AN INTERVENTIONAL, PHASE 3, SINGLE ARM, OPEN LABEL STUDY TO INVESTIGATE LONG-TERM SAFETY OF RIMEGEPANT ORALLY DISINTEGRATING TABLETS FOR THE ACUTE TREATMENT OF MIGRAINE IN CHINESE PARTICIPANTS

Study Intervention Number:	Rimegepant PF-07899801 (BHV3000)
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Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title:

A study to learn about the long-term safety of rimegepant for the acute treatment of migraine in Chinese Participants

DOCUMENT HISTORY

Document	Version Date
Amendment 4 – Version 5.0	18 August 2023
Amendment 3 – Version 4.0	28 June 2022
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Amendment 1 – Version 2.0	05 November 2021
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This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Description of Change	Brief Rationale	Section #
Substantial Modification(s)		
Referenced study number BHV3000-318 to Pfizer C4951018 and compound name BHV-3000 to PF-07899801 to reflect identification changes by sponsor.	Reflected change in sponsorship protocol and compound identification numbers	Title page Headers Section 1.1 Section 2 Section 7.1.1
Sponsor name changed.	Reflected transfer of sponsorship from BioShin (Shanghai) Consulting Services Co., Ltd to Pfizer Inc.	Throughout the document
Updated benefit risk background information and added benefit risk assessment	Updated benefit risk information. Capsuled the content of Pharmarceutical Development Background, and removed the detailed clinical study data which is referred to IB.	Section 2.2 Pharmarceutical Development Background Section 2.5 Benefit Risk Assessment
Updated contraception requirement for WOCBP and removed contraception requirement for males and added sections for “Women of Childbearing Potential” and “Pregnancy”.	Aligned with Pfizer standard and processes.	Section 5.2 Inclusion Criteria #3b Section 5.6 Contraception Section 12.3 Appendix 3 – Contraceptive and Barrier Guidance

Description of Change	Brief Rationale	Section #
		Former Section 5.6 Women of Childbearing PotentialRemoved
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
Non-substantial Modification(s)		
Modification of the wording of primary endpoints	1. Removed "physical examination" because physical examination abnormalities would be captured as AEs or medical history. 2. Modified "ECG, vital signs/physical measurements and clinical laboratory test data" to "ECG, vital signs/physical measurements and clinical laboratory test abnormalities".	Section 1 Section 3.2.1 Section 10.5.2
Clarification of descriptive summary method and addition of the 95% confidence interval (CI) method for the secondary endpoint.	1. Clarified that values, changes and percent changes from Observation Period would be descriptively summarized by total and severity. 2. Added that two-sided 95% CI would be derived based on normal distribution.	Section 10.5.3
Re-organization of protocol summary	Sponsor-required template.	Section 1
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
Modification of exclusion criterion 2b	Added cerebrovascular disease in the exclusionary condition to keep consistent throughout the paragraph.	Section 1 Section 5.3
Clarification of secondary endpoint	Clarified the language for secondary endpoint by specifying that it was change from Observation Period and would be broken down by total and severity	Section 1 Section 3.2.2

Description of Change	Brief Rationale	Section #
	to make it more accurate and clearer.	
Modification of exploratory endpoints	Modification on language of exploratory endpoints by specifying the percentage for Satisfaction with Medication (SM) and Clinical Global Impression-change (CGI-c) and total score for Migraine Disability Assessment (MIDAS) to make them more accurate and clearer.	Section 1 Section 3.2.3
Combined the sections of Study Objectives and Endpoints	Aligned with Pfizer protocol template	Section 3 Former section 4 removed
Added one pregnancy test at each Phone Visit	Added one pregnancy test (urine) at each Phone Visit (Week 20, 24, 32, 36, 44 and 48) to ensure the monthly pregnancy test for each WOCBP.	Section 4.3.2 Section 5.6 Section 6.1.4.2
Modified the description of study drug dispense.	Modified the description of study drug dispense to keep it consistent with footnote 8 of SOA.	Section 4.3.2
Modified the description of End of Trial	To clarify the definition of early termination and criteria of permenant termination.	Section 4.3.6
Definition of wash-out period of prophylactic migraine medication	Definition of wash-out period of prophylactic migraine medication prior to Screening Visit.	Section 5.2 2f Section 5.5
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 Concomitant Medications
Modified the description of efficacy assessment	Removed the sentence of analysis method, and added some texts about how daily migraine will be assessed via eDiary by total and severity.	Section 6.2.1
Change in study drug storage condition.	Removed humidity from study drug storage conditions.	Section 7.1.2
Clarified study drug destruction	Updated destination for study drug destruction	Section 7.5
Change in follow up of AEs/SAEs	Each event should be followed.	Section 8.6

Description of Change	Brief Rationale	Section #
Definition of mapping rule of AE causality	Definition of mapping rule of AE causality between the five-point method and binary method following the guideline of Health Authority.	Section 8.9
Change in SAE reporting destination and electronic reporting system.	Incorporation of non-substantial changes described in previous PACL dated 28 Apr 2023.	Section 8.10 Section 8.11
Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure	Aligned with Pfizer protocol template	Section 8.11
Deletion of texts about statistical test	The texts "all statistical tests will use a test with α=0.05" was deleted as no hypothesis was planned in this study.	Section 10.1
Clarification of sample size rationale	The rationales for study sample size of 233 and interim analysis with 175 participants are added.	Section 10.2 Section 10.3
Modification to the analysis sets	The per protocol set was removed and efficacy analysis set was added	Section 10.4.2
Clarification of safety analysis method	1. Removed the analysis which says "Changes in safety parameters such as laboratory tests and physical examination from baseline will be summarized using cross-tabulations before and after treatment." 2. Added the analyses for liver function test, and abnormality summaries for ECG, vital signs, and laboratory test.	Section 10.5.2
Modification of analyses methods for the secondary endpoints	Added the sentence of analysis method.	Section 10.5.3
Modification of analyses methods for the exploratory endpoints	1. Removed the sentence mentioning appropriate descriptive statistics. 2. Clarified that the normal distribution would be used to	Section 10.5.4

Description of Change	Brief Rationale	Section #
	construct the 95% CIs for continuous endpoints. 3. Added exact Clopper-Pearson method to construct the 95% CIs for categorical endpoints.	
Reorganized the section numbers of Supporting Documentation And Operational Considerations	Aligned with Pfizer protocol template.	Former Section 11-Section 17
Added Pfizer standard text for Data Protection.	Aligned with Pfizer protocol template.	Section 11.2.3
Added Pfizer standard text for Dissemination of Clinical Study Data.	Aligned with Pfizer protocol template.	Section 11.4
Added definition of Sponsor's Medically Qualified Individual.	Aligned with Pfizer protocol template.	Section 11.4
Removed the contact information of sponsor.	Removed the redundant information.	Former Section 17.5.1
Addition of Brief Title	As required by Sponsor Template and in scope of posting on clinicaltrials.gov, pfizerclinicaltrials.com and on advocacy and other websites that potential participants may visit as they consider clinical trial participation.	Page 1
Update of List of Abbreviations	Editorial	List of Abbreviations
Update of references	Editorial	Section 13
Removed PI declaration page	Aligned with Pfizer protocol template	Former PI declaration page removed.
Removed protocol approval form	This page is not required by the relevant Sponsor’s SOPs.	Former Protocol approval form removed.
Updated document header and footer	Updated to align with Pfizer protocol template	Header and Footer
Administrative edits and correction of typos	Some administrative edits/clarifications were made and typographical errors were corrected.	Throughout the document.

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LIST OF ABBREVIATIONS

English abbreviation	English full name
ACS	acute coronary syndrome
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
BUN	blood urea nitrogen
BYOD	bring your own device
CGI-c	clinical global impression – change
CGRP	calcitonin gene-related peptide
CI	confidence interval
CK	creatine kinase
COVID-19	Coronavirus 2019
CPK	creatine phospho kinase
CRA	Clinical Research Associate/Assistant
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTCAE	common terminology criteria for adverse events
CTIS	Clinical Trials Information System
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth edition
DSU	Drug Safety Unit
EAS	efficacy analysis set
ECG	electrocardiogram
eCRF	electronic case report form

English abbreviation	English full name
EDB	exposure during breastfeeding
EDC	electronic data capture system
eDairy	electronic dairy
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EOD	every other day
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice
HbA1c	hemoglobin a1c
HBcAb	hepatitis b core antibody
HBeAb	hepatitis b e antibody
HBeAg	hepatitis b e-antigen
HBsAb	hepatitis b surface antibody
HBsAg	hepatitis b surface antigen
HBV DNA	hepatitis b virus deoxyribonucleic acid
HCV	hepatitis c virus
HIV	human immunodeficiency virus
ICMJE	International Committee of Medical Journal Editors
IA	interim analysis
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional review board
ISF	Investigator Site File
IV	intravenous injection

English abbreviation	English full name
LDH	lactate dehydrogenase
LFT	liver function test
LTT	long-term treatment
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MIDAS	migraine disability assessment
MQI	medically qualified individual
MSQoLQ	migraine-specific quality of life questionnaire
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
ODT	orally disintegrating tablet
OP	observation period
PCI	percutaneous coronary intervention
PoM	preference of medication
PPS	per protocol set
PRN	pro re nata
PSSA	Pfizer SAE Submission Assistant
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SM	satisfaction with medication
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
SS	safety set
SUSAR	suspected unexpected serious adverse event
TEAE	treatment emergent adverse event

English abbreviation	English full name
TIA	transient ischemic attack
UK	United Kingdom
ULN	upper limit of normal
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Tittle: An Interventional, Phase 3, Single-Arm, Open label Study to Investigate Long-Term Safety of Rimegepant Orally Disintegrating Tablets for the Acute Treatment of Migraine in Chinese Participants

Brief Title: A study to learn about the long-term safety of rimegepant for the acute treatment of migraine in Chinese Participants

Regulatory Agency Identification Number(s):

US IND Number:	N/A
EudraCT/EU CT Number:	N/A
ClinicalTrials.gov ID:	NCT05371652
Pediatric Investigational Plan Number:	N/A
Protocol Number:	BHV3000-318 (Pfizer C4951018)
Phase:	3

Rationale: A multicenter, open-label study to assess the safety and tolerability of rimegepant 75 mg ODT (PRN administration, up to 1 tablet per day in mild to severe migraine attacks) for the treatment of acute migraine for up to 52 weeks. This study is designed to provide long-term safety data in Chinese participants of rimegepant 75 mg dose for the acute treatment of migraine.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
To evaluate the long-term safety and tolerability of 75 mg rimegepant ODT [dosed as needed (PRN)].	Adverse events, common adverse events (incidence ≥ 5%), serious adverse events, adverse events leading to study drug discontinuation, etc.; ECG, vital signs/physical measurements and clinical laboratory test abnormalities.
Secondary:	**Secondary:**
To evaluate the number of migraine days and severity of migraine attacks during long-term treatment with 75 mg rimegepant ODT (PRN) in participants compared to the Observation Period.	Change from Observation Period in the number of migraine days by total and moderate or severe pain intensity for every 4-week interval and overall period during long-term treatment with 75 mg rimegepant ODT.

Overall Design:
This is a multicenter, open-label study to assess the safety and tolerability of long-term use of 75 mg rimegepant ODT, dosed as PRN, taken up to one tablet per calendar day, in Chinese participants with migraine.

The Screening phase includes a Screening Visit and a 30-day Observation Period (OP). For participants to be eligible for the study, they must have 6-18 migraine attacks of moderate to severe intensity per month in the 3 months prior to the Screening Visit.

Upon the completion of the Screening Visit, participants will be provided an electronic diary (eDiary) to document each day of the 30-day Observation Period if a migraine occurrs, the intensity of each migraine attack and if the migraine is treated. Participants will record the standard of care migraine treatment received on a personal device APP (BYOD, Bring Your Own Device). After the completion of the 30-day OP, participants will return to the clinic for the Baseline Visit. At the Baseline Visit, eligibility for the continuing participation in the study will be assessed before study medication is dispensed. Participants need have at least 6 migraine days during the 30-day OP to be eligible and women of childbearing potential (WOCBP) must have a negative pregnancy test result prior to dispensing study drug. After the investigator reviews the results of the baseline laboratory assessments and determines the participant's eligibility, the site staff will inform the participant whether or not he/she is eligible to start dosing in the Long-Term Treatment Phase (LTT). The eligible participants will be instructed that they can take a maximum of one tablet of rimegepant per calendar day during the 52-week Long-Term Treatment Phase at the onset of a migraine (of mild to severe intensity).

Participants are required to record their migraine occurrence and severity via eDiary, and all study medication dose and standard of care migraine treatment taken via BYOD. Participants will also use BYOD to complete the Preference of Medication (PoM) questionnaire and the Satisfaction with Medication (SM) questionnaire at specified study visits.

At select study visits, participants will complete or will be administered the Migraine-specified Quality-of-Life Questionnaire v 2.1 (MQoLQ), the Migraine Disability Assessment (MIDAS), and Clinical Global Impression-change (CGI-c) scale in the paper scales provided by study site.

Additional assessments and visit schedule are outlined in the Schedule of Activities in Section 4.3. Activities include study personnel review of the eDiary and BYOD with the participant, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). Study visits will be approximately every 4 weeks until Week16 and then every 12 weeks for on site visits + every 4 weeks phone calls in between every two on site visits until Week 52.

Participants will return to the study site at the end of Week 52 (+/- 7 days) for the End of Treatment (EOT) Visit. There is a Follow-up Visit 14 days (+/- 2 days) after the Week 52/EOT Visit.

Number of Participants: Approximately 330 participants will be screened to enroll approximately 240 participants to receive rimegepant treatment.

Study Population:

Key Inclusion Criteria

- Participant has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, beta version. [1, 2]
- Age of onset of migraines prior to 50 years of age.
- Migraine attacks, on average, lasting 4 - 72 hours if untreated.
- 6-18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit.
- 6 or more migraine days requiring treatment during Observation Phase.
- Ability to distinguish migraine attacks from tension/cluster headaches.
- Participants on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable dose for at least 2 months prior to the Baseline Visit, and the dose is not expected to change during the course of the study. Participants who previously discontinued prophylactic migraine medication must have done so at least 5 half-lives of the prophylactic medication prior to the Screening Visit.
- Participants with contraindications for use of triptans may be included provided they meet all other study entry criteria.

Key Exclusion Criteria

- Participants has a history of basilar migraine with brain stem aura or hemiplegic migraine.
- History of HIV disease.
- Current evidence of poorly controlled, unstable, or recently diagnosed cardiovascular or cerebrovascular disease such as ischemic heart disease, coronary vasospasm, and cerebral ischemia. Myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke, or transient ischemic attack (TIA) during 6 months prior to screening.
- Poorly controlled hypertension (high blood pressure) or poorly controlled diabetes (but participants with stable hypertension and/or diabetes for at least 3 months prior to

screening may be included in the study). Blood pressure greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest is exclusionary.

- Participants with a current diagnosis of major depression or a major depressive episode within the last 12 months, other pain syndromes, psychiatric disorders, dementia, or significant neurological disorders (other than migraine) that, in the opinion of the investigator, might interfere with study assessments.

- History of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric water ball, etc.) or diseases resulting in malabsorption.

- Participant has a history or diagnosis of Gilibert's Syndrome or any other active hepatic or biliary disorder.

- History or presence of significant and/or unstable medical conditions (e.g., history of congenital heart disease or cardiac arrhythmia, known suspected infection, hepatitis B or C or neoplasm) that, in the opinion of the investigator, would expose the participants to undue risk of a significant adverse events (AE) or interfere with the assessment of safety or effectiveness during the trial.

- History or evidence of alcohol or drug abuse within the past 12 months, or treatment for alcohol or drug abuse, or meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for any significant substance abuse disorder within the past 12 months prior to the Screening Visit.

- Participants should be excluded if they have a positive drug screen for drugs of abuse and are considered medically significant by the investigator, would compromise participant safety, or interfere with the interpretation of study results.

- Diagnosis of hematologic or solid malignancy within 5 years prior to screening. Participants with a history of localized basal cell or squamous cell skin cancer may be included in the study if they are cancer-free prior to the Screening Visit for this study.

- Participants with a current diagnosis of schizophrenia, major depression requiring treatment with atypical antipsychotics, bipolar disorder or borderline personality disorder.

- Body mass index (BMI) $\geq$35 kg/m^2.

- Participants with a history of gallstones or cholecystectomy.

Study Arms and Duration: This is a single-arm study.

Statistical Methods:

The statistical analysis is mainly descriptive, and no formal hypothesis testing will be performed. In general, continuous variables will be descriptively summarized using n, mean,

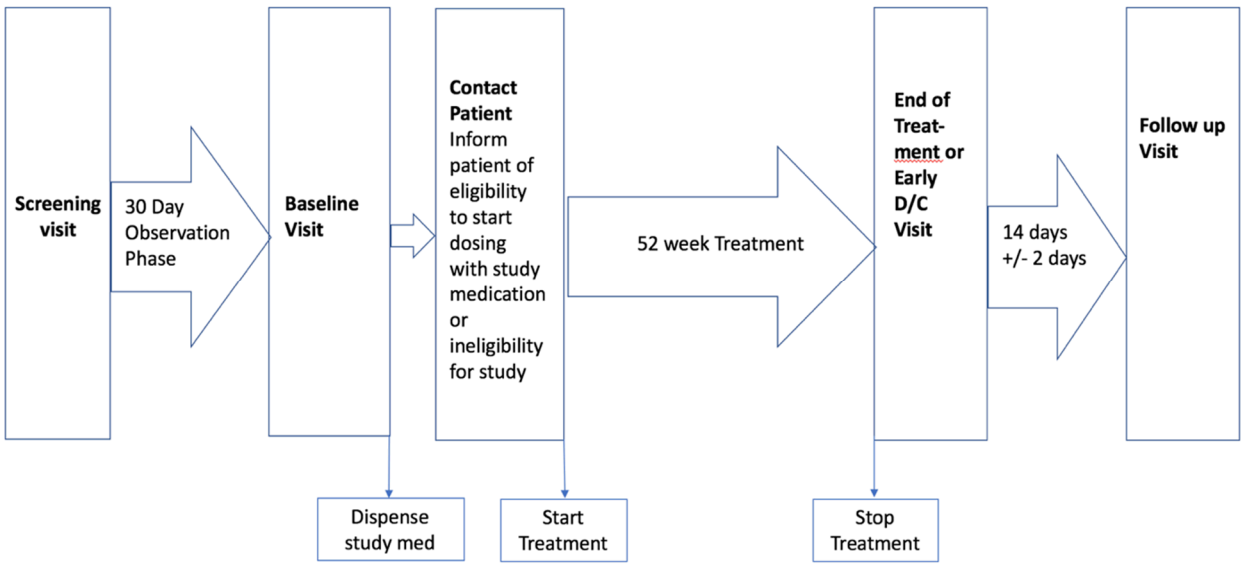
median, standard deviation, minimum and maximum; categorical variables and ordinal variables will be summarized using frequency and percentage of each category or grade.

Analysis of adverse events will be mainly based on treatment-emergent adverse events (TEAEs). All TEAEs, common TEAEs (incidence ≥5%), serious adverse events (SAEs), and TEAEs leading to study drug discontinuation will be summarized and analyzed by system organ class (SOC) and preferred term (PT). Vital signs, ECG parameters, and laboratory tests and their changes from baseline will be summarized by visit using descriptive statistics. The number and percentage of participants with abnormal ECG, vital signs, and laboratory test (according to CTCAE grade) will be presented. Liver function test (LFT) elevations will also be summarized with number and percentage of participants in pre-specified categories.

For continuous endpoints, two-sided 95% CIs based on normal distribution will be calculated, including change from OP in the number of migraine days, and exploratory endpoints defined based on MSQoLQ and MIDAS. For categorical and ordinal endpoints, two-sided exact Clopper-Pearson CIs will be calculated, including the exploratory endpoints defined based on PoM, SM, and CGI-c.

1.2. Study Schematic

Figure 1. Study Schema



2. INTRODUCTION AND RATIONALE

2.1. Therapeutic Area Background

Migraine is a chronic neurovascular disorder characterized by recurrent attacks and high severity. In adults, migraine attacks typically last 4 to 72 hours and are typically characterized by unilateral, pulsatile, moderate or severe in severity, exacerbated by daily physical activity, accompanied by nausea and/or photophobia and phonophobia.

Migraine is also a common disfunctional primary headache, which has a high prevalence in the population and can pose a significant burden to the socioeconomic and personal life Per 2017 Global Burden of Disease Survey, it was estimated that 151.6 million (139.9 million to 163.3 million) of Chinese had migraine, which was the second leading cause of disability for participants worldwide in 2016 [3,4]. In non-elderly adults, the prevalence of migraine in Chinese is about 14.3% [5]. Despite the increasing availability of drugs for the treatment of migraine, inadequate treatment, poor compliance and inadequate access to available drugs remain to be the current challenges.

Rimegepant (PF07899801 [Formerly BHV-3000]) is an oral small molecule calcitonin gene-related peptide (CGRP) receptor antagonist under development. CGRP is an endogenous 37-amino acid peptide from the pain conduction pathway and is thought to be one of the causes of migraine. A variety of clinical evidence suggests that CGRP plays a pathological and physiological role in triggering migraine: 1) serum levels of CGRP are increased in humans during migraine; 2) anti-migraine drugs can restore CGRP levels to normal while relieving pain; and 3) intravenous (IV) CGRP produces long-lasting pain in non-migraine participants and migraine participants. CGRP receptor antagonists relieve migraine symptoms by 1) blocking CGRP-induced neurogenic vasodilation (to normalize dilated intracranial arteries); 2) stopping the cascade of CGRP-induced neurogenic infections (resulting in peripheral sensitization); and, when possible, 3) inhibiting central transmission of pain signals from the trigeminal nerve to the trigeminal caudate. CGRP receptor antagonists reduce migraine symptoms by restoring dilated meningeal arteries to normal, and this process does not result in vasoconstriction.

2.2. Pharmaceutical 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.

As of 26 August 2022, more than 8900 unique participants have participated in Phase 1 studies in healthy participants or Phase 2 and 3 studies in participants with migraine or refractory trigeminal neuralgia, chronic rhinosinusitis, or temporomandibular disorders; of these, approximately 6036 unique participants have received rimegepant at any dose.

Collectively, the current data demonstrates a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine.

2.3. Study Rationale

Migraine is a chronic neurovascular disorder characterized by recurrent attacks that usually last 4 to 72 hours and is accompanied by a variety of symptoms, including typically unilateral, pulsatile, moderate, or severe pain intensity, accompanied by nausea or vomiting, and/or sensitivity to sound (phonophobia) and sensitivity to light (photophobia). The 2016 Global Burden of Disease Survey ranked migraine as the sixth most prevalent disease and the second leading cause of disability worldwide [3, 4]. About 14.3% of adults in China suffer from migraine [5].From 1990 to 2017, the number of headache cases and participants with disabilities in the Chinese population has increased significantly, and most of them are young or middle-aged, but headache treatment is not directly and effectively improved during this period, resulting in a huge health burden. More attention should be paid to the problem[3].

In part, this burden is attributable to the limitations of the current standard medical therapy, i.e., having known cardiovascular disease as well as multiple other cardiovascular risk factors are contraindications to these standard drugs. The prescribing information for triptans includes warnings and precautions for migraineurs with cardiovascular risk factors and states: participants with high risk factors (risk factors include older age, diabetes, hypertension, smoking, obesity, or family history of coronary artery disease) should be evaluated before receiving the first dose of triptans. Triptans are contraindicated in participants with a history of ischemic heart disease, coronary vasospasm, history of stroke, peripheral vascular disease, or poorly controlled hypertension. Even in participants with negative cardiovascular assessments, the package insert for triptans recommends performing the first dose in an environment supervised by a medical professional and examining immediately after dosing. In addition, regular cardiovascular assessment should be considered in participants with cardiovascular risk factors and long-term use of triptans.

Since the first entry of triptans into China in the 1990s, there have been no new drugs approved for the acute treatment of migraine in China. Thus, there remains significant unmet medical needs for novel migraine-specific agents that do not increase cardiovascular risk.

Rimegepant is a small molecule CGRP receptor antagonist under development for the acute phase treatment of migraine, which will address the cardiovascular limitations described above. Clinical and nonclinical studies have shown that rimegepant does not cause adverse vasoconstriction (these adverse vasoconstrictions are thought to cause serious cardiovascular adverse events with triptans) and that its mechanism of action is different from that of other drugs causing cardiovascular problems such as non-steroidal anti-inflammatory drugs (NSAIDs) and ergotamine derivatives. A Phase 2b dose-finding study showed that rimegepant 75 mg was the lowest effective dose and no incremental efficacy benefit was observed at the 150 mg, 300 mg, or 600 mg dose levels. The adequate efficacy of the selected dose of rimegepant 75 mg compared to placebo was demonstrated in 3 subsequent pivotal Phase 3 studies for the treatment of acute migraine, with statistically significant efficacy of rimegepant observed for the primary and numerous endpoints in each pivotal study, as detailed in the most recent version of the IB.

The proposed long-term safety and tolerability study per this protocol will provide further safety data on rimegepant for the treatment of acute migraine in Chinese participants and bridge the existing complete clinical data on rimegepant 75 mg in the treatment of acute migraine. Therefore, this study serves a broad purpose of the rimegepant clinical development program: to confirm the safety, tolerability, and effectiveness of rimegepant for the treatment of acute migraine with or without aura in adults.

2.3.1. Study Design Rationale

A multicenter, open-label study to assess the safety and tolerability of rimegepant 75 mg ODT (PRN administration, up to 1 tablet per day in mild to severe migraine attacks) for the treatment of acute migraine for up to 52 weeks. This study is designed to provide long-term safety data in Chinese participants of rimegepant 75 mg dose for the treatment of migraine.

Approximately 330 participants will be screened for this study and approximately 240 of these participants will be assigned to treatment with 75 mg rimegepant ODT.

2.3.2. Dose Selection Rationale

The current Phase 2b dose finding study (CN170003) has demonstrated a comprehensive and durable efficacy profile for rimegepant at the 75 mg dose, but not at lower doses (eg, 10 mg or 25 mg). 75 mg was selected as the optimal dose to support the Phase 3 clinical trials because the higher doses (150 mg, 300 mg, 600 mg) showed a similar efficacy profile to 75 mg and did not increase benefit. Adequate efficacy of rimegepant 75 mg compared to placebo was also demonstrated in 3 subsequent pivotal Phase 3 studies (BHV3000-301, BHV3000-302, and BHV3000-303), with statistically significant efficacy compared to placebo observed for rimegepant 75 mg across the primary and numerous endpoints in each pivotal study.

At present, the clinical safety results in an open, long-term safety study (BHV3000-201) indicate that multiple doses of rimegepant 75 mg in migraine participants are well tolerated with a good safety profile within up to 52 weeks.

2.4. Study Hypothesis

In the treatment of participants with acute migraine, long-term use of 75 mg rimegepant ODT (up to 1 tablet per day, PRN use) is safe and well tolerated.

2.5. Risk and Benefit 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 1500 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 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 participants with episodic migraine, the potential risks associated with rimegepant are justified by the anticipated benefits that may be afforded to participants 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. Participants 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. Participants are excluded if there is uncontrolled, unstable, or recently diagnosed cardiovascular disease or hypertension. Participants 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 IB, which is the SRSD for this study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

- To evaluate the long-term safety and tolerability of 75 mg rimegepant ODT (PRN).

3.1.2. Secondary Objectives

- To evaluate the number of migraine days and severity of migraine attacks during long-term treatment with 75 mg rimegepant ODT (PRN) in participants compared to the Observation Period.

3.1.3. Exploratory Objectives

- To evaluate the effect of 75 mg rimegepant ODT treatment compared to baseline on the 14-Item MSQoLQ version 2.1.
- To evaluate the effect of 75 mg rimegepant ODT treatment on the PoM.
- To evaluate the effect of 75 mg rimegepant ODT treatment on the Satisfaction with Medication survey.
- To evaluate the effect of 75 mg rimegepant ODT treatment compared to baseline on the MIDAS.
- To evaluate the effect of 75 mg rimegepant ODT treatment on the CGI-c scale.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Adverse events, common adverse events (incidence ≥5%), serious adverse events, adverse events leading to study drug discontinuation, etc.; ECG, vital signs/physical measurements and clinical laboratory test abnormalities.

3.2.2. Secondary Endpoints

- Change from Observation Period in the number of migraine days by total and moderate or severe pain intensity for every 4-week interval and overall period during long-term treatment with 75 mg rimegepant ODT.

3.2.3. Exploratory Endpoints

- Change from baseline in results assessed with the 14-item MSQoLQ version 2.1 following treatment with 75 mg rimegepant ODT;
- Percentage of participants in each of 3 preference categories of the assessment with Migraine PoM for migraine following treatment with 75 mg rimegepant ODT;
- Percentage of participants in each of 7 satisfaction categories of the Satisfaction with Medication survey following treatment with 75 mg rimegepant ODT;
- Change from baseline in total score of the MIDAS following treatment with 75 mg rimegepant ODT;
- Percentage of participants in each of 7 categories of the CGI-c scale after treatment with 75 mg rimegepant ODT.

4. STUDY PLAN

4.1. Overall Design and Duration

This will be a multi-center, open-label, long-term safety study of BHV3000 for the treatment of acute migraine in Chinese participants to provide the long-term safety data in Chinese participants to bridge the existing comprehensive clinical trial data of rimegepant 75 mg dose in migraine. Approximately 240 adult participants were planned to be enrolled to receive 75 mg of rimegepant ODT (PRN use, up to 1 tablet per day).

The screening period will be consisted of a Screening Visit and a 30-day Observation Period. Participants must have a history of 6 to 18 moderate to severe migraine attacks per month within 3 months prior to the Screening Visit in order to meet the entering criteria of this study.

Upon the completion of the Screening Visit, participants will be provided an electronic diary (eDiary) to document each day if a migraine occurrs, the intensity of each migraine attack and if the migraine is treated for the 30-day Observation Period. Participants will record the standard of care migraine treatment received via BYOD. After completing the 30-day Observation Period, the participant will return to the clinic with both records for the Baseline Visit. At the Baseline Visit, eligibility for continued participation in the study will be assessed before study medication will be dispensed. At the Baseline Visit, eligibility for continued participation in the study will be assessed, and eligibility will be determined as much as possible prior to dispensing study drug, participant need have least 6 migraine days during the 30-day Observation Period to be eligible and WOCBP must have a negative pregnancy test result prior to dispensing study drug. After the investigator reviews the results of the baseline laboratory assessments and determines the participant's continued eligibility, the site staff will inform the participant whether or not he/she is eligible to start dosing in the Long-Term Treatment phase. If eligible for the Long-Term Treatment Phase, participants will be instructed that they can take study medication at the onset of a migraine (of mild to severe intensity). Participants will be instructed that they can take a maximum

of one tablet of rimegepant per calendar day during the 52-week Long-Term Treatment phase at the onset of a migraine (of mild to severe intensity).

Participants are required to record their migraine occurrence and severity in the eDiary, to record all study medication doses via BYOD. Participants are also required to continue to record the standard of care migraine treatment taken via BYOD. Participants will also use BYOD to complete the PoM questionnaire and the Satisfaction with Medication questionnaire at specified study timepoints.

At select study visits, participants will complete or will be administered the MQoLQ version 2.1, MIDAS, and CGI-c scale.

Additional assessments and visit schedule are outlined in the procedural table in Section 4.3 Procedures include study personnel review of the eDiary and BYOD with the participant, assessment of study medication compliance, monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). Study visits will be approximately every 4 weeks until Week16 and then every 12 weeks for on site visits + every 4 weeks phone calls in between every two on site visits until Week 52.

Participants will return to the study site at the end of Week 52 (±7 days) for the End of Treatment (EOT) Visit. There is a Follow-up Visit 14 days (±2 days) after the Week 52/EOT Visit.

4.2. Study Schematic

Refer to Section 1.2.

4.3. Schedule of Activities

Table 1. Assessment Schedule

Procedure	Screening Visit	Observational Period (30 days, ±2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on Clinical Laboratory Findings[1]	Weeks 4, 8, 12 (all visits ±3 days)	Weeks 16, 28, 40, 52 (or Early Termination) (all visits ±7 days)	Phone visits Weeks 20, 24, 32, 36, 44, 48(all visits ±7 days)	Follow-up Safety Visit (14 days after EOT visit ±2 days)
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X		X	X				
Medical History	X							
Migraine History (signs/symptoms /frequency/intensity)	X							
Serum virology test	X							
Demographic information	X							
Prophylactic and standard of care migraine medication recorded / Concomitant Medication via BYOD[2]		X	X		X	X	X	X[3]
Safety Assessments								
Physical Examination	X		X			X (Weeks 28 and 52/early termination only)		
Vital Signs/Physical Measurements[4]	X		X		X	X		X

Table 1. Assessment Schedule

Procedure	Screening Visit	Observational Period (30 days, ±2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on Clinical Laboratory Findings[1]	Weeks 4, 8, 12 (all visits ±3 days)	Weeks 16, 28, 40, 52 (or Early Termination) (all visits ±7 days)	Phone visits Weeks 20, 24, 32, 36, 44, 48(all visits ±7 days)	Follow-up Safety Visit (14 days after EOT visit ±2 days)
Clinical Safety Laboratory Testing	X		X		X	X		X
Lipid Panel			X			X (Weeks 28 and 52/early termination only)		
ECG	X		X			X (Weeks 28 and 52/early termination only)		X
Urinalysis	X		X			X (Week 52/early termination only)		
Urine Drug Screen for drugs of abuse	X							
FSH, if applicable, to determine WOCBP status[5]	X							
Pregnancy Test[6]	X (urine)		X (urine and serum)		X(urine)	X (urine)	X (urine)	X (urine)
AE and SAE assessment[7]	X	X	X		X	X	X	X
Clinical Drug Supplies/Study Supplies								
Dispense Study Medication[8]			X		X	X		

Table 1. Assessment Schedule

Procedure	Screening Visit	Observational Period (30 days, ±2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on Clinical Laboratory Findings[1]	Weeks 4, 8, 12 (all visits ±3 days)	Weeks 16, 28, 40, 52 (or Early Termination) (all visits ±7 days)	Phone visits Weeks 20, 24, 32, 36, 44, 48(all visits ±7 days)	Follow-up Safety Visit (14 days after EOT visit ±2 days)
Administer study medication[9]				X	X	X	X	
Enter use of study medication via BYOD				X	X	X	X	
Return unused study medication to site for compliance check					X	X		
Dispense eDiary	X							
Install BYOD APP	X							
Return eDiary and review e Diary and BYOD of completion for completeness[10]			X		X	X		
Other Assessments								
Daily recording of migraine attacks and their severity by eDiary[11]		X	X		X	X	X	
Migraine Specified Quality of Life Questionnaire (MQoLQ) v 2.1			X		X (Weeks 12 only)	X (Weeks 28, 40 and 52/early termination only)		

Table 1. Assessment Schedule

Procedure	Screening Visit	Observational Period (30 days, ±2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on Clinical Laboratory Findings[1]	Weeks 4, 8, 12 (all visits ±3 days)	Weeks 16, 28, 40, 52 (or Early Termination) (all visits ±7 days)	Phone visits Weeks 20, 24, 32, 36, 44, 48(all visits ±7 days)	Follow-up Safety Visit (14 days after EOT visit ±2 days)
Preference of Medication (PoM)						X (Weeks 28 and 52/early termination only)		
Satisfaction with Medication (SM) Survey						X (Weeks 28 and 52/early termination only)		
Clinical Global Impression – change (CGI-c)						X (Weeks 28 and 52/early termination only)		
Migraine Disability Assessment (MIDAS)			X		X (Weeks 12 only	X (Weeks 28, 40 and 52/early termination only)		

1. Eligibility must be confirmed based on clinical laboratory test results at baseline and migraine occurrence during the observational period before the first dose of study drug. Site staff must notify participants by telephone of study eligibility before the participant takes his/her first dose of study drug.
2. All concomitant medications, including prophylactic and standard of care migraine medications, as well as medications taken during the observation and Long-Term Treatment Periods, should be recorded via BYOD and reviewed by study personnel at each study visit.
3. Collect required concomitant medications due to AEs and collect concomitant medications associated with AEs.
4. Height will be measured at the Screening Visit only. Participant weight, temperature, respiratory rate, blood pressure, will be collected at all time points indicated. Sitting systolic and diastolic arterial blood pressure and pulse rate will be measured.
5. If the participant has confirmed the status of WOCBP in the BHV3000-310 trial, the participant is acknowledged to have the same status in this study.

Table 1. Assessment Schedule

Procedure	Screening Visit	Observational Period (30 days, ±2 days)	Baseline Visit (Day 1)	Phone visit to confirm eligibility based on Clinical Laboratory Findings[1]	Weeks 4, 8, 12 (all visits ±3 days)	Weeks 16, 28, 40, 52 (or Early Termination) (all visits ±7 days)	Phone visits Weeks 20, 24, 32, 36, 44, 48(all visits ±7 days)	Follow-up Safety Visit (14 days after EOT visit ±2 days)

6. Upon completion of the Baseline Visit, WOCBP will be provided with urinary pregnancy test kits so that participants can test at home if necessary. When WOCBP participants cannot confirm pregnancy status, a urine pregnancy test must be completed at home before taking study drugs.
7. All SAEs and AEs must be reported by the participant after signing the informed consent.
8. To be determined to be eligible prior to dispensing study drug, participants must have a history of migraine attacks for at least 6 days during the 30-day Observation Period and WOCBP must have a negative pregnancy test result prior to dispensing study drug. Week 4, 8, 2: dispensing 3 wallets to the participant on the monthly visits. Week 16, 28, 40: according to the participant's need to dispense wallets, maximum is 7 wallets. The study drug will not dispense at Week 52 as that is EOT.
9. Participants will be instructed that they can take the study medication at the time of their migraine attack (mild, moderate, or severe), up to 1 tablet per day. The participant must record in the BYOD the study drug taken for each tablet.
10. If a participant lacks 6 or more eDiary reports per month for 2 months (continuous or non-continuous), the participant's continued participation in the study should be terminated due to lack of compliance.
11. The eDiary will be dispensed at the Screening Visit after the participant has completed all screening procedures. Participants will be trained in the use of the eDiary. Participants will use eDiary daily during the observation and Long-Term Treatment Periods to record migraine attacks, migraine severity, and whether they receive migraine treatment.

4.3.1. Screening Visit, Observation Period (30 days ±2 days)

The participant or his/her guardian must sign the informed consent form voluntarily in writing before participating in the screening. Approximately 330 participants will be screened for this study to allow approximately 240 participants to receive treatment of rimegepant.

The main procedures or tests to be completed by the participant at the Screening Visit include:

- Signing the informed consent form;
- Evaluation of inclusion/exclusion criteria;
- Collection of migraine history (signs/symptoms/frequency/intensity) and other medical history;
- Serum virological examination;
- Demographic information;
- Physical examination;
- Vital signs/physical measurements;
- Clinical safety laboratory tests;
- ECG;
- Urine routine;
- Urine drug screen;
- FSH (if applicable);
- Urine pregnancy;
- AE and SAE assessments;
- Dispense eDiary
- Install BYOD APP in the participant mobile phone.

The eDiary will be dispensed and BYOD APP will be installed after the participant has completed all screening procedures at the Screening Visit and the eDiary will be used to record migraine attacks and their severity on a daily basis during the Observation Period, as well as whether they received migraine treatment. BYOD will be used to record prophylactic or standard of care migraine medications/concomitant medications. Participants will be

trained in the use of eDiary and BYOD. Height in the physical measurements will only be measured at the Screening Visit. If a participant's WOCBP status has been confirmed in the BHV3000-310 trial, the participant is recognized to have the same status in this study and a repeat FSH test is not required.

During the Observation Period (30 days ±2 days), the main procedures or examinations to be completed by the participant include:

- Recording prophylactic and standard of care migraine medications/concomitant medications via BYOD;
- AE and SAE assessments;
- Daily recording of migraine attacks and their severity by eDiary.

4.3.2. Long-term Treatment Period (52 weeks)

After completing the 30-day Observation Period, the participants will return to the clinical site for the Baseline Visit (Day 1). The main operations or examinations to be completed by the participants included:

- Evaluation of inclusion/exclusion criteria;
- Recording prophylactic and standard of care migraine medications/concomitant medications via BYOD;
- Physical examination;
- Vital signs/physical measurements;
- Clinical safety laboratory tests;
- Lipid panel
- ECG;
- Urine routine;
- Pregnancy test (urine and serum);
- AE and SAE assessments;
- Dispense study drug;
- Return eDiary and review eDiary and BYOD of completion for completeness;
- Daily recording of migraine attacks and their severity by eDiary;

- MSQoLQ version 2.1;
- MIDAS.

After the completion of the relevant items at the Baseline Visit (Day 1), before the participants take the study drug for the first time, the clinical site staff should confirm the eligibility of the participants for participating in the study based on the examination results at the Baseline Visit, and inform the participants by telephone of the eligibility results. The participants who meet all the inclusion criteria and do not meet the exclusion criteria can participate in the trial. Participants confirmed to be eligible by a telephone visit may start taking the study drug, rimegepant 75 mg (up to 1 tablet per day) at the time of a migraine attack (mild, moderate, or severe) and record the use of the study drug with BYOD.

Participants will make site visits at Weeks 4, 8, 12 (±3 days) and Weeks 16, 28, 40, 52 (±7 days) or Early Termination of the trial and telephone visits at Weeks 20, 24, 32, 36, 44, 48 for the Long-Term Treatment Period as follows:

- Recording prophylactic and standard of care migraine medications/concomitant medications via BYOD;
- Physical examination (Weeks 28 and 52 or early termination);
- Vital signs/physical measurements (at each site visit);
- Clinical safety laboratory tests (at each site visit);
- Lipid panel (at Weeks 28 and 52 or early termination);
- Electrocardiogram (at Weeks 28 and 52 or early termination);
- Urine routine (Week 52 or early termination);
- Urine pregnancy (at each site visit and at each telephone visit);
- AE and SAE assessments (at each site visit and at the telephone visit);
- Dispense study drug (at each site visit);
- Take the study drug;
- Record the use of study medication via BYOD;
- Return unused study drug for compliance check (at each site visit);
- Return eDiary and review eDiary and BYOD of completion for completeness (at each site visit);

- Daily recording of migraine attacks and their severity by eDiary;
- MSQoLQ Version 2.1 (at Weeks 12, 28, 40, 52, or early termination);
- Migraine PoM for migraine (Week 28 and Week 52 or at early termination);
- Satisfaction with Medication survey (Week 28 and Week 52 or Early Termination);
- CGI-c scale (at Weeks 28 and 52 or early termination);
- MIDAS (at Weeks 12, 28, 40, 52 or early termination).

Upon completion of the Baseline Visit, WOCBP will be provided with urinary pregnancy test kits so that participants can test at home if necessary. When WOCBP participants cannot confirm pregnancy status, a urine pregnancy test must be completed at home before taking study drugs.

During the treatment period, participants have to use the last bottle of study drug before opening a new bottle of study drug. Three wallets of study drug will be dispensed to the participants at each visit of Week 4, Week 8, and Week 12. Study drug will be dispensed at Week 16, Week 28, Week 40 visits as needed, the maximum dispensing limit for each visit is 7 bottles per participant. Study drug will be dispensed at site visits as needed. Dispensing of study drug may also occur at unscheduled visits as needed.

If a participant lacks 6 or more diary reports per month for 2 months (continuous or non-continuous), the participant's continued participation in the study should be terminated due to lack of compliance.

4.3.3. End of Treatment (Week 52)

Participants will have an End-of-Treatment Visit at Week 52 (±7 days) when they have completed the trial or at early termination.The site personnel will review the eDiary, assess concomitant medications, and complete participant safety tests (including physical examination, vital signs/physical measurements, clinical laboratory tests, lipid panel, pregnancy tests, and ECGs). Participants will return unused study drug and eDiray to the site.

4.3.4. Safety Follow-up

Participants will return to the clinical study site 14 days (±2 days) after the end of treatment. The main assessments or examinations to be completed for the participants include:

- Recording prophylactic and standard of care migraine medications/concomitant medications via BYOD;
- Vital signs/physical measurements;
- Clinical safety laboratory tests;

- ECG;
- Urine pregnancy;
- AE and SAE assessments;

Concomitant medications required for AEs and associated with AEs will be collected during the safety follow-up period.

4.3.5. Unplanned Visit

In consideration of the safety of the participants, the investigator may require the participants to conduct additional visits or examinations. Results of unscheduled visits or examinations will be recorded on the eCRF.

4.3.6. End of Trial

The end of the trial includes the completion of the trial and early termination of the trial. If either of these situation happens, the trial will be ended, and all participants will complete/discontinue from the trial with no further treatment.

Trial completion is defined as the time when the last participant completes the last visit and the sponsor has the right to terminate the trial at any timepoint throughout the trial for reasonable reasons.

Early termination of the trial implies that not all participants have completed all the scheduled procedures according to the protocol, and the entire trial or a part of the trial (such as a certain site) is terminated. The purpose of premature termination is to protect the rights and interests of participants, ensure the quality of the trial, and avoid unnecessary economic losses.

In general, the trial will not be terminated prematurely. However, the entire trial (or a certain site) can be terminated prematurely if any of the following situations occurs:

1 The total sample size is achieved as a result of competitive enrollment, while the site may have not completed the planned enrollment as per the contract or have completed the trial procedures for all of the participants;

2 The investigator in the site does not follow the protocol, Good Clinical Practice (GCP), etc.;

3 New informationis received, which indicates unfavorable risk-benefit of the investigational drug, including sufficient evidence suggesting lack of efficacy or unacceptable safety;

4 The sponsor considers it to be inappropriate to continue the clinical trial for medical, ethical or business reasons;

5 Enrolling participants is slow, and it is impossible to complete the study within an acceptable time period;

6 The regulatory authority or ethics committee requests termination of the trial for certain reason.

4.4. COVID-19 Emergencies

If a participant is unable to come to the site for a visit due to the COVID-19 pandemic, it is acceptable to conduct remote visits on a case-by-case basis, but the investigator should first contact the sponsor medical monitor (or designee) to discuss the most appropriate of action. If a laboratory test is required for a remote visit, the local laboratory may be used in place of the central laboratory test results and the results are to be obtained and reviewed by the investigator. Direct shipment of study drug to participants via an overnight tracked and certified courier is also permitted with the approval of the sponsor in advance.

4.5. Post-Study Treatment

At the end of the study, the investigator should give the participant appropriate standard treatment recommendations for migraine.

5. PARTICIPANT POPULATION

5.1. Number of Participants

Approximately 240 participants will be enrolled in this study. Participants who have participated in the BHV3000-310 study may be considered for this long-term safety study if they meet all of the criteria for this study, but this cannot be guaranteed.

5.2. Inclusion Criteria

1) Signing Informed Consent

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

2) Target Population

Participant has at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, beta version[1, 2], 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) 6-18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit

d) Six or more migraine days requiring treatment during Observation Phase

e) Ability to distinguish migraine attacks from tension/cluster headaches

f) Participants on prophylactic migraine medication are permitted to remain on therapy if the dose has been stable dose for at least 2 months prior to the Baseline Visit, and the dose is not expected to change during the course of the study. Participants who previously discontinued prophylactic migraine medication must have done so at least 5 half-lives of the prophylactic medication prior to the Screening Visit

g) Participants with contraindications for use of triptans may be included provided they meet all other study entry criteria

3) Age and Reproductive Status

a) Male or female participants ≥18 years;

b) Participant meets reproductive criteria. Refer to Appendix 3 for reproductive criteria for male (Section 12.3.1) and female (Section 12.3.2) participants.;

c) WOCBP must have a negative pregnancy test at the Baseline Visit prior to dispensing study drug;

4) Other Inclusion Criteria

a) No clinically significant abnormality identified on medical or clinical laboratory evalution. A participant 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 the exclusion criteria listed in Section 5.3).

5.3. Exclusion Criteria

1) Target Disease Exclusion

a) Participants has a history of basilar migraine with brain stem aura or hemiplegic migraine;

2) Medical History and Comorbidities

a) History of HIV disease

b) Current evidence of poorly controlled, unstable, or recently diagnosed cardiovascular or cerebrovascular disease such as ischemic heart disease, coronary vasospasm, and cerebral ischemia. Myocardial infarction (MI),

acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke, or transient ischemic attack (TIA) during 6 months prior to screening;

c) Poorly controlled hypertension (high blood pressure) or poorly controlled diabetes (but participants with stable hypertension and/or diabetes for at least 3 months prior to screening may be included in the study). Blood pressure greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest is exclusionary;

d) Participants with a current diagnosis of major depression or a major depressive episode within the last 12 months, other pain syndromes, psychiatric disorders, dementia, or significant neurological disorders (other than migraine) that, in the opinion of the investigator, might interfere with study assessments;

e) History of gastric or small intestinal surgery (including gastric bypass, gastric banding, gastric sleeve, gastric water ball, etc.) or diseases resulting in malabsorption;

f) Participant has a history or diagnosis of Gilibert's Syndrome or any other active hepatic or biliary disorder;

g) History or presence of significant and/or unstable medical conditions (e.g., history of congenital heart disease or cardiac arrhythmia, known suspected infection, hepatitis B or C or neoplasm) that, in the opinion of the investigator, would expose the participants to undue risk of a significant AE or interfere with the assessment of safety or effectiveness during the trial;

h) History or evidence of alcohol or drug abuse within the past 12 months, or treatment for alcohol or drug abuse, or meeting Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for any significant substance abuse disorder within the past 12 months prior to the Screening Visit [7];

i) Participants should be excluded if they have a positive drug screen for drugs of abuse and are considered medically significant by the investigator, would compromise participant safety, or interfere with the interpretation of study results. In addition:

   i. Participants with detectable levels of cocaine, amphetamines, and phencyclidine in drug abuse screening need to be excluded. Participants who are positive for amphetamines on the urine drug screen may have their urine samples evaluated for further analysis at the investigator’s discretion to rule out a false positive result

ii. Participants with detectable levels of marijuana during substance abuse screening may not be excluded if they do not meet DSM-V criteria for substance abuse or dependence in the participant's opinion as documented by the investigator, and a positive result does not signal a clinical condition that would impact the participant safety or interpretation of the study results.

j) Diagnosis of hematologic or solid malignancy within 5 years prior to screening. Participants with a history of localized basal cell or squamous cell skin cancer may be included in the study if they are cancer-free prior to the Screening Visit for this study;

k) Participants with a current diagnosis of schizophrenia, major depression requiring treatment with atypical antipsychotics, bipolar disorder or borderline personality disorder;

l) Body mass index (BMI) ≥ 35 kg/m^2;

m) Participants with a history of gallstones or cholecystectomy;

n) Use of St. John's Wort, products containing St. John's Wort, Coltsfoot root, or extracts within 14 days prior to the Baseline Visit;

o) Use of narcotic drugs such as opioids (e.g., morphine, codeine, oxycodone, and hydrocodone) within 2 days prior to the Baseline Visit.

3) Allergy and Adverse Reactions

a) History of drug or other allergy that, in the opinion of the investigator, would make the participant unsuitable for participation in the study.

4) Sex and Reproductive Status

a) Women of childbearing potential who are unwilling or unable to use an acceptable method of contraception or avoid pregnancy by abstinence for the entire study period and for up to 28 days after last dose of study medication;

b) Women who are pregnant or breastfeeding;

c) Women who have a positive pregnancy test result at screening or prior to study drug administration;

5) ECG and Clinical Laboratory Test Findings

a) Estimated glomerular filtration rate (eGFR) ≤ 40 mL/min/1.73 m^2 according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) study equation;

b) Corrected QT interval > 470 msec (QTc by method of Frederica) at Screening;

c) Left Bundle Branch block;

d) Right Bundle Branch Block with QRS duration ≥150 msec;

e) Intraventricular Conduction Defects with QRS duration ≥ 150 msec;

f) Serum bilirubin (Total, Direct or Indirect) >1 × ULN (Only abnormal values of between 1-1.5 × ULN may be repeated once for assessment of eligibility during the screening period);

g) Neutrophil count ≤1000/µL (or equivalent);

h) AST or ALT > 1 × ULN (Only abnormal values of between 1-1.5 × ULN may be repeated once for assessment of eligibility during the Screening Period.);

i) Glycosylated hemoglobin (HbA1c) >7%.

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated;

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

c) Lack of compliance and/or inability to complete the eDiary during the Observation Period. Lack of compliance was defined as more than 4 missed eDiary times during the Observation Period;

d) Participation in a clinical trial with a non-biologic investigational drug (other than rimegepant) within 30 days prior to the Screening Visit;

e) Participation in a clinical trial with a biological investigational drug within 90 days prior to the Screening Visit;

f) Participation in any other investigational clinical investigators while participating in this clinical study.

5.4. Prohibited Concomitant Medications

The medications listed below are prohibited starting at the Baseline Visit and during the 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;

4) Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone, and hydrocodone) was prohibited for at least 2 days prior to the Baseline Visit;

5) Use of acetaminophen or acetaminophen containing products for the treatment of non-headache symptoms is prohibited after the Baseline Visit. Any use of paracetamol or paracetamol-containing products for symptoms other than headache during the Observation Period must be discontinued at least 2 days before the Baseline Visit; paracetamol may be used during the Long-Term Treatment Period as a standard treatment for migraine, as described in Section 5.5.

6) Use of triptans is prohibited during the Long-Term Treatment Phase;

7) Use of marijuana is prohibited during the study;

8) Concomitant use of strong CYP3A4 inhibitors with rimegepant is prohibited during the study. If a strong CYP3A4 inhibitor is required (eg, with 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 strong CYP3A4 inhibitor. Please see Appendix 1 Section 12.1.

9) Concomitant use of strong CYP3A4 inducers with rimegepant is prohibited during the study. If use of a strong CYP3A4 inducer is required (e.g., carbamazepine, phenytoin, or rifampin), rimegepant should be discontinued and not be resumed until 14 days after initiation of the strong CYP3A4 inhibitor. Please see Appendix 1 Section 12.1.

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) during the Long-Term Treatment Phase;

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

5.5. Prophylactic and Standard of Care Migraine Medications

Participants using prophylactic migraine medications are permitted to remain on therapy if the dose has been stable for at least 2 months prior to the Baseline Visit and this dose is not expected to change during the study. Participants who previously discontinued prophylactic migraine medication must have done so at least 5 half-lives of the prophylactic medication prior to the Screening Visit.

Participants may need to take previously prescribed standard of care medications: aspirin, ibuprofen, acetaminophen (including Excedrin®Migraine) up to 1000 mg/day for a maximum of 2 consecutive days at a time, naproxen (or any other type of non-steroidal anti-inflammatory [NSAID]), antiemetics (eg, metoclopramide or promethazine), or muscle relaxants, which are used during the study (Observation Period and Long-Term Treatment Phase) for the standard of care treatment of migraine.

Use of triptans by participants without a contraindication to their use is allowed during the Observation Phase but must be discontinued at the Baseline Visit. As described above, use of triptans is prohibited during the Long-Term Treatment Phase. With the exception of triptans described in this section, participants are allowed to take standard treatment for migraine during the study, if needed, but are required to meet dose restrictions if taking acetaminophen (no more than 1000 mg/day at a time for 2 consecutive days).

If a participant takes a tablet of study drug and experiences a migraine later that day, the participant can take standard of care medications for migraine (as described in this section above) after taking the study drug that day. Participants are not allowed to take more than 1 tablet of the study medication per calendar day.

Use of standard of care medications during Observation Period and Long-Term Treatment Phase, will be recorded by the participant via BYOD and reported to the site.

5.6. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant from the permitted list of contraception methods (see Section 12.3.4) and will confirm that the participant has been instructed in its consistent and correct use.

The investigator or designee will inform the participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants 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 participant of the need to use acceptable effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants 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.

WOCBP will complete a pregnancy test at the Screening Visit, at the Baseline Visit, at Weeks 4, 8, and at all on-site study visits through the Week 52/end of treatment visit and at the Safety follow up Visit. If a WOCBP suspects that she might be pregnant, she should not take the study drug and should contact the study doctor immediately.

6. STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1. Safety Assessments

6.1.1. Vital Signs and Physical Measurements

Vital signs mainly include blood pressure, pulse rate, respiratory rate and body temperature. Vital signs will be measured at the Screening Visit, at the Baseline Visit, at scheduled site visits (Weeks 4, 8, 12, 16, 28, 40, 52, or early termination), and at the Safety follow up Visit as specified in Table 1.

Physical measurements mainly include height and weight, and height is only measured at the Screening Visit. Weight measurement time and vital signs should be performed according to the schedule in Table 1.

6.1.2. Physical Examination

Physical examination mainly includes skin, lymph nodes, eyes, head and neck, chest, abdomen, spine and limbs. Physical examinations will be performed at the Screening Visit, Baseline Visit, scheduled site visits (Week 28, Week 52, or early termination), etc. as specified in Table 1.

The number of physical examinations may be increased if deemed necessary by the principal investigator.

6.1.3. Electrocardiogram (ECG)

A standard 12-lead ECGs will be performed at the Screening Visit, Baseline Visit, scheduled site visits (Week 28, 52, or early termination), and Safety follow up Visit as specified in Table 1.

ECG examination indicators mainly include heart rate, PR interval, QRS duration, QT interval and QTc interval.

6.1.4. Clinical Laboratory Tests

6.1.4.1. Safety Laboratory Testing

Blood and urine samples for clinical laboratory assessments will be collected as outlined in Table 1. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. If possible, participants should be fasting for a minimum of 8 hours before each blood draw. However, if the participant is not fasting at the specified visit, the participant should still have blood drawn and the non-fasting status should be documented.

1. Clinical Safety Laboratory Tests:

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

Chemistry: Sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, creatine phosphokinase (CPK) (with fractionation test, if CK result is >1.5 × ULN), eGFR using the estimated MDRD formula (calculated at central lab), AST, ALT, ALP and bilirubin (Total, Direct, Indirect);

2. Blood lipid test: cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride;

3. Urinalysis: pH, specific gravity, ketones, nitrite, urobilinogen, leukocyte esterase, protein, glucose and occult blood. Microscopic examination will be performed if occult blood, protein or white blood cells are positive;

4. FSH: for WOCBP at Screening Visit to determine WOCBP status;

Clinical safety laboratory tests will be performed at the Screening Visit, at the Baseline Visit, at scheduled site visits (Weeks 4, 8, 12, 16, 28, 40, 52, or early termination), and at the Safety follow up Visit as specified in Table 1; lipid panel tests will be performed at the Baseline Visit, at scheduled site visits (Weeks 28, 52, or early termination); urinalysiswill be performed at the Screening Visit, at the Baseline Visit, and at scheduled site visits (Week 52 or early termination); and FSH is used by the study to determine WOCBP status at the Screening Visit as appropriate.

6.1.4.2. Pregnancy Test

WOCBP will perform pregnancy testing at the Screening Visit, at the Baseline Visit, at scheduled site visits (Weeks 4, 8, 12, 16, 28, 40, 52, or early termination), and at the Safety follow up Visit as specified in Table 1, along with serum and urine pregnancy tests at the Baseline Visit and urine pregnancy tests at other times. Upon completion of the Baseline Visit, when WOCBP participants cannot confirm pregnancy status, a urine pregnancy test must be completed at home before taking study drugs.

6.2. Efficacy Assessments

6.2.1. Daily Migraine Assessment by Severity

Participants will be asked to submit electronic records every day after receiving the eDiary device including whether migraine occurred, whether migraine was associated with aura, the duration of the headache, symptoms, pain features, use of migraine-specific medications (study medication, triptan, or ergotamine), as well as severity of the headache. A qualified migraine day will be identified using the eDiary data based on the definition in Appendix 2 Section 12.2. The number of migraine days will then be calculated by total and intensity of the migraine headache.

6.3. Urine Drug Screening

A urine drug screen will be performed at the Screening Visit to exclude drug abusers.

6.4. Serum Virology Testing

Serum virological examination will be performed at Screening Visit, including HBsAg, HCV antibody test, HIV antibody test. HbsAb, HbeAg, HbeAb, HbcAb, and HBV DNA quantification will be conducted If HBsAg is positive.

6.5. Other Assessments

6.5.1. Migraine Quality of Life Questionnaire

The MSQoLQ version 2.1 will be used to assess the impact of treatment on participants' quality of life. The MSQoLQ has 14 items that have been validated in migraineurs to measure the impact of treatment (within past 4 weeks of the questionnaire) on migraine-specific domains: work, social function, energy, vitality, feelings, concerns, and migraine symptoms [8].

6.5.2. Migraine Preference of Medicine

The PoM is a brief scale that captures participants' perception of whether the study medication they are taking has a greater benefit compared with previous medications to treat their pain. BYOD will be used to evaluate the Preference of Medication Scale.

6.5.3. Satisfaction with Medication Questionnaire

The Satisfaction with Medication Questionnaire is a brief rating scale that captures participants' perceptions of whether they are satisfied with the medication for migraine. BYOD will be used to evaluate the Satisfaction with Medication Questionnaire.

6.5.4. Migraine Disability Assessment Questionnaire (MIDAS)

The Migraine Disability Assessment Questionnaire is a retrospective participant self-reported rating scale of 5 questions measuring the time lost in headache-related disabilities such as headaches due to paid work or school, housework, and nonwork activities. The MIDAS will be completed on paper forms at the site [9].

6.5.5. Clinical Global Impression-Change (CGI-c)

The CGI-c scale is a brief, observer-rated assment that rates participant total improvement relative to the investigator's past experience with other participants with the same diagnosis, with or without collateral information[9].

6.5.6. Demographic Information

Demographic data including age, date of birth, gender, height, weight, ethnicity, etc. will be collected at the Screening Visit. These data will be recorded in the original records, and the data not involving the participant's personal information or privacy will be recorded in the eCRF.

6.6. Early Termination of Treatment

Participants must discontinue study drug (at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (participant withdrawal for any reason);
- The investigator considers the participant should be discontinued from investigational product for safety reasons (e.g., the participant develops intolerable adverse events);
- Participant is pregnant;
- The participant experiences a serious protocol devation, and the investigator considers that the protocol deviation seriously affects the evaluation of primary endpoint of this trial, the investigator considers that the participant should terminate the treatment;
- Other conditions that, in the opinion of the investigator, would make the participant discontinue trial medication.

During the trial, all participants who prematurely discontinue treatment should make every effort to complete subsequent safety visits.

6.7. Early Withdrawal Criteria

Participants who meet the following criteria will be withdrawn from the study:

- Poor participant compliance and inability to comply with the study protocol;
- Participant lost to follow-up;
- The participant withdraws consent and requests withdrawal from the study and subsequent follow-up.

During the trial, the participant may decide to withdraw from the trial treatment and late follow-up for any reason at any time. After the participant decides to withdraw, the investigator should record the information of withdrawal event of the participant, including at least withdrawal date and reason. Lost to follow-up is defined as failure to contact the participant after 3 times of telephone calls or other methods, such as mail/registered mail/express mail. The investigator should record the specific situation of lost to follow-up, including at least the date and way of trying to contact.

7. STUDY DRUG MANAGEMENT

7.1. Overview of Study Drug

7.1.1. Basic Information

Drug name: Rimegepant;

Code: PF-07899801 (Formerly BHV3000);

Specification: 75 mg;

Dose form: Orally Disintegrating Tablets (ODT);

Submitter: Pfizer Inc.

For additional details, please refer to the study drug instruction manual provided by Pfizer Inc.to the clinical study site.

7.1.2. Packaging, Labeling and Storage

In accordance with the requirements of GCP and national regulations, the application of the label on the packaging box of investigational drugs will be performed by Pfizer Inc. Investigational drugs will be packaged uniformly for all Participants.

The content of the labels of investigational drugs shall comply with the requirements of GCP and national regulations, and shall only be indicated for clinical trials, clinical trial information and information of investigational drugs. The specific packaging shall be participant to the physical objects.

Investigational medicinal products should be stored under ambient conditions (temperature and light) as specified by the sponsor and in a secure, limited access area.

The medication will be stored in a locked, environmentally controlled, limited access medicine room.

7.2. Dosage and Administration

7.2.1. Method of Assigning Participant Numbers

Participants will be assigned a unique participant number consisting of 5-digit Arabic numerals after signing the informed consent form and prior to relevant study examinations: the first 2 digits will be the "site number" and the last 3 digits will be the "screening serial number". For example, the screening number of the second screener at site 01 is "01002". The participant number will be used to identify the participant throughout the study and the assigned number will not be reused for other participants in the study.

7.2.2. Dosage and Administration

Study drug will be dispensed at the Baseline Visit, and participants will be notified by phone after the site staff confirms that the participant is enrolled. Participants confirmed to be

eligible can start taking the study drug rimegepant 75 mg (up to 1 tablet per day) at the time of their migraine attack (mild, moderate, or severe), and use of the study drug will be recorded with BYOD.

7.2.3. Dose Modification

There will be no dose adjustment in this study.

7.3. Blind and Unblinding

This study is a single-arm trial, blind method and unblinding are not applicable.

7.4. Treatment Compliance

Study drug will be dispensed by the responsible study personnel. Drug accountability and compliance check results should be documented in the participant's study records.

Participants should be instructed on the importance of taking the study drug as directed when a migraine attack occurs (mild, moderate, or moderate). At site visits, the responsible study personnel will review the use of study drug recorded in the BYOD and the returned study drug to assess treatment compliance. Dose discrepancies reported by BYOD, review of study drug, and information provided by the participant must be documented in the original medical record. Data in BYOD for incorrect or missing doses and migraine headaches will be corrected by the Data Clarification Record or Study Drug Reconciliation Form. The investigator shall inform the participants participating in the study that if it is confirmed that the participants are lack of compliance, the participants will be terminated to continue to participate in the study. During monthly study visits, if a participant's BYOD records a lack of compliance, the study staff should contact the participant and document this contact in the original medical record to identify potential participant loss to follow-up as early as possible.

Investigators should monitor participants for possible abuse of the study drug (participants taking the study drug for non-therapeutic purposes, such as for elevated or excited mental effects). The investigator should also assess study drug accountability discrepancies (e.g., missed study drug, lost study drug, overuse of study drug). In the event of a study drug accountability discrepancy, the investigator should obtain additional information and explanation from the participant.

Potential cases of study drug abuse or overdose (including failure to return study drug for participants who fail to take the study drug as instructed or discontinue treatment) should be recorded in original medical records, and AEs or SAEs should be reported as appropriate. Protocol deviations should be documented in the event of dose errors (e.g., taking more than 1 tablet on a calendar day).

7.5. Investigational Product Management

The sponsor/its authorized personnel are responsible for providing the investigational product to the investigator and the site. The sponsor/its authorized personnel shall not provide the investigational drugs to the investigators and clinical trial institutions before the clinical trial is approved by the ethics committee and approved or filed by drug regulatory authorities.

The sponsor / its authorized personnel should provide the investigator and institution with a written description of the investigational product, specifying the use, storage, and records of the investigational product. The sponsor/ its authorized personnel will establish procedures for investigational product administration and management, including receipt, storage, dispensing, use, and return. Investigational products returned from participants and unused by study personnel should be returned to the sponsor or destroyed by the study site upon authorization by the sponsor.

The sponsor / its authorized person should ensure that the investigational product is delivered to the investigator and institution in a timely manner to ensure that it is used by the participants; keep the records of transportation, receipt, distribution, recovery and destruction of the investigational product; establish the investigational product recovery management system to ensure the recall of defective products, recovery after the trial is completed and recovery after expiration. 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.

The management of investigational product in the study site is in the charge of the investigator's authorized study staff; the investigational product could only be prescribed by the principal investigator or the study doctor authorized by the principal investigator, and it was necessary to ensure that all investigational products are only used for the participants in the clinical trial and their dosage and administration should follow the study protocol; if there is a problem in the quality or appearance of the investigational product, the sponsor should be contacted immediately; the unused remaining investigational product and empty packages of the used investigational product will be returned by the investigator's authorized study staff.

The investigator should designate a person to be responsible for the receipt, storage, dispensing, use, recovery, inventory, and recording of the investigational product, and the records should ensure that the contents are completed in a timely and accurate manner; the drug receipt form must be signed in duplicate, with the study site and the sponsor holding one copy.

The Clinical Research Associate is responsible for monitoring the receipt, storage, use, inventory, and recovery of the remaining investigational product and empty packages of used product. After drug accountability at the visit, medication errors, overdose, and drug loss should be recorded in the original medical records and eCRF. After checking by the Clinical Research Associate, the remaining investigational products and empty packages of used drugs will be returned by the sponsor (both parties will sign the drug recovery form). At the end of the trial, investigational product shipment records must be consistent with used and destroyed/returned quantities. Any discrepancies will be documented and the reason for the discrepancy noted.

The sponsor / its authorized person should take measures to ensure the stability of the investigational product during the trial. The retention period of the samples of investigational drug shall be preserved until the end of clinical trial data analysis or the time limit required by relevant laws and regulations within the storage period of investigational drug, and the longer time limit shall be taken if the two are inconsistent.

8. ADVERSE EVENTS

During this study, the investigators (or authorized qualified person) should detect and record all adverse events/serious adverse events and pregnancy events observed according to the criteria and definitions in this study protocol. Investigators will evaluate adverse events, monitor the safety status of participants and provide corresponding protective measures to ensure the safety of participants, and report according to relevant requirements.

8.1. Definition of Adverse Events

According to the definition in GCP, an adverse event is any untoward medical occurrence in a clinical trial participant administered an investigational product that may present with symptoms/signs, disease, or laboratory abnormalities and which do not necessarily have a causal relationship with the investigational product.

In order to collect more sufficient information, following the participant's written consent to participate in the study, information on clinical adverse events will be collected in this study. Any clinical adverse event that occurs after signing the informed consent form and before the first use of the investigational product and meets one of the following conditions should be recorded as a pretreatment adverse event: injury/damage caused by any clinical laboratory test procedure; adverse event caused by drug discontinuation related to the trial protocol; adverse event caused by drugs other than the study product (or investigational product) taken as part of the treatment regimen. TEAEs are events that start after the first dose of trial drug and do not occur or worsen relative to the first dose.

Examples of an AE include:

1. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.

2. Exacerbation of a chronic or intermittent pre-existing condition including either increase in frequency and/or intensity of the condition.

3. New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.

4. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Examples of NOT meeting definition of an AE include:

1. Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease. However, it was considered an AE if the investigator considered the intensity to be more severe than the expectation for the participant 's status.

2. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied. However, it should be considered an AE when its severity exceeds the expected severity of the participant 's condition.

3. Medical or surgical procedures (e.g., endoscopy, appendectomy). Note that the condition leading to this procedure was an AE.

4. No adverse medical condition, but hospitalization for social reasons and/or convenience.

5. Daily fluctuations within the expected range without significant deterioration in the underlying disease or condition that were present or detected at the start of the study.

6. Pre-existing conditions or signs and/or symptoms unrelated to the study intervention before the first study drug administration; These events will be documented in the medical history section of the eCRF.

8.2. Definition of Serious Adverse Events

SAE refers to any untoward medical occurrence that meets any of the following criteria at any dose for a participant after receiving the investigational product: death, life-threatening, permanent or severe disability or incapacity, hospitalization or prolongation of hospitalization required or congenital anomaly or birth defect.

1. Causing death.

2. Life-threatening: This refers to an adverse event in which the participant was already at risk of death at the time of the event, and does not refer to an assumption that the adverse event, if more severe, may have caused death.

3. Permanent or significant disability or incapacity: The adverse event result may cause serious inconvenience or interference with the participant 's normal life and activities.

4. Requires hospitalization or prolongation of hospitalization: The participant has to be hospitalized for treatment due to an adverse event or has been prepared to be discharged but has prolonged hospitalization due to an adverse event; it is necessary to clarify that the cause of this condition is due to an adverse event rather than admission due to elective surgery, non-medical reasons, etc.

5. Congenital anomaly or birth defect: The participant 's offspring have malformation or congenital functional defect.

6. Other important medical events: Medical and scientific judgment must be used to determine whether expedited reporting is appropriate for other situations, such as important medical events that may not be immediately life-threatening, fatal, or hospitalized, but medical measures to prevent one of the above situations are usually considered serious. For example, important treatment in the emergency room or allergic bronchospasm at home, cachexia or convulsion without hospitalization, drug dependence or addiction.

When it is unclear whether the SAE is considered, the investigator should discuss with the sponsor and the Ethics Committee.

8.3. Definition of Suspected and Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Event (SUSAR) refers to a suspected and unexpected serious adverse reaction whose nature and severity of the clinical manifestations exceed those in the IB of the investigational product, the package insert of the marketed drug or the summary of product characteristics.

8.4. Method of Collection of Adverse Events and/or Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and undirected verbal questioning of the participant is the preferred method to inquire about the occurrence of AEs. For example:

- "How do you feel?"
- "Has your health improved or worsened since the last study visit?"
- "Have you taken any new medications since your last study visit? Did you stop taking or change any medication that you were taking?"

8.5. Time Periods for Collection of Adverse Events and/or Serious Adverse Events

Adverse events, including serious adverse events, will be collected in this study from the time the participant signs the informed consent form until the end of the safety follow-up period. Investigators were not required to actively collect AEs or SAEs following the participant 's safety follow-up period. However, if the investigator learns of any SAE, including death, at any time after a participant leaves the study, and considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly collect and report.

8.6. Follow-up of Adverse Events

Following the initial AE/SAE report, the investigator is required to follow each participant for further information at subsequent visits/contacts. Each event should be followed until the event has resolved (including return to baseline values), the status has changed to long-term stability, loss to follow-up, death, or the investigator does not consider continued follow-up or other reasonable explanation. The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as

requested by sponsor to elucidate as fully as possible the nature and/or causality of the AE or SAE.

8.7. Recording of Adverse Events

When an AE/SAE occurs, investigator shall review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event, and then record all relevant information regarding an AE/SAE into the CRF. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (rather than individual signs/symptoms) was recorded as an AE/SAE. If the diagnosis is unknown, AE verbatim terms may be temporarily reported as symptoms, signs and abnormal examinations, and each symptom, sign and examination should be recorded separately; when the diagnosis is confirmed later, the records should be updated.

During the collection and evaluation of AEs and SAEs, truthfully fill in the AE record form, including:

- AE verbatim term (sign, symptom, diagnosis or syndrome);
- Start date, end date, whether continuous;
- Severity (CTCAE V5.0: Grade 1 ~ 5);
- The investigator's judgment on the causal relationship between the event and the investigational product (definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated), including the application for suspected procedures;
- Action taken for investigational drug;
- Event outcome;
- Whether it is an SAE (if yes, list the specific criteria for SAE);
- Medications and other interventions for AEs treatment.

8.8. Severity of Adverse Events

The investigator will summarize the severity of each adverse event by describing the clinical symptoms according to the five-grade determination criteria established by NCI CTCAE V5.0, which are:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

8.9. Indicators for Judging Causality of Adverse Events

Causality assessment is one of the criteria used in determining regulatory reporting requirements. The investigator is obligated to assess the relationship between study drugs and the occurrence of each AE/SAE using clinical judgement. When the investigator determines whether an AE is causally related to the drug, the investigator 's brochure should be consulted and the following should be considered:

- Whether there is a temporal reasonable relationship between the AE onset and the investigational product? AE onset time interval between first and last dose?
- Whether the symptoms and signs present can be caused by the mechanism of action of the drug itself or by the action of metabolic components?
- Whether the symptoms/signs abated or improved following dose reduction or discontinuation and in the absence of other treatment for AEs?
- Whether the symptoms/signs reoccures or worsens after re-administration of the study drug?
- Whether the adverse event can be explained by the participant 's concomitant diseases, concomitant medications or other reasons?
- Whether similar situations have been reported in domestic and foreign literatures?

Then, a 5-point method (definitely related, probably related, possibly related, possibly unrelated, definitely unrelated) was used to provide a causality assessment of the relationship between the reported AE and the use of the investigational product. Definitely related, probably related and possibly related will be mapped into ‘related’ and possibly unrelated and definitely unrelated will be mapped into ‘unrelated’ via a binary method in the safety data base and clinical study report.

For each AE/SAE, the investigator must record, review, and provide a causality assessment (although information that the investigator may have known was limited in the event of an SAE at some time) and update the causality assessment based on follow-up information.

8.10. Reporting of Serious Adverse Events

Any SAE must be reported immediately or no later than 24 hours after awareness of the event to Pfizer DSU either via the Pfizer SAE Submission Assistant (PSSA) tool or as a

written description using the Pfizer CT SAE report form, that must be sent by facsimile (fax or eFax) to the Pfizer DSU at 10800714-1806 (north)/ 10800140-1838 (south).Reporting was to be completed within 24 hours even if all information on the SAE was not available at that time. The investigator should update the SAE report within 24 hours of obtaining additional relevant information:

For the reporting of death events, the investigator should provide the sponsor/authorized designee and the Ethics Committee with other required information, such as autopsy report and final medical report.

The Investigator shall properly maintain written evidence of all reports above to show that each event received has been properly reported.

The sponsor will comply with country-specific regulatory requirements regarding safety reporting to regulatory authorities, IRBs / IECs, investigational institutions, and investigators, and will notify local and other regulatory authorities of safety information about the investigational drug as required and in accordance with sponsor policy. The investigator will review investigator safety reports received from the sponsor which describing SUSARs or other specific safety information, and file them with the IB and notify the Ethics Committee.

The sponsor will promptly investigate SAEs with the investigator and take necessary measures to ensure the safety and rights and interests of the participants.

The procedures for follow-up reporting of SAEs are the same as those for initial reporting.

8.11. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include Exposure During Pregnancy (EDP), Exposure During Breastfeeding (EDB), and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.11.1. Exposure During Pregnancy

If, following the Baseline Visit it is subsequently discovered that a study participant 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 participant safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the participant 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 (EDP) Supplemental Form following the SAE reporting procedures as described in Section 8.2.

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

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

If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the CT SAE Report Form or via PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 66 hours after the last dose.

If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form or via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

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

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

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

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

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

8.11.2. Exposure During Breastfeeding

An EDB occurs if:.

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.

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

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

the exposure information does not pertain to the participant 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.

8.11.3. 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 participant 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.

9. RISK CONTROL AND MANAGEMENT

According to the information from the previous clinical trial of the investigational drug and the clinical study of related products, the most common treatment-related adverse event that may occur in participants participating in this trial is nausea. The most frequently reported (occurring in ≥2% of participants overall) adverse events, regardless of causality, were: upper respiratory tract infection (8.8%), nasopharyngitis (6.8%), sinusitis (5.1%), urinary tract infection (3.8%), influenza (3.3%), back pain (3.1%), bronchitis (2.9%), nausea (2.8%), dizziness (2.3%), and arthralgia (2.0%).[6]

In consideration of the above information, the participant's participation in this study may cause one or several risks including but not limited to the above adverse events. In this study, if the participant experiences adverse drug events, timely intervention should be performed according to the protocol requirements and clinical routine treatment measures.

The trial site must be equipped with necessary medical rescue equipment, emergency drugs and emergency measures. If necessary, an emergency medical incident team shall be established to handle emergency medical incidents and accidental injuries according to relevant standard operating procedures. The investigators must closely observe possible adverse events, especially unexpected adverse events, timely analyze and communicate, and record adverse events in detail. Contact procedures with the hospital intensive care unit for participant transfer and care should be established. The communication and exchange between the investigator and the laboratory and the sponsor should be established to ensure the timely communication and handling of possible adverse events.

In this trial, the organ functions (including liver, kidney, hematopoiesis, cardiac function) of participants are specified in the inclusion/exclusion criteria, and the participants with cardiac diseases, pulmonary diseases and other severe and uncontrolled systemic diseases are excluded to avoid the disease aggravation in these participants during the trial. Corresponding safety examinations will be performed at the scheduled site visits during the treatment period, mainly including vital signs, physical examination, hematology, blood

biochemistry (liver function, renal function, electrolyte, etc.), and ECG. Vital signs, physical examination, hematology, blood biochemistry, urinalysis, pregnancy test and ECG will be performed at the end of treatment period. Through the above examination and the observation of the investigator, adverse events should be detected as early as possible, and necessary intervention treatment should be given. During the follow-up period, if any adverse event or concomitant use or treatment related to adverse event occurs to the participants, it is required to report to the investigator in time and come to the hospital for necessary intervention if necessary. If the drug is withdrawn due to adverse events related to the investigational product, follow-up should be performed until the outcome.

10. STATISTICAL CONSIDERATIONS

10.1. General Consideration

All statistical analyses will be completed using SAS Version 9.4 or higher. In general, continuous variables will be statistically described using n, mean, median, standard deviation, minimum and maximum; categorical variables and ordinal variables will be statistically described using frequency and percentage of each category or grade, and unless otherwise specified, the category of missing data will be provided.

The statistical analysis is mainly descriptive, and no formal hypothesis testing will be performed. However, some statistical estimation methods will be used to generate 95% CI.

10.2. Sample Size

The sample size for this study is primarily based on historical data, considering the safety evaluation and estimation precision for the secondary endpoint.

For the secondary endpoint of change from Obervation Period in the number of migraine days per month from Week 9-12 in participants treated with rimegepant, data from previous long-term migraine study BHV3000-201[6] showed:

- 848 participants with a history of 6-18 days of migraine within 3 months prior to baseline;
- Mean (SD) baseline migraine days: 9.92 (3.09);
- Migraine days mean (SD) Weeks 9-12: 8.84 (4.97);
- Change from OP in mean (SD) number of migraine days at Weeks 9-12: -1.08 (4.74);

Based on the above historical trial data results and a t distribution assumption, in this single-arm study, 205 evaluable participants will provide 90% power to observe a negative change from baseline in migraine days at Weeks 9-12 for a 1-sided 2.5% significance level, and finally 233 participants are required to be included considering 12% dropout rate based on BHV3000-201 trial. Considering other possible data loss, approximately 240 participants will be finally included.

In the case of 240 participants, if the adverse event rate is 5% and 1%, then the probability of observing at least one adverse event is >99.9% and 91.0%, respectively, thus providing sufficient information for safety and tolerability assessment after LTT with 75 mg rimegepant ODT in Chinese participants to bridge the available comprehensive clinical trial data of rimegepant 75 mg in the treatment of migraine.

10.3. Interim Analysis (IA)

This study is an open-label, single-arm study to evaluate the safety and tolerability of rimegepant. The primary objective is safety evaluation and the analysis will be descriptive. There will be no alpha spending consideration for the interim analysis. An interim analysis is planned when the time is sufficient for at least 175 participants to complete the 12-week visit.

At IA, with 154 evaluable participants (i.e. 175 treated participants), there will be 80% power to observe a negative change from baseline in migraine days at Weeks 9-12 at the 1-sided 2.5% significance level. The interim analysis is not for efficacy or futility purpose, but to provide some early descriptive readouts for agency communication. Therefore, no decision criteria is needed.

Laboratory test, safety and exposure data will be monitored continuously during the study, and be reviewed and summarized by the sponsor/its authorized representative. The final clinical study report will be completed when the last participant completes the last visit.

10.4. Analysis Populations

10.4.1. Full Analysis Set (FAS)

All participants who are enrolled and received at least one dose of the investigational product. It will be used for the analysis of participant disposition, demographic and baseline characteristics, as well as the analyses of exploratory endpoint measures.

10.4.2. Efficacy Analysis Set (EAS)

All participants in the FAS with ≥14 eDiary days (not necessarily consecutive) in both the Observation Period analysis period and ≥1 month (4-week interval of the LTT analysis period). The EAS will be used to assess the secondary endpoint.

10.4.3. Safety Set (SS)

All participants who received at least one dose of investigational product. The SS will be used for safety analyses for this trial.

10.5. Statistical Methods

10.5.1. Demographic and Baseline Characteristics

Demographic data and other baseline characteristics (medical history, prior medications) will be tabulated and summarized using descriptive statistics.

10.5.2. Safety Analysis

The primary endpoints of this study are adverse events, common adverse events (incidence ≥ 5%), serious adverse events, adverse events leading to study drug discontinuation, etc.; ECG, vital signs/physical measurements and clinical laboratory test abnormalities.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Analysis of adverse events will be mainly based on TEAEs. All TEAEs, common TEAEs (incidence ≥5%), SAEs, and TEAEs leading to study drug discontinuation will be summarized and analyzed by SOC and PT, and the AEs will be listed by participant.

Vital signs/physical measurements, ECG parameters, and laboratory tests and their changes from baseline will be summarized by visit using descriptive statistics. The number and percentage of participants with abnormal ECG, vital signs, and laboratory test (according to CTCAE grade) will be presented. LFT elevations will also be summarized with number and percentage of participants in pre-specified categories. In addition, these safety data will also be listed by participant.

Additional details can be found in the SAP.

10.5.3. Secondary Endpoints

The number of migraine days and severity of migraine attacks will be analyzed for every 4-week interval and overall period during long-term treatment with rimegepant in participants compared to the Observation Period.

Values, changes, and percent changes from OP in the number of migraine days during the LTT period will be descriptively summarized by total and moderate or severe pain intensity for every 4-week interval in LTT and overall LTT period. Two-sided 95% CIs based on normal distribution will be calculated for the change from Observation Period and percent change from Observation Period in migraine days.

10.5.4. Exploratory Endpoints

For MSQoLQ and MIDAS rating scales, total and/or domain scores, and changes from baseline in the total and/or domain scores will be descriptively summarized by visit with two-sided 95% CIs based on normal distribution.

For PoM, SM, and CG-c rating scales, number and percentage of participants in each category will be summarized by visit with two-sided exact Clopper-Pearson 95% CIs for the percentage of participants in each category.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Ethical Conduct and Informed Consent

11.1.1. Review and Approval by Ethics Committee

The Sponsor shall not carry out the clinical trial until obtaining the approval from the Ethics Committee. The sponsor/its authorized person should obtain the name and address of the Ethics Committee from the investigator and clinical trial institution, a list of Ethics Committee members participating in the project review, a review statement in compliance with GCP and relevant laws and regulations, as well as documents of approval from the Ethics Committee and other relevant materials.

After ethical review, if it is necessary to modify the protocol, informed consent form, and provide the participants and/or other relevant documents, the sponsor should first negotiate with the investigator and clinical trial institution, then modify the relevant documents and re-submit them to the Ethics Committee.

11.1.2. Informed Consent

Prior to the initiation of any study procedures, written informed consent will be obtained from the participant in accordance with GCP, national laws and regulations. The investigator should conduct informed consent in accordance with the basic ethical principles that have their origin in the Declaration of Helsinki and in compliance with:

1. The investigator should use the latest version of ICF approved by the Ethics Committee and other information provided to the participants. If necessary, the participants shall re-sign the latest version of the ICF during the clinical trial.

2. When the investigator obtains new information that may affect the participant's continued participation in the trial, he/she should promptly inform the participant or his/her guardian and make corresponding records.

3. The investigator shall not force or induce the participants to participate in or continue the clinical trial in any improper way.

4. The investigator or designated study personnel should fully inform the participants or their guardians of all the matters related to the clinical trial, including the written information and the approval comments from the Ethics Committee.

5. The oral and written materials provided to participants in the informed consent form should be expressed in the language and way that are easy to understand by the participants or their guardians and witnesses.

6. Before signing the informed consent form, the investigator or designated study personnel should give the participant or his/her guardian sufficient time and opportunity to understand the details of the clinical trial and answer the questions related to the clinical trial raised by the participant or his/her guardian in detail.

7. The participant or his/her guardian, as well as the investigator who conducted the informed consent, should sign and date the informed consent form, respectively, and if not signed by the participant, the relationship should be noted.

8. If the participant or his/her guardian lacks reading ability, an impartial witness should be present to witness the entire informed consent process. The investigator should explain the contents of the informed consent form and other written materials to the participants or their guardians and witnesses in detail. If the participant or his/her guardian orally agrees to participate in the trial, he/she should try his/her best to sign the informed consent form when capable, and the witness should also sign and date the informed consent form to prove that the participant or his/her guardian accurately explained the informed consent form and other written information by the investigator, understood the relevant contents, and agreed to participate in the clinical trial.

9. The participant or his/her guardian should obtain the original or copy of the signed and dated informed consent form and other written materials that should be provided to the participant, including the original or copy of the latest version of the informed consent form and other revised text that should be provided to the participant.

10. If the participant is incapable of civil conduct, written informed consent shall be obtained from his guardian; if the participant is a person with limited civil conduct capacity, written informed consent shall be obtained from himself and his guardian. When the guardian provides informed consent on behalf of the participant, he/she should inform the participant of the relevant information of the clinical trial to the extent that the Participant can understand, and try to have the participant personally sign and date the informed consent form.

11. The specific time of informed consent and the operator should be recorded in the medical history record.

11.2. Data Management and Storage

11.2.1. Source Data and Source Documents

Source Data

Source data refers to all information recorded in original records or certified copies in a clinical trial, including clinical findings, observations, and other relevant activity records necessary for the reconstruction and evaluation of the clinical trial.

Source Documents

Source documents refer to original records, documents and data generated in the clinical trial, such as hospital medical records, medical images, laboratory records, memoranda, participant diaries or evaluation forms, drug dispensing records, recorded data from automated instruments, microfiches, photographic negatives, magnetic media, X-ray films, participant files, and documents and records related to the clinical trial maintained by pharmacies,

laboratories and medico-technical departments, including certified copies. Source documents include source data and may be in the form of paper or electronic carriers.

CRF

Electronic case report forms will be used in this trial, and the contents will be filled in by the investigator or his/her authorized personnel through the clinical electronic data capture and management system (EDC). Before the trial, CRFs are set up in the EDC system and assigned to each account of the investigator and/or his/her authorized personnel responsible for completing the CRF at the trial site.

1. For all the participants who have signed the informed consent form, any item in the case report form shall be carefully and detailedly recorded according to the instructions for filling in the case report form;

2. All the data in the case report form should be checked with the participant's source documents to ensure correctness;

3. Data significantly deviated from or outside the clinically acceptable range shall be verified and, if necessary, judged by the investigator;

4. See eCRF Completion Guidelines for additional details.

After the completed eCRFs are reviewed by the CRA, the data manager performs data verification and management. After completion of data collection and cleaning, it will be signed and confirmed online by the investigator.

The participant source documents are the original participant records kept at the site. Trial data must be entered into the CRF in a timely manner.

Completed CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate regulatory authorities or ethics committees, without written permission from the sponsor.

11.2.2. Data Management

An electronic data management system will be used for this study.

1. Construction of Electronic Case Report Form: Data managers constructed eCRF according to the study protocol.

2. Authority assignment: Data administrators shall create accounts and grant different authorities according to different identities of entry personnel, investigators and clinical research associates. The data entry personnel have the permission of data entry, modification and query feedback, the investigator has the permission of modification, browsing, query feedback and review, the CRA has the permission of browsing and sending query, and the data manager has the permission of browsing, sending query and data locking.

3. Data entry: Data from the study medical records are entered into the eCRF in a timely and accurate manner by the clinical investigator or a data entry clerk (clinical coordinator) designated by the investigator.

4. Query sending and resolution: The monitor and data manager send all queries via eCRF, and the entry personnel or investigator answer the questions and modify the wrong data. If necessary, the queries can be sent repeatedly, and all records are stored in the eCRF.

5. Modification and review of data: Data entry personnel or investigators can modify the data after verifying the data. For modified data, the reason for modification should be filled in the eCRF. The investigator has access to review all final data.

6. Data locking and export: After all data are reviewed correctly, the data manager locks the data. Any modification after data locking can only be implemented after being signed and confirmed by the sponsor, investigator, data management personnel and statistician. All data are finally exported by data management personnel and submitted to statisticians for analysis.

11.2.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' 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 participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' 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 participant data are to be deleted, the

investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

11.2.4. Preservation of Data

The sponsor, investigator and clinical trial institution should confirm that there are places and conditions for preserving the essential documents of clinical trial. The equipment and conditions for document preservation shall be equipped with such conditions as preventing direct light exposure, water resistance and fire prevention, which is conducive to the long-term preservation of documents. Standard operating procedures for document management should be established. The saved document shall be easy to identify, find, access and home. The media used to store the clinical trial data should ensure that the source data or its certified copies are kept intact and readable during the retention period and should be tested regularly or checked for their ability to resume reading without intentional or unintentional alteration or loss.

For some documents generated in the implementation of clinical trial, if they are not listed in the Directory of Essential Documents for Clinical Trial, the sponsor, investigator and clinical trial institution may also include them in their respective Essential Documents Files according to necessity and relevance.

For the clinical trial for drug registration application, the essential documents shall be at least 5 years after the investigational drug is approved for marketing for a clinical trial not used for drug registration application, the essential documents shall be kept for at least 5 years after the termination of the clinical trial. All materials of this clinical study are proprietary to Pfizer Inc. The Investigator shall not provide the information in any form to any third party without the written consent of sponsor, unless required by the National Health Commission.

The sponsor should ensure that the data in the case report forms reported to the sponsor are always accessible and can be entered and corrected by the investigator during the trial and should not be under the sole control of the sponsor.

The sponsor should ensure that the investigator can retain the CRF data that has been submitted to the sponsor. Copies used as source documents should meet the requirements for certified copies.

At the beginning of the clinical trial, the investigator, clinical trial institution and sponsor should establish the archive management for essential documents. At the end of the clinical trial, the CRA should review and confirm the essential documents of the investigator, clinical trial institution and sponsor, which should be properly kept in the respective clinical trial file.

11.3. 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.

11.3.1. Data sharing

Pfizer provides researchers secure access to participant 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. Participant 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.

11.4. 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, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant'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 participant 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 participant. 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 participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

11.5. Clinical Monitoring

In order to ensure the rights and interests of participants in the trial, ensure the accuracy and completeness of trial records and reported data, and ensure that the trial complies with the approved protocol, GCP and relevant regulations, the sponsor shall assign qualified monitors who have received corresponding training, have sufficient scientific knowledge and clinical knowledge required for clinical trial monitoring to monitor the clinical trial. The responsibilities of CRA shall comply with the current GCP regulations. After monitoring at each visit, the monitor should promptly report to the sponsor in writing and provide the sponsor with a monitoring report in compliance with GCP requirements. The sponsor should review and follow up the issues in the monitoring report, and form a document for preservation.

11.6. Quality Control and Assurance

1. The sponsor and/or the contract research organization entrusted by the sponsor shall be responsible for developing, implementing and timely updating the standard operating procedures for quality assurance and quality control system of the clinical trial to ensure that the implementation of the clinical trial and the generation, recording and reporting of data comply with the requirements of the trial protocol, GCP and relevant laws and regulations. The sponsor may delegate some or all of its clinical trial work and tasks to the CRO, but the sponsor is still the ultimate responsible person for the quality and reliability of the clinical trial data and should supervise the various work undertaken by the CRO. CRO shall implement quality assurance and control.

2. The whole process of clinical trials and laboratory testing should be conducted in strict accordance with the standard operating procedures for quality management. Quality control should be performed at each stage of data processing to ensure that all data are reliable and that the data processing process is correct. The investigator should receive the training on the study protocol, current GCP and relevant standard operating procedures before the initiation of the trial, so that the investigator can have a full understanding and understanding of the clinical trial protocol and the specific connotation of each indicator.

3. The sponsor shall sign a contract with the investigator, the clinical trial institution and other relevant units participating in the clinical trial to clarify the responsibilities of all parties.

4. The monitoring and audit responsibilities of the sponsor shall be indicated in the contract signed by the sponsor and relevant units. The inspection by drug regulatory authorities can directly go to the trial site to consult source data, source documents and study report.

11.7. Protocol Compliance, Deviations, and Amendments

The investigator and clinical trial institution should conduct the trial in accordance with the clinical trial protocol approved by the Ethics Committee. The investigator should not modify or deviate from the trial protocol without the consent of the sponsor and the Ethics Committee, unless it is to eliminate the emergency hazard to the participants in a timely manner, or it only involves the changes in the management of the clinical trial, such as changing the monitor, telephone number, etc. The investigator or designated study personnel should record and explain the deviation from the study protocol.

In order to eliminate the urgent harm to the participants, the investigator should promptly report to the Ethics Committee and the Sponsor, explain the reasons and report to the drug regulatory authorities when necessary, in case of modifying or deviating the trial protocol without obtaining the consent from the Ethics Committee.

The CRA should timely communicate with the investigator about the deviation from the study protocol, standard operating procedures and relevant laws and regulations, and take appropriate measures to prevent recurrence.

When the investigator, clinical trial institution and sponsor's personnel are found to be non-compliant with the trial protocol, standard operating procedures, GCP and relevant laws and regulations during the clinical trial, the sponsor should immediately take measures to correct them and ensure good compliance with the trial protocol.

In case of identifying important compliance issues that may affect the safety and rights and interests of participants or have a significant impact on the reliability of clinical data, the sponsor shall timely conduct root cause analysis and take appropriate corrective and preventive measures. If the violation of the study protocol or GCP is serious, the sponsor may hold the relevant personnel accountable and report it to the drug regulatory authority.

When the investigator or clinical trial institution is found to have serious compliance problems or the compliance problems still exist after dissuasion, the sponsor shall terminate the continued participation of the investigator or clinical trial institution in the clinical trial and timely report to the drug regulatory authority in writing. Meanwhile, the sponsor and the investigator should take corresponding emergency safety measures to protect the safety and rights and interests of the participants.

11.8. Study Report and Publication

11.8.1. Clinical Trial Report

For the data and information collected during this trial, the clinical trial report will be prepared by Pfizer Inc. or its authorized party, and submitted to the signed investigator for review and signature.

11.8.2. Publication and Public Disclosure

11.8.3. Publication Policy

At the end of the trial, the investigator may cooperate in the writing of one or more articles for co-publication with the consent of Pfizer Inc., and the investigator acts as the first author or corresponding author.

According to the International Committee of Medical Journal Editors (ICMJE) standard (see current official version: http://www.ICMJE.org), to determine copyright. The total number of authors is based on the guidelines of the relevant journal or conference. In case of any disagreement on the contents of the publication, the opinions of the investigator and Pfizer Inc. will be fairly and fully reflected in the publication.

Any external CRO or laboratory participating in the conduct of this trial has no right to publish this trial.

If the investigator wants to independently publish/present any results about the trial, the draft of the manuscript/publication must be submitted to Pfizer Inc. in written form before submission for comments. Pfizer Inc. will give comments on the draft manuscript received. Except for limiting the disclosure of intellectual property rights of Pfizer Inc., this statement does not grant Pfizer Inc. any right to edit the publication. If the content of a publication is considered patentable by Pfizer Inc., it is not allowed to be published in scientific publications until the patent application submitted is published. In this case, the investigator may decide to modify or postpone the publication, so that Pfizer Inc. has enough time to seek the patent protection of the invention.

11.8.4. Public Disclosure Policy

The trial registration policy has been adopted by ICMJE member journals as a condition of publication. This policy requires that all clinical trials for publication be first registered on a publicly available clinical trial registration network. Therefore, Pfizer Inc. will be responsible for the implementation of the study on the appropriate public registration network (i.e., designated by NMPA) http://www.chinadrugtrials.org.cn/), registered on this trial.

11.9. Liability and Insurance

11.9.1. Participant Benefits and Privacy Protection

Participants in this trial may not have direct health benefits, but their findings may be of benefit to later participants. The participanta are free to participate in all examinations or other trial-related operations in this trial. The participants included in this trial will be given

traffic compensation each time they come to the hospital, as well as nutritional compensation for the participants whose kinetic-related blood samples are collected. Traffic compensation and nutrition compensation will be distributed to participants for many times according to the progress of the trial.

All medical records that identify participants by name and test materials will be kept confidential as required by law. When reporting adverse events and other trial-related data in participants, investigator uses corresponding codes to replace participants' names to protect their privacy. The personal information of participants participating in the trial and during the trial, including medical history and case records, will be strictly kept confidential. To the extent permitted by laws and regulations, representatives of the sponsor, IEC members, and representatives of government regulatory authorities may inspect the medical records to verify the authenticity, accuracy, and reliability of the study data, without violating the principle of confidentiality.

11.9.2. Liability and Insurance

The responsibilities of Pfizer Inc., monitor and investigator should be consistent with GCP, relevant guidelines and requirements of relevant regulatory authorities in China. The investigator shall be responsible for distributing the investigational drugs according to the protocol approved by the Ethics Committee or its amendment in accordance with the investigator's responsibilities specified in GCP, and the sponsor shall ensure that the investigational drugs are timely delivered to the investigator and clinical trial institution, and ensure the safe storage and safe handling of the investigational drugs throughout the clinical trial.

Pfizer Inc. will purchase clinical trial liability insurance in accordance with relevant laws in China. The costs of treatment for adverse events related to the trial drug or participation in the trial will be provided by the sponsor/insurance company.

11.10. Archive

11.10.1. Investigator File

The investigator and clinical trial institution should properly keep the trial documents according to the "essential documents for clinical trial" and relevant requirements of drug regulatory authorities. The sponsor should specify in the contract with the investigator and clinical trial institution the retention time, cost and handling after expiration of essential documents.

The investigator is responsible for completing and maintaining a confidential participant identification code list, which refers to the unique code assigned to participants in a clinical trial to identify them. When reporting adverse events and other trial-related data in participants, investigators use this code instead of participants' names to protect their privacy.

The trial documents shall not be destroyed without the written authorization of Pfizer Inc. and the investigator. If the investigator retires or the site is no longer able to retain the trial documents, the trial documents may be transferred to a qualified third party for retention.

11.10.2. Trial Core Document

Pfizer Inc. will archive the core documents of the trial in accordance with GCP and applicable regulatory requirements.

11.11. Duties Assumed by All Parties and Other Relevant Regulations

1) Sponsor

In accordance with GCP regulations, the sponsor shall earnestly perform the following responsibilities:

- Initiate and manage the clinical trial and provide the funds required for the trial.
- The sponsor shall take the protection of the rights and interests and safety of participants as well as the authenticity and reliability of clinical trial results as the basic consideration for clinical trial.
- Select the institutions and investigators for clinical trials, and identify their qualifications and conditions to ensure the completion of the trial.
- Before each party to a clinical trial participates in the clinical trial, the sponsor shall specify the responsibilities of each party and indicate them in the signed contract.
- The responsibilities, rights and interests of all parties involved in the trial shall be specified in the contracts signed by the sponsor with the investigators and clinical trial institutions, and the possible conflicts of interest of all parties shall be avoided. The test funds in the contract shall be reasonable and comply with the market laws. The sponsor, investigator and clinical trial institution should sign the contract for confirmation.
- The sponsor should have sufficient safety and efficacy data to support the route, dose, and duration of administration when preparing the clinical trial protocol. When important new information becomes available, the sponsor will promptly update the Investigator's Brochure.
- Before the start of a clinical trial, the sponsor shall submit the relevant clinical trial data to the drug regulatory authority and obtain the license for the clinical trial or complete the filing. The version number and version date should be specified for the documents submitted.
- The sponsor shall obtain from the investigator and clinical trial institution the name and address of Ethics Committee, list of Ethics Committee members participating in the project review, review statement in compliance with this protocol and relevant laws and regulations, documents of approval from Ethics Committee and other relevant materials.

- The sponsor shall select qualified biostatisticians, clinical pharmacologists and clinicians to participate in the trial, including designing trial protocol and case report form, preparing statistical analysis plan, analyzing data and writing interim and final trial summary report.

- The investigator will be provided with investigational products that are easily identified, correctly coded, and specially labeled, and qualified. Investigational medicinal products should be appropriately packaged and stored as described in the trial protocol. The sponsor shall establish management system and record system for investigational drugs.

- The sponsor is responsible for assessing the safety of the investigational product during the drug trial. The sponsor shall timely notify the investigators, clinical trial institutions and drug regulatory authorities of the problems identified in the clinical trial that may affect the safety of participants, may affect the implementation of clinical trial and may change the approval comments of Ethics Committee.

- A qualified monitor will be appointed and accepted by the investigator.

- The sponsor and/or entrusted CRO shall establish quality control and quality assurance system for the clinical trial and may organize the audit on the clinical trial to ensure the quality.

- The sponsor shall specify the access to trial records. The sponsor should specify in the trial protocol or contract that the investigators and clinical trial institutions allow the monitors, auditors, reviewers of the ethics committee and inspectors from drug regulatory authorities to have direct access to source data and documents related to the clinical trial. The sponsor should confirm that each participant agrees in writing to the direct access of original medical records related to the clinical trial by the monitor, auditor, reviewers of the ethics committee and inspectors from drug regulatory authorities.

- The sponsor should designate a qualified medical expert to answer and consult the medical questions related to the clinical trial in a timely manner.

- The sponsor shall report adverse drug reactions as required and within the time limit.

- If the sponsor terminates or suspends the clinical trial in advance, the sponsor shall immediately inform the investigator, clinical trial institution and drug regulatory authority, and explain the reasons.

- The sponsor should take appropriate measures to ensure that compensation or indemnity can be provided to the participants and investigators. The sponsor shall provide legal and economic insurance or guarantee related to the clinical trial to the investigator and clinical trial institution, which shall be adapted to the nature and

degree of risks of the clinical trial, but excluding the damage caused by the negligence of the investigator and clinical trial institution. The sponsor shall bear the cost of diagnosis and treatment and corresponding compensation for the damage or death of participants related to the clinical trial. The sponsor and investigator should pay compensation or indemnity to the participants in a timely manner. The way and method of compensation provided by the sponsor to the participants shall comply with relevant laws and regulations. The sponsor shall provide the investigational drugs to the participants for free and pay the medical test fees related to the clinical trial.

- The sponsor should ensure the protocol compliance during the implementation of the clinical trial. If the investigator or clinical trial institution is found to have serious compliance problems or still does not change after dissuasion, the sponsor shall terminate the continued participation of the investigator or clinical trial institution in the clinical trial and timely report to the drug regulatory authority in writing. Meanwhile, the sponsor and the investigator should take corresponding emergency safety measures to protect the safety and rights and interests of the participants.

- Upon completion or early termination of a clinical trial, the sponsor shall submit a clinical trial report to the drug regulatory authority in accordance with applicable laws and regulations. The clinical trial close-out report shall comprehensively, completely and accurately reflect the clinical trial results. The safety and effectiveness data in the close-out report shall be consistent with the source data of the clinical trial.

2) Study Site and Investigator

In accordance with GCP regulations, the investigator and clinical trial institution shall earnestly perform the following responsibilities:

- The investigator and clinical trial institution should have the qualifications required by GCP.

- The investigator and clinical trial institution should have the necessary conditions to complete the clinical trial.

- The investigator should provide appropriate medical treatment for the participant.

- The investigator should communicate with the Ethics Committee.

- The investigator should follow the trial protocol.

- The investigator and clinical trial institution have administrative responsibility for the investigational product provided by the sponsor.

- The investigator should follow the randomization procedure of the clinical trial.
- The investigator should conduct informed consent in accordance with the ethical principles that have their origin in the Declaration of Helsinki, in accordance with GCP, and provide the informed consent form and other necessary materials to the participants.
- The records and reports of the trial should meet the requirements of GCP.
- The investigator's safety report should meet the GCP requirements.
- When the Ethics Committee decides to terminate the clinical trial in advance, the investigator should immediately report to the study site and the sponsor with reasons stated.
- In case of premature termination or suspension of the clinical trial, the investigator should timely inform the participants, give the participants appropriate treatment and follow-up visit, and fulfill other requirements stipulated in GCP.
- The investigator should provide a trial progress report.

3) Data Management/Statistical Unit

According to the provisions of GCP, the data management and statistical personnel of this trial shall earnestly fulfill their responsibilities. Upon completion of the trial, the data management and statistical personnel is responsible for data management, making statistics for the data according to the formulated statistical plan and issuing the statistical analysis report.

11.12. Study Site and Study Staff

11.12.1. Main Study Site

Name of study institution: Chinese PLA Gerneral Hospitcal

11.12.2. Data Management and Statistics Unit

Organization name: Hangzhou Tigermed Consulting Co., Ltd

11.12.3. Clinical Monitoring Institution

Organization name: Hangzhou Tigermed Consulting Co., Ltd

12. APPENDICES

12.1. Appendix 1 - Potent CYP3A4 Inhibitors and Inducers (Not All)

The following medications and concomitant medications are potent inhibitors of some CYP3A4. This list does not include all such drugs. Concomitant use of strong CYP3A inhibitors is prohibited as described in the study protocol.

Strong CYP3A Inhibitors
Boceprevir, cobicistat, konivaptan, danoprevir and ritonavir, etegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paraprevir and ritonavir (obitavir and/or dalatavir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, teiranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir

The following medications and supplements are strong inducers of some CYP3A4. This list does not include all such drugs. Concomitant use of strong CYP3A inducers is prohibited as described in the study protocol.

Strong CYP3A Inducers
Carbamazepine, phenytoin, rifampin, St. John's Wort

12.2. Appendix 2 - The definition of "migraine day"

The term "migraine day" referred in the term "migraine attack days" in the secondary objective of Section 3.1.2 of protocol are interpreted as follows:

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

a) ≥2 of the following pain features:

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

b) ≥1 of the following associated symptoms:

- Nausea and/or vomiting
- Photophobia and phonophobia

If the participant took a migraine-specific medication (i.e., study medication [open-label, extension phase only], triptan or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

The use of study medication on non-scheduled dosing days is only permitted during the openlabel, extension phase.

12.3. Appendix 3 - Contraceptive and Barrier Guidance

12.3.1. Male Participant Reproductive Inclusion Criteria

No contraception methods are required for male participants 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.

12.3.2. Female Participant 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 participants. Refer to Section 12.3.4 for a complete list of contraceptive methods permitted in the study.

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

- Is not a WOCBP (see definitions below in Section 12.3.3).

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 intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

12.3.3. 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 intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy

- Documented bilateral oophorectomy

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

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

3. Postmenopausal female:

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

    - A high FSH level in the postmenopausal range 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.

12.3.4. 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:

<u>Highly Effective Methods That Have Low User Dependency</u>

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

2. Intrauterine device.

3. Intrauterine hormone-releasing system.

4. Bilateral tubal occlusion.

5. Vasectomized partner:

    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
8. Sexual Abstinence
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Other Effective Methods

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

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