) 75 mg ODT dosed daily.

- All subjects, regardless of the treatment phase, will take study drug every day.

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 the following day's assigned dose until the next calendar day at the specified time. 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.

7.1.2 Concomitant Therapy

Other medications used as support or rescue medication for diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as concomitant therapy.

In this protocol, concomitant therapy(ies) is/are standard of care for acute treatment and rescue medication for migraine treatment.

7.1.3 Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. Please see the Pharmacy Manual 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/RTSM system will be utilized for obtaining subject identification and as the electronic data capture (EDC) system. Each subject will be assigned a unique 8-digit subject number through the appropriate study-related system. The subject number will consist of the 3-digit site number, a hyphen, and a unique 4-digit subject number. This subject number must not be reused for any other subject in the study. Subjects will maintain their subject number assigned at screening throughout the study 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 1:1:1 ratio to rimegepant 75 mg ODT dosed EOD alternating with matching placebo, rimegepant 75 mg ODT dosed daily, or placebo for matching rimegepant 75 mg ODT dosed daily.

Randomization will be stratified by use of prior prophylactic migraine medication generally considered to have efficacy (yes or no). In addition, randomization of prophylactic migraine treatment-naïve subjects ("no" category) will be capped at approximately 30% in order to allow approximately 70% of randomized subjects to be prophylactic migraine treatment-experienced ("yes" category"). Subjects should be categorized as "yes" if they have ever taken any specified prophylactic migraine medication generally considered to have efficacy prior to informed consent, i.e., the medication start date is before the informed consent date. Otherwise, subjects should be categorized as "no". See Section 16.5 Appendix 5 for a list of prophylactic migraine medications generally considered to have efficacy.

After confirming subject eligibility, registering a subject for Baseline (Randomization) will trigger a container number for the study drug. Study drug will be dispensed at the Baseline Visit 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 appropriate study-related system. There are no dose adjustments in this study and subjects will receive 8 tablets of study drug in a blister card heat-sealed into a wallet; subjects will be assigned appropriate supply

between visits. Subjects will be dispensed study drug at the Baseline Visit, and the subjects will be instructed that they must take ***1 tablet daily regardless of whether they have a migraine on that day.*** This is the scheduled dosing regimen for the Double-blind Treatment Phase and the Open-label Extension Phase. Site staff should mark each wallet with the scheduled date of each dose to be taken when dispensing the study drug.

Dosing should occur around the same time for each scheduled dose. It is preferred that subjects dose in the morning; however, it is more important that the subject consistently dose at approximately the same time for each scheduled dose. The time of dosing should be consistent throughout the study. If the subject has a migraine on a day when they ***already took study drug***, then the subject can take permitted acute migraine medication as needed (see Section 5.5.1). Subjects **must** be instructed that they CANNOT take more than 1 tablet of study drug daily during the study.

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 the following day's assigned dose until the next calendar day at the specified time.

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.

7.2.3 Dose Modification

There will be no dose adjustments in this study.

7.2.4 Dose Interruptions

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

7.3 Blinding and Unblinding

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

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, (i.e., that it will alter the subject's immediate management). In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt to preserve the blind is made.

7.4 Treatment Compliance

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

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

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

Cases of 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 tablets 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), subjects who are <80% compliant must be re-educated on the importance of daily selfadministration 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. Destruction at a study site may only occur 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 investigational product, whether or not considered related to the investigational product.

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

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 AEs (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).

8.1 SERIOUS ADVERSE EVENT

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 study drug
        - Potential study drug abuse (including cases of excessive non-compliance with study drug dosing instructions or subjects who discontinue study drug 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):

1. 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).

2. Elective surgery planned prior to signing consent;

3. Admissions as per protocol for a planned medical/surgical procedure;

4. Routine health assessment requiring admission (i.e., routine colonoscopy);

5. 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 through the Follow-up Week 8 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 **Error! Reference source not found.**) must be reported within 24 hours of the Investigator becoming aware of the event. For this study we will be capturing SAEs 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) 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 intensity).

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 using the Pfizer CT SAE report, that must be sent by facsimile (fax or eFax), to your country's Pfizer DSU. 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

All non-serious AEs must be collected that occur from signing the ICF through the Follow-up Week 8 Visit. Non-serious AEs should be followed until conclusion or stabilization or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug or those that are present at the end of study treatment.

8.2.2 Laboratory Test Abnormalities

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

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

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

8.3 Overdose

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

All occurrences of overdose (suspected or confirmed) must be communicated to Pfizer or a specified designee within 24 hours and be fully documented as 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 2 tablets in one calendar day) should be reported as deviations.

8.4 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 8.1.2.

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3 times the upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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:

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).

If any potential DILI is identified and meets the criteria above, the Pfizer Medical Monitor (or designee) should immediately be contacted for further instruction and whether the subject must discontinue from the study and appropriate follow up requirements. As with any adverse event, as stated per Section 6.5, the Principal Investigator has the ability and the responsibility to determine whether a subject can safely continue in the study.

Process for abnormal liver function tests: If at any visit after initiation of study drug the AST or ALT is > 3x ULN, the following steps should be taken as soon as the investigator is aware: 1. The subject must be informed of the results and instructed to stop study drug, 2. The subject must be instructed to return to the clinic within 3-5 days for Unscheduled visit for repeat LFT panel and further clinical evaluation and testing as appropriate (with consultation with the Medical Monitor), and 3. The Pfizer Medical Monitor should immediately be contacted. Guidance will be provided to augment management as appropriate.

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

Environmental exposure occurs when a person not enrolled in the study as a subject receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.
Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.5.1 Exposure During Pregnancy

If, following the Baseline Visit it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational produce exposure, including during at least 6 half-lives after the product administration, the investigational product will be permanently discontinued in an appropriate manner (ie, dose tapering if necessary for subject safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the subject unless contraindicated by the pregnancy (ie, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. 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 or 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 nonsubject is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion or skin contact.
- A male family member or healthcare provider who has been exposed to the study intervention by ingestion or skin contact then inseminates his female partner prior to or around the time of conception.

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

If EDP occurs in a subject/subject's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form or via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 66 hours after the last dose.
If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form or via PSSA. Since the exposure information does not pertain to the subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.
Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate

can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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

8.5.2 Exposure During Breastfeeding

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

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

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

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

8.5.3 Occupational Exposure

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

8.6 Lack of Efficacy

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

8.7 Medication Errors

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

Medication errors are recorded and reported as follows:

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

8.8 Adverse Events of Special Interest

Not applicable for this study.

9 STATISTICS

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

9.1 Sample Size

The study will randomize approximately 220 subjects with confirmed episodic migraine per treatment group. Based on data from study BHV3000-305, we estimate that this will result in roughly 200 subjects per treatment group in the migraine analysis set. Assuming rimegepant provides roughly a 1.1 day advantage over placebo on the primary endpoint, and assuming a common standard deviation of 3.5 days, then the study will have roughly 80% power on the primary endpoint at a 2-sided alpha level of 0.025.

In study BHV3000-305, rimegepant provided a 0.8 day advantage over placebo. With daily dosing, we expect the treatment effect to increase. Using the data from study BHV3000-305, the standard deviation of the primary endpoint was estimated to be roughly 3.5 days.

9.2 Analysis Sets

The following analysis sets will be used in this study:

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

9.3 Statistical Methods

Results will be summarized by treatment group.

9.3.1 Efficacy Analyses

9.3.1.1 Primary Efficacy Endpoint

The primary endpoint will be assessed for the migraine analysis set using a linear mixed effects model with repeated measures that will include the following variables: change from the Observation Phase in the number of migraine days per month as the dependent variable; number of migraine days per month in the Observation Phase as a covariate; and fixed effects for treatment group, randomization stratum (i.e., use of prior prophylactic migraine medication generally considered to have efficacy), 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 account for days with missing migraine data. The difference estimate (rimegepant – placebo), standard error (SE), p-value and 97.5% confidence interval (CI) will be reported for the entire Double-blind Treatment Phase (Weeks 1 to 12) for each rimegepant treatment group versus placebo.

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

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

9.3.1.2 Secondary Efficacy Endpoints

The proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate or severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be analyzed using Mantel-Haenszel risk estimation with stratification by randomization stratum for the migraine analysis set. Missing data are imputed as non-response (i.e., failure). The difference estimate (rimegepant – placebo), SE, p-value and 97.5% CI will be reported for each rimegepant treatment group versus placebo.

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

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

The mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed for the migraine analysis set using a model that is similar in structure to that used for the primary efficacy 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 change from baseline in the MSQ restrictive role function domain score at Week 12 will be analyzed for the double-blind treatment efficacy analysis set using a linear model 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, p-value and 97.5% CI will be reported for each rimegepant treatment group versus placebo.

9.3.1.3 Multiplicity Correction

Type 1 error is controlled by splitting the alpha level between the 2 rimegepant treatment groups and the use of hierarchical testing. The significance of the primary endpoint for each treatment group is evaluated at a 2-sided alpha level of 0.025. If the primary endpoint is significant for a treatment group, then the secondary efficacy and outcomes research endpoints for that treatment group will be tested hierarchically, each at a 2-sided alpha level of 0.025, in the following order:

- Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).
- Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.
- Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the Double-blind Treatment Phase.
- Mean number of acute migraine-specific medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12). Acute migraine-specific medications are triptans and ergotamine.
- Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the Double-blind Treatment Phase.

9.3.2 Safety Analyses

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

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

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

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

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

9.4 Schedule of Analyses

There is 1 planned database lock at the end of the study. The final clinical study report will be produced to support regulatory requirements after the database lock at the end of the study. No interim analysis is planned.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

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

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

All serious breaches must be reported to Pfizer (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

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

10.2 Data and Safety Monitoring Committee

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

10.3 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, if the subject has not opted out of the CTSdatabase portion of the study, they must read, sign and date an IRB/IEC approved written informed consent form for study participation and CTSdatabase participation. 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.

10.4 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 collections fields when electronic data capture (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.

10.5 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.

10.5.1 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.

10.6 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 AND RETENTION

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

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

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

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

It is the responsibility of the Investigator to ensure that the current disposition record of investigational product (those 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:

1. amount of study drug received and placed in storage area
2. label ID number or batch number or Kit number as specified for the protocol
3. amount dispensed to and returned from each subject
4. amount transferred to another area or site for dispensing or storage if applicable
5. amount of drug lost or wasted
6. amount destroyed at the site, if applicable
7. amount returned to sponsor, if applicable
8. retain sampled for bioavailability/bioequivalence, if applicable
9. record of dates and initials of personnel responsible for IM dispensing and accountability

11.1 Source Documentation

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

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

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

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

11.2 Study Files and Record Retention

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

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

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Pfizer. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately. Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. Pfizer will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the investigator, and/or Pfizer, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study subject, the currently approved written 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 if needed 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 – Country Specific Requirements

16.1.1 Italy

Contraceptive Use

The primary method should be a birth control method which may be considered highly effective.

This includes:

- Combined hormonal contraception associated with inhibition of ovulation (containing estrogen and progesterone), types: oral, intravaginal, and transdermal.
- Hormonal contraception (progesterone-only) associated with inhibition of ovulation, types: oral, injectable, and implantable (progesterone-only-containing drugs that do not inhibit ovulation and pregnancy are not permitted)
- Other types: intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, and vasectomized partner (must be sole sexual partner and have surgical proof of vasectomy's success)

The secondary method should include a barrier method (eg. Condom with or without spermicidal gel, cervical cap, diaphragm, or sponge with spermicide)

16.2 Appendix 2 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)

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

Strong CYP3A4 inhibitors
Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir, mifepristone, mibefradil.

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

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

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

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

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

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

Resources:

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

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

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

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

16.3 Appendix 3 – 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 either Criteria A or B below:

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., triptan) during aura or to treat headache, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms. Use of ergotamine medication is prohibited throughout the entire duration of the study. However, use of this medication, if taken for migraine treatment, must be documented for the purposes of assessing migraine days and must be captured as a protocol deviation.

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 Day: Any calendar day during which the subject took a migraine-specific medication (i.e., triptan or ergotamine). Use of ergotamine medication is prohibited throughout the entire duration of the study, however reporting of any use of ergotamine medication is required for the purpose of defining migraine days.

Monthly eDiary Data: Data collected by the eDiary based on the subject's monthly investigational product 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., $\leq$ 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., $\leq$ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

16.4 Appendix 4 – Categories of Migraine Prevention Medications (Reference for Exclusion Criteria 7h)

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**: Antiepileptics (for example: divalproex sodium, sodium valproate)
- **Category 2**: Antiepileptics (for example: 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**: Calcium channel blockers (for example: flunarizine, 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 intensity 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

16.5 Appendix 5 – Medications for Migraine Prevention Generally Considered to Have Efficacy

- **Antihypertensives**
  - *Beta blockers*
    - *Propranolol*
    - *Metoprolol*
    - *Nadolol*
    - *Atenolol*
    - *Timolol*
    - *Bisoprolol*
  - *Calcium channel blockers*
    - *Verapamil*
    - *Flunarizine*
    - *Nifedipine*
    - *Nimodipine*
  - *ACE inhibitors/ARBs*
    - *Lisinopril*
    - *Candesartan*

- **Antidepressants**
  - *Tricyclic antidepressant*
    - Amitriptyline
    - *Nortriptyline*
  - *Serotonin-norepinephrine reuptake inhibitor*
    - *Venlafaxine*
    - *Desvenlafaxine*

- **Anti-epileptics**
  - *Divalproex sodium, sodium valproate*
  - *Topiramate*
  - *Gabapentin*

- **CGRP antagonists**
  - *Erenumab (Aimovig®)*
  - *Fremanezumab (Ajovy®)*
  - *Galcanezumab (Emgality®)*
  - *Eptinezumab (Vyepti®)*
  - *Rimegepant (Nurtec®)*
  - *Atogepant (Qulipta™)*

- **OnabotulinumtoxinA** (*Botox®*)
- Butterbur root or extracts
- Feverfew
- Pizotifen
- Oxetrone

16.6 Appendix 6 - ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as SAEs
• QTcF prolongation >500 ms. • Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms. • New ST-T changes suggestive of myocardial ischemia. • New-onset LBBB (QRS complex >120 ms). • New-onset right bundle branch block (QRS complex >120 ms). • Symptomatic bradycardia. • Asystole • In awake, symptom-free subjects in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node; • In awake, symptom-free subjects with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer. • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm. • Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute). • Ventricular rhythms >30 second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]). • Type II second-degree (Mobitz II) AV block. • Complete (third-degree) heart block.
ECG Findings That Qualify as SAEs
• Change in pattern suggestive of new myocardial infarction. • Sustained ventricular tachyarrhythmias (>30-second duration).

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

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

16.7 Appendix 7 – Protocol Amendment History

Version Number	Brief Description of Change	Date
Version 1.0 - Original	Not Applicable	22 November 2021
Version 2.0	Updated format of "Summary of Changes" page. Updated Section 4.3, the Schedule of Assessments / Table 1 to remove the reference to "(vital signs only)" from the Vital Signs/Physical Measurements procedure at: Baseline (Randomization) Visit, Week 2 Visit, and Follow-up Week 2 and Follow-up Week 8 Visits. Updated Section 4.3, the Schedule of Assessments / Table 2 to remove the reference to "(vital signs only)" from the Vital Signs/Physical Measures procedure at Week 14 Visit, and Follow-up Week 2 and Follow-up Week 8 Visits. Updated Section 5.2, inclusion criteria #3 and removed reference to understanding English and Spanish. Updated Section 5.3, exclusion criteria #7, separating exclusion criteria #7i and #7j. Corrected inconsistencies and typographical errors throughout the protocol.	04 January 2022
Version 3.0	Updated Section 4.3, the Schedule of Assessments / Table 1 and Table 2 to clarify physical exam procedure and HbA1c collection. Updated Section 5.3, exclusion criteria 5b and removed reference to "at screening".	17 March 2022

Version Number	Brief Description of Change	Date
	Updated Section 5.3, exclusion criterion; 2l, 6a -6e, and 7e to clarify restrictions around prohibited medication use. Updated Section 5.3 and removed exclusion criteria 7k. Updated Section 5.4 to clarify restrictions around prohibited medication use. Updated Section 6.2.4.1 to clarify HbA1c collection. Updated Section 9.2 to clarify one of the Analysis Sets. Corrected inconsistencies and typographical errors throughout the protocol.	
Version 4.0	Updated Section 5.3, exclusion criterion 6c to clarify low dose aspirin use for cardiovascular prophylaxis. Updated Section 5.3, exclusion criterion 7g to include additional studies; BHV3000-406 and BHV3000-407. Updated Section 5.3, added exclusion criterion 7k. Updated Section 5.4, #14 to clarify low dose aspirin use for cardiovascular prophylaxis.	01 July 2022

Version Number	Brief Description of Change	Date
	Updated Section 6.6, CTS database to clarify that this applies only "where approved locally". Updated section 8.2.1 to correct typographical error and align the collection of Non-serious Adverse Events through the Follow-up Week 2 Visit as noted in Table 1 and Table 2 footnotes. Updated section 9.2 to clarify the definition of the "Migraine" Analysis Set.	

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Document Approval Record

Document Name:	PF-07899801_Protocol Amendment 5_C4951010_FINAL CLEAN_23Jun2023
Document Title:	PF-07899801_Protocol Amendment 5_C4951010_FINAL CLEAN_23Jun2023

Signed By:	Date(GMT)	Signing Capacity
PPD	26-Jun-2023 17:33:14	Final Approval
PPD	27-Jun-2023 12:13:12	Final Approval