DRUG:	BHV-3000 (PF-07899801) (rimegepant)
STUDY NUMBER(S):	BHV3000-405 (C4951011)
PROTOCOL(S) TITLE:	A Phase 4, Open-label Study to Evaluate the Safety and Tolerability of Daily Dosing of Rimegepant in Episodic Migraine Prevention
IND NUMBER:	109886
SPONSOR:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001
ORIGINAL PROTOCOL DATE:	22 November 2021
VERSION NUMBER:	6.0
VERSION DATE:	07 August 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.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 5 (Protocol Version 6.0)

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 BHV3000-405 to C4951011 and compound name BHV-3000 to PF-07899801 to reflect identification changes by sponsor.	Reflects change in sponsorship protocol and compound identification numbers	Throughout Document Headers Title page
Updated the planned number of subjects from 230 to 285.	Increased sample size needs in order to account for up to 40% drop out rate through 24 weeks	Study Summary (Synopsis) Section 1.5 Study Rationale Section 5.1 Number of Subjects Section 9.1 Sample Size
Clarified the procedure for unused, non-expired, and partial wallets during Open-label Treatment Phase.	Added clarity on study procedures	Section 4.3.2 Open-label Treatment Phase
Removed criteria pertaining to “Signed Written Informed Consent”.	Allowed for subjects that were unable to read and/or understand English or Spanish to be included. Removed need to provide all demographic information and aligned with Pfizer’s standards and processes	Section 5.2 Inclusion Criteria
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	Section 5.3 Exclusion Criteria #2
Clarified that blood pressure must be less than 150/100 mg Hg at the screening and baseline visit.	Clarified that BP must be within range prior to dosing of IP	Section 5.3 Exclusion Criteria #2b
Removed the exclusion criterion for patients with gallstones and cholecystectomy.	Aligned with rimegepant prescribing information where there is no exclusion for use in subjects with biliary disorder	Section 5.3 Exclusion Criteria #2
Removed Gilbert's Syndrome from the exclusionary criteria.	Aligned with rimegepant prescribing information where there is no exclusion for use in Gilbert’s Syndrome	Section 5.3 Exclusion Criteria #2
Clarified the exclusion criterion of narcotics.	Updated for clarity.	Section 5.3 Exclusion Criteria #2j

Amended the exclusion criterion for body mass index to >35.0 kg/m^2 from >33.0 kg/m^2.	Aligned definition to be inclusive of all Class 1 Obesity subjects	Section 5.3 Exclusion Criteria #2n
Updated requirement for duration of contraception use after last dose of study drug.	Aligned with Pfizer standard and processes	Section 5.3 Exclusion Criteria #4a
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	Section 5.3 Exclusion Criteria #5g
Amended the hepatic exclusion criteria to allow subjects with 1.5xULN of ALT, AST and 1.5xULN of 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	Section 4.3.1 Screening Phase Section 5.3 Exclusion Criteria #5c and #5d
Removed specific exclusionary ECG criteria.	Allowed for investigator opinion on exclusionary ECG findings	Section 5.3 Exclusion Criteria #5b
Changed eGFR 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.	Section 5.3 Exclusion Criteria #5a
Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members.	Aligned with Pfizer protocol template	Section 5.3 Exclusion Criteria #7k
Allowed for re-screening of subjects due to prior failed eligibility criteria.	Allowed for re-screening of subjects who previously were screen failed for an amended exclusionary criterion	Section 4.3.1 Screening visit Section 5.3 Exclusion Criteria #7i
Removed “but did not participate in any multiple dose rimegepant study” from exclusion criteria.	Editorial, redundant sentence	Section 5.3 Exclusion Criteria #7f
Removed “any reason which, in opinion of the Investigator, would prevent the subject from participating in the study” from exclusion criteria.	Removed redundant exclusion criteria	Section 5.3 Exclusion Criteria #8
Removed tacrolimus from the strong CYP3A4 inhibitors list. Added telithromycin and troleandomycin to the list of strong CYP3A4 inhibitors, and avasimibe to the list of strong CYP3A4 inducers.	Aligned with nonclinical and clinical DDI information available on rimegepant	Section 16.2 Appendix 2 Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)

Changed term “non-migraine” to “non-headache”, and term “acute migraine” to “acute headache”.	Clarified to include broader definition of headache which includes non-migraine and migraine headache	Section 5.4 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.	Updated definition to align with revised LFT exclusion criteria	Section 8.4 Potential Drug Induced Liver Injury (DILI)
Added Appendix for ECG findings of Potential Clinical Concern.	Aligned with Pfizer protocol template	Section 16.4 Appendix 4 ECG Findings of Potential Clinical Concern
Added the definition of Sponsor's Medically Qualified Individual.	Aligned with Pfizer protocol template	Section 10.7 Sponsor’s Medically Qualified Individual
Updated benefit risk background information, regulatory status, and clinical development status. Added benefit risk assessment.	Updated benefit risk information to include up to date data	Study Summary (Synopsis) Section 1.3 Product Development Background Section 1.4 Benefit Risk Assessment
Updated contraception requirement for WOCBP, and removed contraception requirement for males and sections for “Women of Childbearing Potential” and “Pregnancy”.	Aligned with Pfizer standard and processes	Section 5.2 Inclusion Criteria #2b Section 5.6 Contraception Section 16.5 Appendix 5 – Contraceptive and Barrier Guidance Section 5.6 Women of Childbearing Potential (Removed) Section 8.4 Pregnancy (Removed)
Non-substantial Modification(s)		
Updated protocol synopsis.	Aligned with Pfizer protocol template	Study Summary (Synopsis)
Removed “Male and female” from inclusion criteria #2a.	Aligned with Pfizer protocol template	Section 5.2 Inclusion Criteria #2a
Removed the bullet name of “Other Inclusion Criteria” for previous inclusion criteria #6.	Aligned with Pfizer protocol template	Section 5.2 Inclusion Criteria #3
Added galcanezumab and eptinezumab as prohibited concomitant use of CGRP antagonists, updated the generic and trade names.	Added comprehensive list of CGRP antagonists instead of examples for clarity	Section 5.2 Inclusion Criteria #1e, ii
Clarified that this amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any PACL.	Aligned with Pfizer protocol template	Title page

Added the detail that this is a post marketing required study.	Clarified that this is a post marketing required study.	Study Summary (Synopsis) Section 1.5 Study Rationale
Clarified that subjects may start study drug on the day of the baseline visit or the following day, depending on the time of day of their visit.	Allowed IP to be started the day after the baseline visit if subjects have already missed their scheduled dosing time, to keep dosing around the same time each day.	Section 4.3 Schedule of Assessment, Table 1 Section 4.3.2.1 Baseline Visit Section 7.2.2 Selection and Timing of Dose and Administration
Removed "SAE forms and SAE Reporting instructions" and "Pregnancy Surveillance Forms" form study materials, and added "Back-up forms for CT SAE report, Exposure During Pregnancy and Pregnant Partner Release of Information".	Aligned with Pfizer SAE reporting process and applicable study materials	Section 6.1 Study Materials
Removed "(and non-investigational product at the discretion of the investigator)".	Clarified that management of non-investigational products is not protocol driven for early discontinuation subjects.	Section 6.5 Early Discontinuation from the Study
Updated SAE reporting destination and electronic reporting system administrative changes and clarifications.	Incorporation of non-substantial changes described in previous PACL dated 28 Apr 2023	Section 8.1.2 Collection and Reporting Serious Adverse Events
Updated text for Data Protection.	Aligned with Pfizer protocol template	Section 15 Data Protection
Added compliance aim for IP of 80%.	Defined compliance for clarity	Section 7.4 Treatment Compliance
Clarified study drug destruction.	Updated destination for study drug destruction	Section 7.5 Destruction and Return of Study Drug
Removed Clinical Protocol Approval Form.	Aligned with Pfizer protocol template	Section 16 Clinical Protocol approval form (removed)
Removed CONFIDENTIAL AND INVESTIGATOR STATEMENT.	Aligned with Pfizer protocol template	CONFIDENTIAL AND INVESTIGATOR STATEMENT (removed)
Updated the time for database lock and the type of CSR to be produced.	Updated for clarity	Section 9.4 Schedule of Analyses
Clarified that acetaminophen would be allowed during the study for acute headache.	Updated for clarity	Section 5.4 Prohibited and Restricted Concomitant Medications and Devices #5
Added reference to quality tolerance limits.	Aligned with Pfizer protocol template	Section 9.3 Statistical Methods
Removed Phase 1 study exception and the statement regarding Principal Investigator and the Sponsor's representative signatory. Added Sponsor's	Aligned with Pfizer protocol template	Section 10.1 Good Clinical Practice

regulatory and ethics responsibilities.		
Add the section for IRB/IEC.	Aligned with Pfizer protocol template	Section 10.3 Institutional Review Board/Independent Ethics Committee
Added Pfizer standard text for Dissemination of Clinical Study Data.	Aligned with Pfizer protocol template	Section 10.6 Dissemination of Clinical Study Data
Added AE information on lack of efficacy and medication errors.	Aligned with Pfizer protocol template	Section 8.5.4 Lack of Efficacy Section 8.5.5 Medication Errors
Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure.	Aligned with Pfizer protocol template and incorporated changes made in PACL dated 28 Apr 2023	Section 8.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
Removed “read”, and clarify that subjects must sign and date an ICF for study participation.	Aligned with Pfizer standard and processes	Section 10.4 Informed Consent
Removed Names of Study Personnel.	Removed to protect personal information	Section 16.1 Appendices Names of Study Personnel (removed)
Moved prior Protocol Amendment Summary of Changes to Appendix.	Editorial	Section 16.1 Appendix 1 Protocol Amendment History
Updated List of abbreviations	Editorial	List of Abbreviations
Changed term “Non-Investigational Product”, to “Concomitant Therapy”, and updated the definition for concomitant therapy.	Aligned definition with current regulations.	Section 7.1.2 Concomitant Therapy
Corrected that non-serious AEs should be reported from signing of consent through Follow up Week 8 Visit.	Correction	Section 4.3 Schedule of Assessment, footnote #10 Section 4.3.3.2 Follow-up Week 8 Visit
Removed “provided the IRB/IEC is notified within 5 days”.	Amended to allow for immediate action to be implemented	Section 12 Amendments
Updated Publications Policy.	Updated per investigator’s Clinical Research Agreement	Section 13 Publications Policy
Updated details on confidentiality and renamed section, Data Protection.	Replaced with Pfizer Data protection policy	Section 15 Data Protection
Updated the exclusion criterion number as 7g in the title.	Editorial update	Section 16.3 Appendix 3 – Categories of Migraine Prevention Medications (Reference for Exclusion Criteria 7g)
Removed the subtitle for Clinical Adverse Event Profile.	Editorial	Section 1.3.1 Clinical Adverse Event Profile

Updated document header and footer.	Updated to align with Pfizer protocol template	Header and Footer
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, Open-label Study to Evaluate the Safety and Tolerability of Daily Dosing of Rimegepant in Episodic Migraine Prevention

Brief Title: The purpose of this study is to further evaluate the long-term safety and tolerability of daily dosing of rimegepant for the prevention of episodic migraine.

Regulatory Agency Identification Number(s):

US IND Number:	109886
EudraCT Number:	NA
ClinicalTrials.gov ID:	NCT05207865
Pediatric Investigational Plan Number:	NA
Protocol Number:	BHV3000-405 (C4951011)
Phase:	4

Rationale: This is a post marketing required study being conducted to further evaluate the long-term safety and tolerability of a more frequent daily dosing regimen of rimegepant for the prevention of episodic migraine.

Primary Objectives:

To evaluate the long-term safety and tolerability of rimegepant taken daily for episodic migraine prevention.

Primary Endpoint:

Frequencies of the following safety events and findings on treatment: AEs that occur in at least 5% of subjects by intensity; serious adverse events (SAEs); AEs leading to study drug discontinuation; and grade 3 to 4 laboratory test abnormalities.

Overall Design:

This is a multicenter, open-label study to assess the safety and tolerability of rimegepant in migraine prevention. The Screening Phase is 3-14 days in duration, followed by a Baseline Visit at which time eligibility for continued participation in the study will be assessed before study drug is dispensed. Subjects will take 1 tablet (rimegepant 75 mg ODT) each day during the Open-Label Treatment Phase. If subjects have a migraine during the Open-label Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed while continuing to take the study drug.

Study visits will occur at Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and End of Treatment (EOT) for early discontinuation. After the Week 24 or EOT Visit, subjects should complete the Follow-up Week 2 and Follow-up Week 8 visits for assessment of AEs and laboratory assessments.

Number of Subjects:

A sufficient number of subjects will be screened to treat up to 285 subjects with study drug to ensure that at least 170 subjects will complete 24 weeks of treatment. All subjects will be assigned to rimegepant 75 mg ODT dosed daily.

Study Population:

The study will recruit 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. 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.

WOCBP who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study and for 28 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.

Subjects with a history of or current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia are excluded. 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 will be excluded. Subjects will also be excluded who have uncontrolled hypertension (high blood pressure), uncontrolled diabetes, or a history or current evidence of any unstable medical conditions 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

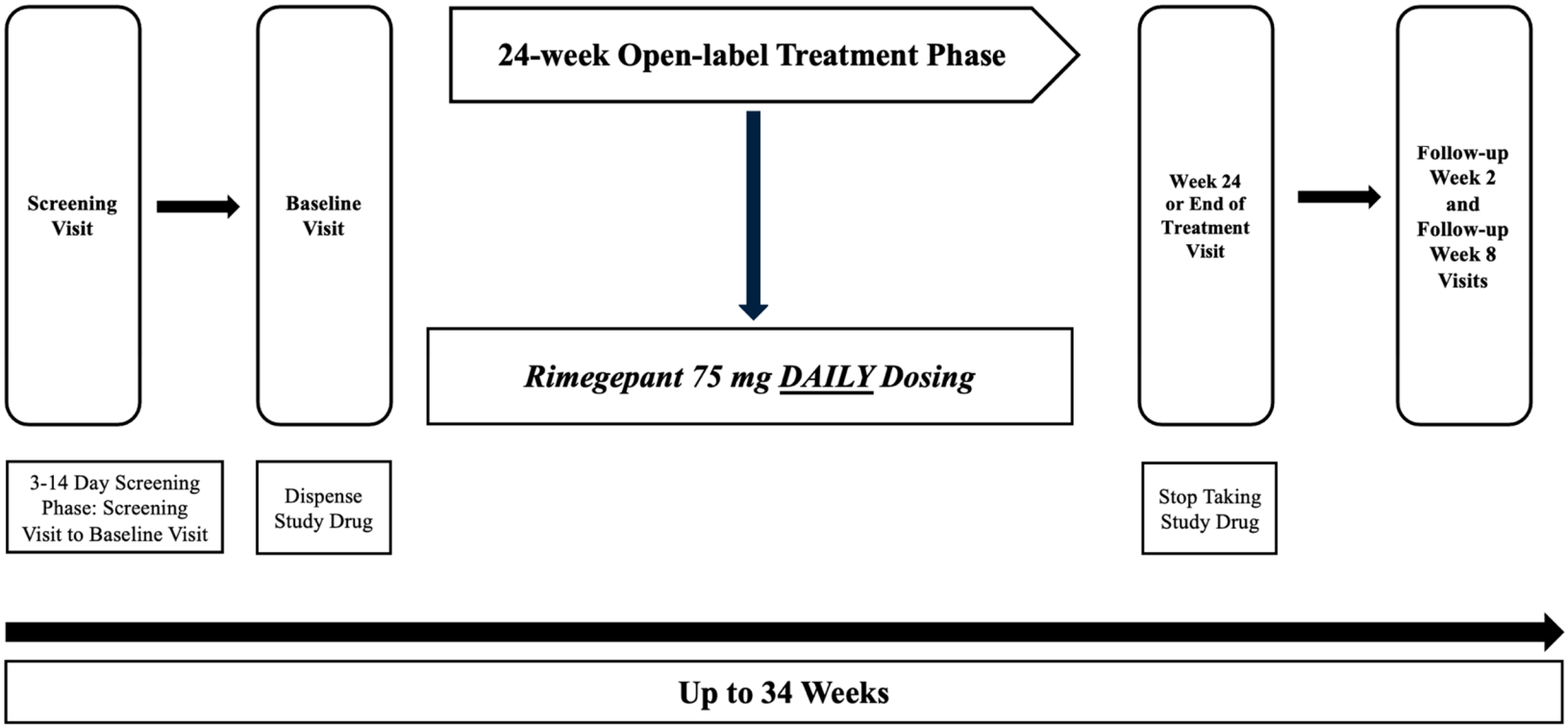
History of use of opioid- (morphine, codeine, oxycodone, hydrocodone) or barbiturate- (e.g. butalbital) containing medication for ≥4 days per month during the 3 months (12 weeks) prior to the Screening Visit is exclusionary.

Statistical Methods:

The frequencies of the following on-treatment safety events and findings will be presented for the safety analysis set: AEs by intensity in ≥5% of subjects (mild, moderate, severe, total); SAEs; AEs by relationship to study drug (related, possibly related, unlikely related, not related); AEs related to study drug by intensity; 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; LFT elevations based on fold change above ULN; and vital sign, physical measurement, and ECG abnormalities. Frequencies of safety events will be based on the number and percentage of subjects with events.

Ethical Considerations:

It is not known if it is safe to take more than 18 doses of rimegepant in 30 days. Taking into account the measures to minimize risk to subjects with episodic migraine, the potential risks associated with rimegepant are justified by the anticipated benefits that may be afforded to subjects with daily dosing regimens.



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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AD	Anxiety Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
ADIS	Animal Diseases Information System
AE	Adverse Event
ALT	Alanine Aminotransferase
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
AV	Atrioventricular
BHV	Biohaven
BP	Blood Pressure
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
CBD	Cannabidiol
CGRP	Calcitonin Gene-Related Peptide
CK	Creatine Kinase
COVID-19	Coronavirus Disease 2019
(e)CRF	(Electronic) Case Report Form
CRO	Clinical Research Organization
CRPS	Complex Regional Pain Syndrome
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CTS	Clinical Trial Subject
CV	Cardiovascular
CYP	Cytochrome P450
DAIDS	Division of AIDS
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DSMC	Data and Safety Monitoring Committee

DSM-V	Diagnostic and Statistical manual of Mental Disorders Fifth edition
DSU	Drug Safety Unit
EC	Ethics Committee
ECC	Emergency Contact Card
ECG	Electrocardiogram
EDB	Exposure During Breastfeeding
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
eGFR	Estimated Glomerular Filtration Rate
EOD	Every Other Day
EOT	End of Treatment
ET	Early Terminated
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FU	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
HbA1c	Hemoglobin A1C
HCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	investigational product

IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL	Low-density Lipoprotein
LFTs	Liver Function Tests
MDD	Major Depressive
MDE	Major Depressive Episode
MDMA	3,4-Methyl-enedioxy-methamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial Infarction
min	Minute
mL	Milliliter
MQI	Medically Qualified Individual
mRNA	Messenger Ribonucleic Acid
msec	Millisecond
NA	Not Applicable
NOAEL	No Observed Adverse Effect Level
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODT	Orally disintegrated tablet
OTC	Over-the-Counter
PACL	Protocol Administrative Change Letter
PCI	Percutaneous Coronary Intervention
PCP	Phencyclidine
PE	Physical Examination
P-gp	P-glycoprotein
PI	Principal Investigator
PRN	As Needed

PSSA	Pfizer SAE Submission Assistant
PVC	Premature Ventricular Contraction
QRS	Ventricular Depolarization
QT	Time to Ventricular Depolarization to Repolarization
QTc	Interval between Q-wave and T-wave in the cardiac cycle
QTcF	QTc corrected using Fridericia's formula
QTL	Quality Tolerance Limit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF	Screen Fail
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
TBili	Total Bilirubin
THC	Tetrahydrocannabinol
TIA	Transient Ischemic Attack
(e)TMF	(Electronic) Trial Master File
UK	United Kingdom
uL	Microliter
ULN	Upper Limit of Normal
UNS	United States
US	United States
W#	Week #
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 (IV) 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.[2,3] Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine;[2] 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief;[2,3] and 3) intravenous (IV) CGRP infusion produces lasting pain in non-migraineurs and migraineurs.[4,5]

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 (IB). A summary of the relevant data to the study are presented below.

Rimegepant is approved for acute treatment and prevention of episodic migraine in the US, EU and UK 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.[6]

As of 26 August 2022, more than 8900 unique subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine or refractory trigeminal neuralgia, chronic rhinosinusitis, or temporomandibular disorders; of these, approximately 6036 unique subjects have received rimegepant at any dose. Collectively, the current data demonstrates a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine.

1.4 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. It is not known if it is safe to take more than 18 doses of rimegepant in 30 days. Taking into account the measures to minimize risk to subjects with episodic migraine, the potential risks associated with rimegepant are justified by the anticipated benefits that may be afforded to subjects with daily dosing regimens.

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 must use an acceptable method 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

This post marketing required study is being conducted to further evaluate the long-term safety and tolerability of a more frequent daily dosing regimen of rimegepant for the prevention of episodic migraine for up to 24 weeks. Up to 285 subjects will dose with open-label study drug every day to ensure that at least 170 subjects will complete 24 weeks of treatment.

1.5.1 Study Design Rationale

This is a 24-week, multicenter, open-label evaluation of the long-term safety of rimegepant 75 mg taken daily for the prevention of episodic migraine. 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 medications as needed (see Section 5.5.2) while continuing to take 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 safety and tolerability of a more frequent daily dosing regimen in episodic migraine prevention.

1.6 Research Hypothesis

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

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the safety and tolerability of rimegepant taken daily for episodic migraine prevention during the Open-label Treatment Phase.

2.2 Secondary

Not applicable.

2.3 Exploratory Objectives

1. To evaluate the frequency of AEs potentially associated with drug abuse during the Open-label Treatment Phase.

2. To evaluate the frequency and intensity of hepatic-related AEs during the Open-label Treatment Phase.

3. To evaluate the frequency of liver function test (LFT) elevations (ALT, AST, alkaline phosphatase, and total bilirubin) based on fold changes above ULN during the Open-label Treatment Phase.

4. To evaluate the frequency of ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN during the Open-label Treatment Phase.

5. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue during the Open-label Treatment Phase.

6. To evaluate the Columbia-Suicide Severity Rating Scale (C-SSRS) during the Open-label Treatment Phase.

3 STUDY ENDPOINTS

3.1 Primary

Frequencies of the following safety events and findings on treatment: AEs that occur in at least 5% of subjects by intensity; serious adverse events (SAEs); AEs leading to study drug discontinuation; and grade 3 to 4 laboratory test abnormalities.

AEs are determined from electronic case report forms (eCRFs).

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

3.2 Secondary

Not applicable.

4 STUDY PLAN

4.1 Study Design and Duration

This is a multicenter, open-label study to assess the safety and tolerability of rimegepant in migraine prevention.

The Screening Phase is 3-14 days in duration; subjects should return to the study site as soon after screening laboratory results are available, and within 14 days, for the Baseline Visit. For subjects to be eligible for the study, they must have reported having had ***4-14 migraine attacks*** per month in the 3 months prior to the Screening 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 Screening Visit.

Upon the completion of the Screening Visit, subjects will be provided with a concomitant medication paper diary to document use of all concomitant medications, including standard of care migraine medications (both prophylactic and acute, prescribed and OTC) (see Sections 5.5.1 and 5.5.2). After completing the Screening Phase, subjects will return to the clinic with the paper diary for the Baseline Visit. Subjects found to be ineligible will be considered screening failures; subjects should return the concomitant medication paper diary which will be maintained as a source document.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before study drug is dispensed. Subjects will be instructed that they must take 1 tablet (rimegepant 75 mg ODT) each day during the Open-label 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. If subjects have a migraine during the Open-label Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.2) while continuing to take the study drug.

During the Open-label Treatment Phase, subjects will continue to record all concomitant medications, including standard of care migraine medications (both prophylactic and acute, prescribed and OTC), taken and all study drug taken. The concomitant medication paper diary will continue to be used during the Follow-up Phase.

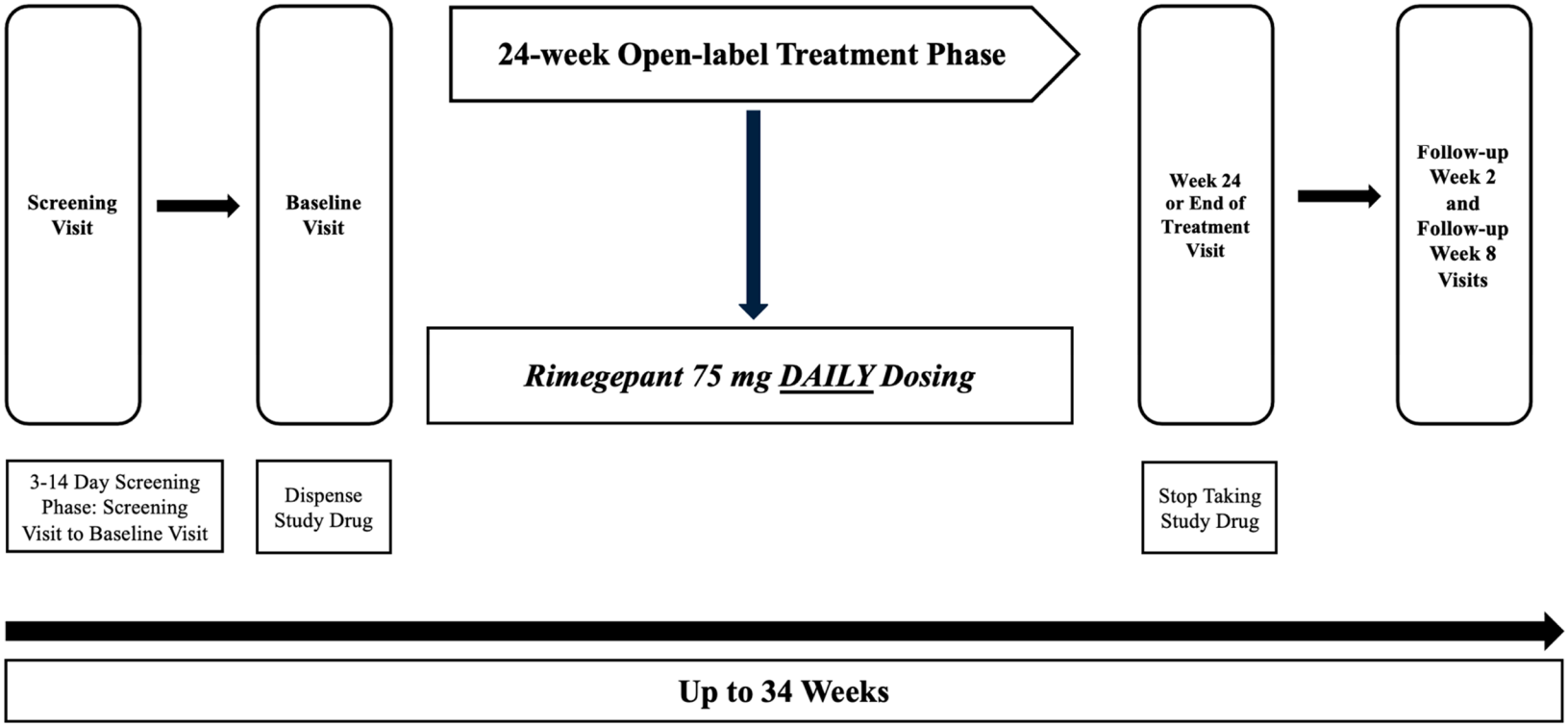
Assessments and the visit schedule are outlined in the procedural table in Section 4.3. Procedures include study personnel review of the concomitant medication paper diary with the subject, assessment of study drug compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography).

Study visits will occur at Screening, Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and End of Treatment (EOT) for early discontinuation. Subjects will return to the study site for the Week 24 or EOT Visit. There are follow-up visits approximately 2 weeks and 8 weeks after the Week 24 or EOT Visit for assessment of AEs and laboratory assessments. Subjects ***who take study drug and discontinue early from the Open-label Treatment Phase*** should complete the EOT Visit. All subjects ***who take study drug*** should complete the Follow-up Week 2 and the Follow-up Week 8 Visits, regardless of completing the Open-label Treatment Phase.

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 an SAE. See Section 8.4, Potential Drug Induced Liver Injury (DILI).

4.2 Study Schematic

Figure 1 Study Schematic Up to 24 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

	Screening Phase (3-14 days)[1]	**Open-label Treatment Phase**[2,3]				**Follow-up Phase**[2]
Procedure	**Screening Visit**	**Baseline Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28), **Week 8** (Day 56), **Week 12** (Day 84), **Week 16** (Day 112), & **Week 20** (Day 140) (all visits +/-2 days)	**Week 24 (**Day 168) (+/- 2 days) **or EOT Visit**	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]
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[5]
Enroll subject / IWRS[6]		X				
Safety Assessments						
Physical Examination[7]	X			X (Week 12 Only)	X	
Vital Signs / Physical Measurements[8]	X	X	X	X	X	X
Clinical Safety Laboratory Testing [9]	X		X	X (Weeks 4, 8, 12, 16 Only)	X	
Liver Function Test (LFTs)[9]	X	X	X	X	X	X
Lipid Panel[9]		X		X (Week 12 only)	X	

Table 1 Schedule of Assessments

	Screening Phase (3-14 days)[1]	**Open-label Treatment Phase**[2,3]				**Follow-up Phase**[2]
Procedure	**Screening Visit**	**Baseline Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28), **Week 8** (Day 56), **Week 12** (Day 84), **Week 16** (Day 112), & **Week 20** (Day 140) (all visits +/-2 days)	**Week 24 (**Day 168) (+/- 2 days) **or EOT Visit**	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]
ECG	X		X	X (Week 4, 8, 12 Only)	X	
Urinalysis	X				X	
Urine Drug Screen for drugs of abuse	X					
FSH, if applicable, to determine WOCBP status	X					
Pregnancy Test	X (urine, 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
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		
Administer study drug[11,12]			X	X		

Table 1 Schedule of Assessments

	Screening Phase (3-14 days)[1]	**Open-label Treatment Phase**[2,3]				**Follow-up Phase**[2]
Procedure	**Screening Visit**	**Baseline Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28), **Week 8** (Day 56), **Week 12** (Day 84), **Week 16** (Day 112), & **Week 20** (Day 140) (all visits +/-2 days)	**Week 24 (**Day 168) (+/- 2 days) **or EOT Visit**	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]
Return used and unused study drug to site for compliance check			X	X	X	

1. The duration between the Screening Visit and the Baseline Visit is 3-14 days. Every effort should be made to perform the Baseline Visit (or Screening Failure Visit, where applicable) as soon as the screening laboratory results are available and within the 14 days.
2. All subjects ***who take study drug and discontinue the Open-label Treatment Phase early*** should complete the EOT Visit. All subjects ***who take study drug*** should complete the Follow-up Week 2 and Follow-up Week 8 Visits, regardless of completing the Open-label Treatment Phase.
3. 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 Visit.
4. 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 standard of care migraine medications (both prophylactic and acute, prescribed and OTC), taken during the Screening Phase, Open-label Treatment Phase, or 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 will 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, full PE is required at screening and brief symptom directed PEs are required at all other visits as noted.
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 only collected at screening, repeat or UNS.
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 Follow up Week 8 Visit.

Table 1 Schedule of Assessments

	Screening Phase (3-14 days)[1]	**Open-label Treatment Phase**[2,3]				**Follow-up Phase**[2]
Procedure	**Screening Visit**	**Baseline Visit** (Day 1)	**Week 2** (Day 14 +/- 2 days)	**Week 4** (Day 28), **Week 8** (Day 56), **Week 12** (Day 84), **Week 16** (Day 112), & **Week 20** (Day 140) (all visits +/-2 days)	**Week 24 (**Day 168) (+/- 2 days) **or EOT Visit**	**FU Week 2 and FU Week 8 Visits** (both visits +/-2 days) for all subjects[4]

11. 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.
12. Subjects must take their 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 and should NOT take the following day's assigned dose until the next calendar day at the specified time.

4.3.1 Screening Phase

The Screening Phase will be 3-14 days and will have 1 scheduled visit, the Screening Visit, which should be completed in person. Subjects will undergo all screening procedures as detailed in Table 1.

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.

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

The duration between the Screening Visit and the Baseline Visit is 3-14 days. Every effort should be made to perform the Baseline Visit after as soon as the screening laboratory results are available and within the 14 days.

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

4.3.2 Open-label Treatment Phase

The Open-label Treatment Phase will be up to 24 weeks from the Baseline Visit through the Week 24 or EOT Visit.

During the Open-label Treatment Phase, subjects will be instructed that they must take 1 tablet of study drug (rimegepant 75 mg ODT) daily. If subjects have a migraine during the Open-label Treatment Phase, then they may treat the migraine with permitted acute migraine medication as needed (see Section 5.5.2) while continuing to take the study drug.

Subjects will continue to record all concomitant medications, including standard of care migraine medications (both prophylactic and acute, prescribed and OTC), taken during the entire Open-label Treatment Phase on 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 24 or EOT Visit (Table 1). At each visit, the concomitant medication paper diary will be reviewed by site staff for completeness and compliance. Study drug compliance and concomitant medication use will be reviewed at each visit and subjects will be dispensed additional study drug as needed. Unused, non-expired, partial wallets will be returned to the subjects for completion prior to starting a new wallet. Additional safety assessments (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 1.

Due to the COVID-19 pandemic, visits may be conducted remotely (ex: telephone, telemedicine) unless specified otherwise, and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.

4.3.2.1 Baseline Visit

Once completing the Screening Phase, subjects will return to the study site for the Baseline Visit, which must be completed in person. Subjects who continue to meet all eligibility criteria and have been compliant with the concomitant medication paper diary may enter the Open-label Treatment Phase.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before study drug is dispensed. Subjects will be instructed that they must take 1 tablet of study drug (rimegepant 75 mg ODT) each day, and dosing should occur around the same time for each scheduled dose. Subjects may start study drug on the day of the Baseline Visit or the following day, depending on the time of day of their visit. Subjects **must** be instructed that they CANNOT take more than 1 tablet of study drug daily during the Open-label 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 24 or EOT Visit

Subjects will return to the study site at the Week 24 Visit (Day 168 +/- 2 days), or at the EOT Visit for early discontinuation, for review of the concomitant medication paper diary, assessment of study drug compliance, and assessment of safety (including vital signs, laboratory tests, and electrocardiography) (Table 1). Subjects must return the unused study drug and concomitant paper diary to the study site.

All subjects ***who take study drug and discontinue early from the Open-label Treatment 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 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 24 or EOT Visit occurring remotely do not need to be repeated.

4.3.3 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 after the Week 24 or EOT Visit, respectively. All subjects ***who take study drug*** should complete both follow-up visits, regardless of completing the Open-label Treatment Phase.

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

4.3.3.1 Follow-up Week 2 Visit

Subjects will return to the study site approximately 2 weeks (14 days +/- 2 days) after the Week 24 or EOT Visit 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).

4.3.3.2 Follow-up Week 8 Visit

Subjects will return to the study site approximately 8 weeks (56 days +/- 2 days) after the Week 24 or EOT Visit to collect vital signs, LFTs, assessment of AE/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

A sufficient number of subjects will be screened to treat approximately 285 subjects with study drug to ensure that at least 170 subjects will complete 24 weeks of treatment. All subjects will be assigned to rimegepant 75 mg ODT dosed daily.

5.2 Inclusion Criteria

1. 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[7], 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 of moderate or severe intensity per month within the last 3 months prior to the Screening Visit (month is defined as 4 weeks for the purpose of this protocol).

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

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

      i. Subjects may remain on one (1) medication with possible migraine-prophylactic effects (see Section 5.4).

      ii. Concomitant use of a CGRP antagonist, such as rimegepant (Nurtec® ODT), erenumab (Aimovig™), fremanezumab (Ajovy™), atogepant (Qulipta™), ubrogepant (Ubrelvy™), galcanezumab (Emgality™), or eptinezumab (Vyepti™) is prohibited.

      iii. Subjects who previously discontinued oral prophylactic migraine medication must have done so at least 30 days prior to the Screening Visit.

      iv. Subjects who previously discontinued biologic migraine medication must have done so at least 3 months (12 weeks) prior to the Screening Visit.

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

2. Age and Reproductive Status

   a) Subjects ≥ 18 years.

   b) Subject meets reproductive criteria. Refer to Appendix 5 for reproductive criteria for male (Section 16.5.1) and female (Section 16.5.2) subjects.

   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.

3. 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[7].

   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 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest at the screening or baseline visit is exclusionary. Blood pressure measurement may be repeated once at screening visit and baseline 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 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) 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.

g) Subject has a history or diagnosis of an active hepatic or biliary disorder.

h) 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.

i) 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 [8] for any significant substance use disorder within the past 12 months (48 weeks) from the date of the Screening Visit according to PI assessment.

j) History of use of narcotics such as opioids (morphine, codeine, oxycodone, hydrocodone) or barbiturate- (e.g., butalbital) containing medication for $\geq$4 days per month during the 3 months (12 weeks) prior to the Screening Visit.

k) Subjects should be excluded if the subject has reported current use of, or has tested positive at the Screening visit for, drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiates, MDMA, methamphetamines, oxycodone, phencyclidine). In addition:

   i. Detectable levels of cocaine 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 24 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[8] 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.

l) 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.

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

n) 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 28 days after 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).

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

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

   b) Use of medication accepted for treatment of acute migraine (Section 5.5.2) for a non-migraine indication on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit.

   c) Subjects taking a prohibited medication (Refer to 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) Exposure to non-biological investigational agents (other than rimegepant) within the 30 days prior to the Screening Visit.

   d) Exposure to biological investigational agents within 3 months (12 weeks) prior to the Screening Visit.

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

   f) Previous enrollment in any multiple dose BHV3000 (rimegepant) study, such as BHV3000-201, BHV3000-305, or BHV3000-404 regardless of the number of doses taken. Subjects may be considered for BHV3000-405 (C4951011) if the subject participated in any of the following single dose studies: BHV3000-301, BHV3000-302, BHV3000-303. 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.

   g) 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 3 after an adequate therapeutic trial. Additional details can be found in Section 16.3 Appendix 3.

   h) 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.

i) 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.

j) Please see Section 5.4 for prohibited medications and Section 5.5.2 for permitted acute migraine medications.

k) 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 after screening until the last study day will be documented as concomitant medications including vaccinations.

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

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

2. Butterbur root or extracts should not be taken 14 days prior to the Baseline Visit and throughout the study.

3. History of use of ergotamine medications on ≥ 10 days per month on a regular basis for ≥ 3 months (≥ 12 weeks). Note that use of ergotamine medication is prohibited throughout the entire duration of the study (Screening Visit to Follow-up Week 8 Visit), however reporting of any use of ergotamine medication is required for the purpose of defining migraine days.

4. Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone, and hydrocodone) or barbiturates is prohibited starting from 2 days prior to the Baseline Visit and throughout the study, including the Follow-up Week 8 Visit.

5. Use of acetaminophen or acetaminophen containing products for non-headache indications after the Baseline Visit is prohibited. Any use of acetaminophen or acetaminophen containing products for non-headache indications during the Screening Phase must be stopped at least 2 days prior to Baseline Visit. Acetaminophen as acute headache medication as described in Section 5.5.2 is allowed during the study.

6. The use of CGRP antagonists (biologic [e.g., Aimovig® or Ajovy®] or small molecule [e.g., Nurtec® ODT or Ubrelvy™]) other than rimegepant provided for this clinical study is prohibited during the study including through the Follow-up Week 8 Visit.

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

8. Concomitant use of moderate to strong CYP3A4 inhibitors is prohibited during the study. If use of a moderate or strong CYP3A4 inhibitor is required, such as use of HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, dosing with rimegepant should be stopped and should not start again until 14 days after the last dose of the moderate or strong CYP3A4 inhibitor. Please see Section 16.2 Appendix 2.

9. Concomitant use of moderate to strong CYP3A4 inducers is prohibited during the study. If use of a moderate or strong CYP3A4 inducer is required, such as use of carbamazepine, phenytoin, or rifampin, dosing 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.

10. Concomitant use of atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate) is prohibited during the study.

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

12. Use of analgesics other than acetaminophen for non-migraine use (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) on ≥ 15 days per month is prohibited. during the study. Use of acetaminophen or acetaminophen containing products for non-headache indications after the Baseline Visit is prohibited.

13. Use of Cefaly™ or any other device for migraine treatment within 12 weeks of the Screening Visit.

14. Use of any investigational agent other than rimegepant (provided for the purpose of this clinical study) from the Screening Visit through the Follow-up Week 8 Visit.

15. Concomitant use of strong inhibitors of the P-gp transporter with rimegepant is prohibited during the study.

5.5 Standard of Care Migraine Medications

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

5.5.1 Prophylactic Migraine Medications

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

Prophylactic migraine medications that are permitted during the study include:

- Topiramate, gabapentin
- Beta blockers (such as: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)

- Tricyclic antidepressants (such as: amitriptyline, nortriptyline, protriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Flunarizine, lomerizine
- Lisinopril, candesartan
- Clonidine, guanfacine
- Cyprohepatdine
- Methysergide
- Pizotifen
- Feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- Botox®

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

5.5.2 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 for rescue during the study.

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, then the subject may take their ***permitted acute migraine medication*** as described in this section of the protocol. ***During the Open-label Treatment Phase, subjects are not allowed to take more than 1 tablet of study drug daily.***

5.6 Contraception

The investigator or their designee, in consultation with the subject, will confirm that the subject is utilizing an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see Section 16.5.4) and will confirm that the subject has been instructed in its consistent and correct use.

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

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

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

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant medication paper diary (take home for subject)
- Investigator Brochure (IB)
- 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.
- 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

- Study system access:
  - Electronic Data Capture (EDC) tool to submit study data to Sponsor / CRO
  - IWRS
  - Central Laboratory vendor portal
  - Central ECG 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.

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. 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 16.4 Appendix 4).

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 Table 1. 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 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.

1. 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 collecting at screening, repeat, or UNS), BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin, CK

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

2. **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.

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

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

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

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

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

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

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.[9] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[10] 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 (Table 1).

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

Not applicable.

6.4 Other Assessments

Not applicable.

6.5 Early Discontinuation from the Study

Subjects MUST discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Exclusionary laboratory abnormality identified on the Baseline Laboratory Report.
- Pregnancy
- Termination of the study by Pfizer
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Poor compliance with study procedures and visits, including poor completion compliance with the concomitant medication paper diary.
- 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 24 or EOT Visit procedures as outlined in Table 1. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

6.5.1 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. 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.

- In this protocol, investigational product (study drug) is rimegepant ODT (BHV-3000, PF-07899801) 75 mg dosed daily.

- 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

In this protocol, concomitant therapy is/are standard of care for acute and preventive 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 and light) 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 system will be utilized for obtaining subject identification and as the electronic data capture (EDC) system. Each subject will be assigned a unique sequential 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.

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

7.2.2 Selection and Timing of Dose and Administration

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

Subjects may start study drug on the day of the Baseline Visit or the following day, depending on the time of day of their study visit. 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, the subject can take permitted acute migraine medication as needed (see Section 5.5.2). Subjects must be instructed that they CANNOT take more than 1 tablet of study drug daily during the Open-label 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.

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

Not applicable to this protocol.

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Subjects should finish a wallet of study drug before starting a new wallet. Accountability and compliance verification should be documented in the subject's study records. Subjects must be counseled on the importance of taking the study drug as directed. 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 and document the contact in the source, to identify potential lost to follow-up subjects as early as possible.

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.
- at each dispensation visit (refer to SoA-Table 1), subjects who are <80% compliant must be re-educated on the importance of daily self administration of study drug;
- Overall aim: maintain ≥80% compliance over the duration of dosing.

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 study drug, or non-compliance cases in which more study drug was used, as compared to expected). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies. See Section 8.1.1.

Cases of potential study drug abuse or overdose (including cases of non-compliance with study drug dosing instructions or subjects who discontinue 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 on 1 calendar day) should be reported as deviations.

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 relate 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 treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor subjects for possible cases of abuse of study drug (subjects taking study drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies
  - Potential study drug overdose is defined in Section 8.3

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

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

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 at the Screening Visit and up to and including 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 8.5.1) 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 form.

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 as a written description using the Pfizer CT SAE report form, that must be sent to by facsimile (fax or eFax) to the Pfizer DSU at 1-866-997-8322.

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 following written consent 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 on 1 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.

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.

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.

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.

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 Medical Monitor and Pfizer Medical Monitor (if separate) 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 drug. 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 drug under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.5.1 Exposure During Pregnancy

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

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

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

An EDP occurs if: A female subjects found to be pregnant while receiving or after discontinuing study drug.

- A male subject who is receiving or has discontinued study drug inseminates a female partner. A female nonsubject is found to be pregnant while being exposed or having been exposed to study drug 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 drug by ingestion or skin contact.
    - A male family member or healthcare provider who has been exposed to the study drug 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 Form and EDP supplemental form or via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study drug 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 Form and EDP supplemental form or via PSSA. Since the exposure information does not pertain to the subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

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

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

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

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

Additional information regarding the EDP may be requested by the sponsor. Further followup of birth outcomes will be handled on a case by case basis (eg, followup on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the 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 drug.

- A female nonsubject is found to be breastfeeding while being exposed or having been exposed to study drug (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 drug by ingestion or skin contact.

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

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

8.5.3 Occupational Exposure

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

8.5.4 Lack of Efficacy

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

8.5.5 Medication Errors

Medication errors may result from the administration or consumption of the study drug 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

Medication errors include:

- Medication errors involving subject exposure to the study drug.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study subject are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

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

8.6 Adverse Events of Special Interest

Not applicable for this study.

9 STATISTICS

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

9.1 Sample Size

With a target sample size of 285 subjects in the safety analysis set and no events observed, the upper bound of a one-sided 95% confidence interval for zero observations is 0.01. Hence this sample size is large enough to rule out events that occur at rates greater than 1 case per 100 subjects.

In BHV3000-305 (C4951025) migraine-prevention study with EOD dosing, 73% of subjects in the rimegepant treatment group had ≥ 6 months (defined as ≥ 23 weeks) of double-blind or open-label rimegepant (i.e., 27% non-completion rate). In this study, it is expected that the 24-week non-completion rate will be higher due to early termination from baseline laboratory test

elevations. Assuming a 40% non-completion rate, approximately 170 subjects in the safety analysis set are expected to complete 24 weeks of treatment.

9.2 Analysis Sets

- Enrolled: Subjects who sign the informed consent form and are assigned a subject identification number.

- Safety: Subjects in the enrolled analysis set who take ≥ 1 dose of study drug (rimegepant).

9.3 Statistical Methods

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

The frequencies of the following on-treatment safety events and findings will be presented for the safety analysis set: AEs by intensity in ≥ 5% of subjects (mild, moderate, severe, total); SAEs; AEs by relationship to study drug (related, possibly related, unlikely related, not related); AEs related to study drug by intensity; 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; LFT elevations based on fold change above ULN; and vital sign, physical measurement, and ECG abnormalities. Frequencies of safety events will be based on the number and percentage of subjects with events.

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 presented 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 which will occur after the last subject completes the Follow-up Week 8 Visit. The final clinical study report (CSR) will be produced to support regulatory requirements after the final database lock.

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 Institutional Review Board/Independent Ethics Committee

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

In the event that the protocol is amended, the revised protocol must be approved by the IRB/IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial.

10.4 Informed Consent

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

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

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, if the subject has not opted out of the CTSdatabase portion of the study, they must 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.

10.5 Case Report Forms

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

Electronic CRFs will be prepared for all data 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.

10.6 Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are

posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

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

10.6.1 Data sharing

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

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

10.7 Sponsor's Medically Qualified Individual

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

To facilitate access to their investigator and the sponsor's MQI for study related medical questions or problems from non-study healthcare professionals, subjects are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study drug 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 - Protocol Amendment History

Change	Section(s) Affected		Summary (changes are noted in bold)
Not Applicable	Not Applicable		Original Protocol
V2.0	Table 1		Typographical Errors and Addition of Physical Measurements.
V2.0	Inclusion Criteria 4e.i.		Removed reference to CGRP and added referral to section 5.4
V2.0	Exclusion Criteria 5h.		Removal of equals sign
V2.0	Section 5.4 and Appendix 17.2		Removal of P-gp restrictions
V2.0	Section 6.2.4.1 Chemistry		Clarified timing of HbA1C testing
V2.0			Correction of other minor typographical errors throughout protocol
V3.0	Section 5.4 and Appendix 17.2		Retraction of removal of P-gp restrictions
V3.0	Section 5.4.12		Clarification of analgesic usage
V4.0	Appendix 17.1		Update to Signatories
V4.0	Synopsis, Sections 1.4, 5.1, 9.1		Update to number of expected screened and enrolled
V4.0	Section 8.2.1		Correction to NSAE reporting
V4.0	Added Exclusion Criteria 8.		Criteria added for any subjects in PI opinion do not qualify
V4.0	Exclusion Criteria 2m		Clarified wording around drugs of abuse
V4.0	Appendix 17.2		Removal of Grapefruit and Seville Orange as moderate CYP3A4 inhibitors
V5.0	Synopsis, Section 5.1, Section 9.1		Update to number of subjects and samples size.

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 or 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, telithromycin, troleandomycin

Moderate CYP3A4 inhibitors
Amprenavir, aprepitant, casopitant, cimetidine, ciprofloxacin, diltiazem, dronedarone, erythromycin, fluconazole, 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, phenytoin, phenobarbital, apalutamide, avasimibe

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 – Categories of Migraine Prevention Medications (Reference for Exclusion Criteria 7g)

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**: Neuromuscular blocker: (Botox®)

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

16.4 Appendix 4 - ECG Findings of Potential Clinical Concern

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

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

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

16.5 Appendix 5 - Contraceptive and Barrier Guidance

16.5.1 Male Subject Reproductive Inclusion Criteria

No contraception methods are required for male subjects in this study, as the calculated safety margin is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

16.5.2 Female Subject Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 2.b (Age and Sex; Section 5.2) and specify the reproductive requirements for including female subjects. Refer to Section 16.5.4 for a complete list of contraceptive methods permitted in the study.

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

· Is not a WOCBP (see definitions below in Section 16.5.3).

OR

· Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study drug). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug.

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

16.5.3 Woman of Childbearing Potential

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

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

Women in the following categories are not considered WOCBP:

1. Premenarchal.

2. Premenopausal female with 1 of the following:

· Documented hysterectomy

· Documented bilateral salpingectomy

· Documented bilateral oophorectomy

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

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

1. Postmenopausal female:

· A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

· A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.

· A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

16.5.4 Contraceptive Methods

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

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

· Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

· Oral

· Intravaginal

· Transdermal

7. Progestogen-only hormone contraception associated with inhibition of ovulation:

· Oral

· Injectable

8. Sexual Abstinence

· Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

Other Effective Methods

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.

10. Male or female condom, with or without spermicide.

11. Cervical cap, diaphragm, or sponge with spermicide.

12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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