

AN INTERVENTIONAL, PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RIMEGEPANT FOR MIGRAINE PREVENTION IN CHINESE PARTICIPANTS

Study Number(s):	BHV3000-319 (C4951019)
Study Intervention Number:	Rimegepant PF-07899801 (BHV-3000)
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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 Safety and Efficacy of Rimegepant to Prevent Migraine in Chinese Participants.

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Document History

Document	Version Date
Amendment 1 – Version 2.0	30 August 2023
Original protocol – Version 1.0	23 September 2022

Protocol Amendment Summary of Changes Table

Amendment 1 Version 2.0 (30 Aug 2023)

Overall Rationale for the Amendment: Change in sponsorship from Biohaven (BioShin [Shanghai] Consulting Services Co., Ltd) to Pfizer with alignment of the protocol template.

Description of Change	Brief Rationale	Section #
Substantial Modification(s)		
Referenced study number BHV3000-319 to Pfizer C4951019 and compound name BHV-3000 to PF-07899801 to reflect identification changes by sponsor.	Reflected change in sponsorship for protocol and compound identification numbers	Throughout the document
Sponsor name changed.	Reflected transfer of sponsorship from BioShin (Shanghai) Consulting Services Co., Ltd to Pfizer Inc.	Throughout the document
Added section of Benefit Risk Assessment	Added benefit risk background information and added benefit risk assessment	Section 2.4.4 Benefit Risk Assessment
Updated contraception requirement for WOCBP and removed contraception requirement for males. and sections for "Women of Childbearing Potential" (formerly Section 4.6) and "Pregnancy" (formerly Section 7.4). Added Appendix 5	Aligned with Pfizer standard and processes.	Section 5.2 Inclusion Criteria – Inclusion Criterion 3b revised Section 5.3 Exclusion Criteria – Exclusion Criterion 4a revised Section 5.3 Exclusion Criteria – Exclusion Criterion 4d removed Section 5.4 Contraception revised Section 15.5 Appendix 5, Contraceptive and Barrier Guidance added, Formerly Section 4.6 and 9.4 Women of Childbearing Potential and Pregnancy (Removed)
Removed inclusion criterion 5 and added exclusion criterion 5g. "Any other abnormality identified on the medical or laboratory	Allowed for inclusion participants with clinically significant finding, but it will not introduce additional risk factors, or interfere with the study procedures.	Section 5.2 Inclusion Criteria – Inclusion Criterion 5 removed.

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Description of Change	Brief Rationale	Section #
evaluation. if the investigator considers the finding clinically significant, and it will introduce additional risk factors, or interfere with the study procedures".		Section 5.3 Exclusion Criteria – Exclusion Criterion 5g added
Removed the exclusion criterion 1b for participants with headaches occurring 19 or more days per month (migraine or non-migraine) in any of the 3 months prior to the Screening Visit	Collection of headache or migraine days before the participant joining in the study is unfeasible in China. And the inclusion criterion 2e works for the same purpose of this exclusion criterion.	Formerly Section 5.3 Exclusion Criteria – Exclusion Criterion 1b removed.
Removed the exclusion criterion #2a for patients with HIV disease.	Aligned with rimegepant prescribing information where there is no exclusion for use in patients with HIV	Section 5.3 Exclusion Criteria – Exclusion Criteion #2a removed.
Removed Gilbert's Syndrome from the exclusion criterion #2e.	Aligned with rimegepant prescribing information where there is no exclusion for use in Gilbert's Syndrome	Section 5.3 Exclusion Criteria - Exclusion Criterion #2e
Removed the exclusion criterion #2f for patients with gallstones and cholecystectomy	Aligned with rimegepant prescribing information WHERE there is no exclusion for use in participants with biliary disorder	Section 5.3 Exclusion Criteria - Exclusion Criterion #2f removed.
Amended the exclusion criterion for body mass index to >35.0 kg/m^2 from 33.0 kg/m^2.	Aligned definition to be inclusive of all Class 1 Obesity participants	Section 5.3 Exclusion Criteria – Exclusion Criterion #2o
Updated requirement for duration of contraception use after last dose of study intervention	Aligned with Pfizer standard and processes	Section 5.3 Exclusion Criteria - Exclusion Criterion #4a
Removed specific exclusionary ECG criteria	Allowed for investigator opinion on exclusionary ECG findings	Section 5.3 Exclusion Criteria - Exclusion Criterion #5a
Changed eGFR from 40 to 30 mL/min/1.73m^2.	Allowed for participants with moderate renal impairment to be included in the trial consistent with the prescribing information.	Section 5.3 Exclusion Criteria - Exclusion Criterion #5b
Amended the hepatic exclusion criteria to allow participants with 2×ULN of ALT, AST and 1.5×ULN of Total Bilirubin.	Relaxed this criterion based on existing safety data to improve the inclusivity by allowing participants with AST≤ 2×ULN, ALT≤ 2×ULN, Bilirubin≤ 1.5×ULN to be included. Patients with elevated total Bilirubin due to Gilbert's syndrome will be eligible if the direct bilirubin is within normal limit. The current safety profile of IP with no instance meeting Hy's Law rule (potential DILI) allow	Section 5.3 Exclusion Criteria #5c Section 5.3 Exclusion Criteria - Exclusion Criteria #5c and #5d

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Description of Change	Brief Rationale	Section #
	the inclusion of these participants without significant impact on risk factor of benefit/risk ratio for the participants.	
Amended exclusion criterion for HbA1c to >7.5%.	Allowed inclusion of well controlled diabetics aligned with rimegepant prescribing information where there is no exclusion for participants with diabetes	Section 5.3 Exclusion Criteria - Exclusion Criterion #5f
Removed "Participant is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason" from exclusion criterion #7gf	Removed redundant exclusion criteria	Section 5.3 Exclusion Criteria - Exclusion Criterion #7g
Added exclusion criterion for involvement in the conduct of the clinical trial by staff or family members.	Aligned with Pfizer protocol template	Section 5.3 Exclusion Criteria - Exclusion Criterion #7g
Allowed for re-screening of participants due to prior failed eligibility criteria.	Added Section 5.7 Screen Failures, to define the screen failures and data collection requirements of participant who screen failed. And allowed for re-screening of participants who previously were screen failed for an amended inclusion/exclusionary criterion	Section 4.3.1.1 Screening visit Section 5.7 Screen Failure
Added Open-label efficacy, Open-label migraine,and follow-up safety set.	Aligned with Statistical Analysis Plan	Section 10.2 Analysis Sets
Changed statistical method from Kenward Roger to Huber-White robust "sandwich" estimator.	Clarified statistical methodology and aligned with recent FDA guidance.	Section 10.3.1 Primary endpoint Section 10.3.2 Secondary endpoint
Changed "Cochran-Mantel-Haenszel test" to be "Mantel-Haenszel risk estimation".	To be more accurate in terms of analysis	Section 10.3.2 Secondary endpoint
Added Appendix for ECG findings of Potential Clinical Concern.	Aligned with Pfizer protocol template	Section 15.6 Appendix 6 ECG Findings of Potential Clinical Concern Section 6.2.2 Electrocardiogram
Non-substantial Modification(s)		
Re-organization of protocol summary	Sponsor-required template.	Section 1 Protocol Summary
Added 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
Clarified that this amendment incorporates all revisions to date, including amendments made at the	Aligned with Pfizer protocol template.	Summary of Changes

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Description of Change	Brief Rationale	Section #
request of country health authorities and IRBs/ECs and any PACL.		
Combined the sections of Study Objectives, Endpoints and Estimands	Aligned with Pfizer protocol template	Section 1 Protocol Summary Section 3 Study Objectives, Endpoints, Estimands. Former Section 4 and Section 5 removed
Removed the prefix "28 days" or "the first 28 day" of Observation Phase	To avoid confusion since there is a "+3 days" window of the 28-day Observation Phase.	Section 1.1 Protocol Summary Section 4.3 Schedule of Assessment Section 5.2 Inclusion Criteria - inclusion criterion #4 Section 8.2.1 Method of Assigning Participant Identification
Updated the Study Week and Study Day	Correction of typographical errors. Incorporation of non-substantial changes described in previous PACL dated Feb 22 2023	SOA Table 1, Table 2; Section 4.3.2.3 Week 12 Visit
Changed that participants start study intervention on the day of the baseline visit.	Changing First Dose to be on the same day as Randomization Day (Day 1) to ensure the participants take first dose as expected. Incorporation of non-substantial changes described in previous PACL dated Feb 22 2023	SOA Table 1; Section 4.3.2.1 Baseline (Randomization) Visit paragraph 3
Changed the "Clinical Safety Laboratory Testing" to "Hematology, Chemistry, eGFR"	To keep consistent with the classification of Clinical Safety Laboratory Testing in Section 7.2.4. Incorporation of non-substantial changes described in previous PACL dated Feb 22 2023	SOA Table 1 and Table 2
Reduced the frequency of ECG test.	Keep the ECG at Screening Visit, Week 12 and Week 24, removed the ECG at Baseline Visit, Week 4 and Week 16.	SOA Table 1 and Table 2
Added Lipid Panel and Urinalysis at Week 12 Visit.	To keep consistent with that of Week 24/EOT Visit. In that case the participants who complete the Week 12 Visit but will not enter the OLE phase can enter the 2-week follow-up visit directly and no need an additional EOT Visit.	SOA Table 1
Changed the Follow-up Week2 Visit to Follow-up Week 4 Visit	Aligned with Pfizer template and study procedure.	Section 1.2 Study Schematic Section 4 Study Plan Section 5.4 Contraception Section 5.5 Other Restrictions and Precautions Section 7.1 Discontinuation of Study Intervention

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Description of Change	Brief Rationale	Section #
		Section 9.2 Non-serious Adverse Events
Deleted the location of pulse rate assessment "radial artery".	Removed the unnecessary wording.	SOA Table 1 footnote 3 SOA Table 2 footnote 4
Corrected the typographical errors of SOA Table 1 footnote 4.	Incorporation of non-substantial changes described in previous PACL dated Feb 22 2023	SOA Table 1 footnote 4
Added 'moderate to severe' to the variable of the 1st secondary objective: proportion of participants who have ≥50% reduction in migraine days	To align with the wording of the corresponding endpoint.	Section 3.3.2 Secondary Estimands
Updated from 'Change from Observation Phase in the mean number' to "Mean number" for the variable of objective: mean number of acute migraine medication days per month.	To align with the wording of the corresponding endpoint.	Section 3.3.2 Secondary Estimands
Changed the recording and treatment of "migraine" to that of "headache".	Changed the recording and treatment of "migraine" to that of "headache" to align with the study design. e.g. changed "the participants will report migraine occurrence, migraine pain features…" to "the participants will report headache (including migraine and non-migraine) occurrence pain features…". And changed "If participants have a migraine, they may treat the migraine with permitted acute migraine medications" to "If participants have a headache, they may treat the headache with permitted medications" as well.	Section 2.4.1 Study Design Rationale Section 4.1 Study Design and Duration Section 4.3 Schedule of Assessment Section 6.1 Study Materials Section 6.3 Efficacy Assessments Section 8.6.1 Prohibited and Restricted Concomitant Therapy Section 8.6.2 Standard of Care Headache Medication Section 15.1 APPENDIX 1 – Definition of Migraine Days
Modified the language of eDiary reporting.	Changed recording eDiary "every day" during the OP to "once the eDiary device has been received" recording "daily". To have flexibility for participants who do not receive the device at Screening visit day.	Section 4.3.1.1 Screening Visit
Replacement of language regarding COVID-19 pandemic with language regarding public health emergencies	COVID-19 pandemic does not meet the criteria of world health emergency anymore and the current impact on study conduct is not considered significant. The language regarding precautions related to impact of public health emergencies on study conduct was adjusted.	Section 4.3.6 Public Health Emergencies
Modified the language of End of treatment.	Editorial	Section 1.2 Study Schematic

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Description of Change	Brief Rationale	Section #
		Section 4.3.4 End of Treatment
Modified the language of Follow-up Week 4 Visit	Editorial	Section 1.2 Study Schematic Section 4.3.5 Follow-up Week 4 Visit
Modification of exclusion criterion 2b	Added cerebrovascular disease in the exclusionary condition to keep consistent throughout the paragraph.	Section 5.3 Exclusion Criteria - Exclusion Criterion 2b
Simplified Exclusion Criterion of alcohol and drug abuse	Removed the wording of investigator's judgement and the redundant sentence.	Section 5.3 Exclusion Criteria -Exclusion Criteria #2l & 2m
Removed "but did not participate in BHV3000-318 study" from exclusion criteria	Editorial, redundant sentence	Section 5.3 Exclusion Criteria -Exclusion Criteria #7f
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 8.6.1 Prohibited and Restricted Concomitant Medications
Changed "OnabotulinumtoxinA (Botox®)" to "Botulinum toxin injections (e.g., Botox®)"	Editorial	Section 5.3 Exclusion Criterion # 6 ii Section 8.6.1 Prohibited and Restricted Concomitant Medications 1b
Modified the language of Deviation from Inclusion/Exclusion Criteria	Editorial	Section 5.6 Deviation from Inclusion/Exclusion Criteria
Clarifications and guidance related to the term complete physical examinations	Focusing on physical examination of most critical, from the perspective of safety and study conduct, anatomical systems.	Section 6.2.3 Physical Examination
Added "Serum pregnancy tests will be performed in the central lab, and urine pregnancy tests will be performed in local site" in section of Pregnancy Testing.	Incorporation of non-substantial changes described in previous PACL dated Feb 22 2023 with minor edits.	Section 6.2.4.2 Pregnancy Testing
Amended the Reflex/add-on tests of LFT.	Aligned with Liver Safety: Suggested Actions and Follow Up Assessments and Study Intervention Rechallenge Guidelines	Section 6.2.4.1) Safety Laboraotry Testing
Amended the Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Defined Discontinuation of Study Intervention and Discontinuation/Withdrawal from the Study aligned with Pfizer protocol template.	Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal
Updated study intervention storage condition.	Removed humidity from study intervention storage conditions.	Section 8.1.2 Packaging, Labeling and Storage
Added reference to IP Manual	Reference to IP Manual regarding Packaging, Shipment and Storage	Section 8.1.2 Packaging, Labeling and Storage
Changed the recommended dosing time.	Administration of study intervention after the eDiary reminder to enhance the adherence with the protocol and avoid missing dose.	Section 8.2.2 Selection and Timing of Dose and Administration

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Description of Change	Brief Rationale	Section #
	Incorporation of non-substantial changes described in previous PACL dated Feb 22, 2023	
Amended language regarding blinding and unblinding	Sponsor-required language.	Section 8.3 Blinding and Unblinding
Changed term "Non-Investigational Product", to "Prior and Concomitant Therapy", and updated the definition for concomitant therapy	Editorial changes Aligned definition with current regulations.	Section 8.6 Formerly Section 8.1.2 removed. Formerly section 6.4 & 6.5 to section 8.6
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 9
Updated SAE reporting destination and electronic reporting system administrative changes and clarifications	Aligned with Pfizer protocol template	Section 9.1.2 Collection and Reporting Serious Adverse Events
Change of language regarding overdosing	Change of safety handling of overdose and update as per sponsor-required AE identification and reporting language.	Section 9.3 Overdose
Clarified that in case of DILI the PI should determine if the patient can safely continue in the study and expanded DILI definition to include participants with abnormal hepatic function at study entry.	Updated definition to align with revised LFT exclusion criteria	Section 9.4 Potential Drug Induced Liver Injury (DILI)
Added Pfizer standard safety language for environmental exposure, exposure during pregnancy, exposure during breastfeeding, occupational exposure	Aligned with Pfizer protocol template	Section 9.5 Environmental exposure, Exposure during Pregnancy, and Occupational exposure Former Section 9.5 removed.
Added AE information on lack of efficacy, medication errors and adverse events of special interest	Aligned with Pfizer protocol template	Section 9.6 Lack of Efficacy Section 9.7 Medication Errors
Added Sponsor's regulatory and ethics responsibilities.	Aligned with Pfizer protocol template	Section 11.1 Good Clinical Practice
Updated language regarding informed consents and assents	Sponsor-required language.	Section 11.4 Informed Consent
Updated details on confidentiality and renamed	Replaced with Pfizer Data protection policy	Section 11.6 Data Protection

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Description of Change	Brief Rationale	Section #
section, Data Protection Policy		Formerly Section 16 Confidentiality removed
Added section of Dissemination of Clinical Study Data	Sponsor-required language.	Section 11.7 Dissemination of Clinical Study Data
Added section of Sponsor's Medically Qualified Individual	Sponsor-required language.	Section 11.8 Sponsor's Medically Qualified Individual
Added language regarding the handling of redacted copies of participant medical records	Sponsor-required language.	Section 12.2 Use of Medical Records
Moved formerly Section 14 Study Report and Publication to Section 12.4	Aligned with Pfizer protocol template	Section 12.4 Study Report and Publication Formerly section 14 removed.
Removed Clinical Protocol Approval Form	Aligned with Pfizer protocol template	Protocol approval form removed
Removed PI declaration page	Aligned with Pfizer protocol template	PI declaration page removed
Removed Appendix 1 Names of Study Personnel	Aligned with Pfizer protocol template	Formerly section 18.1 Appendix 1 removed.
Removed tacrolimus from the Strong CYP3A4 inhibitors list.	Aligned with nonclinical and clinical DDI information available on rimegepant	Section 15.3 Appendix 3 Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein
Removed grapefruit from the Moderate CYP3A4 inhibitors list.	Aligned with nonclinical and clinical DDI information available on rimegepant	Section 15.3 Appendix 3 Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein
Update of List of Abbreviations	Editorial update	List Of Abbreviations
Updated document header and footer	Updated to align with Pfizer protocol template	Header and Footer
Changed "study drug" to "study intervention".	Editorial update	Throughout the document.
Correction of typo errors	Typo error were corrected.	Throughout the document.

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.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

TABLE OF CONTENTS

LIST OF TABLES 14
LIST OF FIGURES 14
LIST OF ABBREVIATIONS 15
1. PROTOCOL SUMMARY 18
1.1. Synopsis 18
1.2. Study Schematic 25
2. INTRODUCTION AND RATIONALE 27
2.1. Background 27
2.2. The role of CGRP and CGRP receptor in migraine 27
2.3. Product Development Background 28
2.3.1. Clinical Experience 28
2.3.2. Clinical Adverse Event Profile 29
2.4. Study Rationale 29
2.4.1. Study Design Rationale 29
2.4.2. Dose Selection Rationale 30
2.4.3. Research Hypothesis 30
2.4.4. Benefit Risk Assessment 31
3. OBJECTIVES, ENDPOINTS, ESTIMANDS 32
3.1. Study Objectives 32
3.1.1. Primary Objective(s) 32
3.1.2. Secondary Objective(s) 33
3.1.3. Exploratory Objective(s) 33
3.2. Study Endpoints 34
3.2.1. Primary Endpoint 35
3.2.2. Secondary Endpoint(s) 35
3.2.3. Exploratory Endpoint(s) 35
3.3. Study Estimands 37
3.3.1. Primary Estimands 37
3.3.2. Secondary Estimands 37
4. STUDY PLAN 38
4.1. Study Design and Duration 38

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

4.2. Study Schematic 40
4.3. Schedule of Assessment 41
4.3.1. Observation Phase 48
4.3.1.1. Screening Visit 48
4.3.2. Randomized, Double-Blind Treatment Phase (12 weeks) 48
4.3.2.1. Baseline (Randomization) Visit 48
4.3.2.2. Week 2, Week4 and Week 8 Visit 49
4.3.2.3. Week 12 Visit 49
4.3.3. Open-label Extension Phase (12 weeks) 50
4.3.4. End of Treatment 51
4.3.5. Follow-up Week 4 Visit 51
4.3.6. Public Health Emergencies Contingencies 51
4.4. Post Study Access to Therapy 52
5. STUDY POPULATION 52
5.1. Number of Participants 52
5.2. Inclusion Criteria 52
5.3. Exclusion Criteria 53
5.4. Contraception 56
5.5. Other Restrictions and Precautions (if applicable) 57
5.6. Deviation from Inclusion/Exclusion Criteria 57
5.7. Screen Failures 57
6. STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES 58
6.1. Study Materials 58
6.2. Safety Assessments 58
6.2.1. Vital Signs and Physical Measurements (Height and Weight) 58
6.2.2. Physical Examination 58
6.2.3. Electrocardiogram (ECG) 58
6.2.4. Laboratory Assessments 59
6.2.4.1. Safety Laboratory Testing 59
6.2.4.2. Pregnancy Testing 60
6.2.5. Columbia-Suicide Severity Rating Scale (C-SSRS) 60
6.3. Efficacy Assessments 60

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

6.4. Other Assessments 60
6.4.1. Migraine-Specific Quality-of-Life Questionnaire v 2.1 60
6.4.2. Migraine Disability Assessment (MIDAS) Questionnaire 61
6.4.3. EQ-5D-5L 61
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 61
7.1. Discontinuation of Study Intervention 61
7.2. Discontinuation/Withdrawal from the Study 62
7.2.1. Participant Discontinuation/Withdrawal from the Study 62
7.2.1.1. Withdrawal of Consent 62
7.2.1.2. Lost to Follow-Up 62
8. STUDY INTERVENTION AND CONCOMITANT THERAPY 63
8.1. Description of Study intervention 63
8.1.1. Investigational Product 63
8.1.2. Packaging, Shipment and Storage 63
8.2. Dose and Administration 63
8.2.1. Method of Assigning Participant Identification 63
8.2.2. Selection and Timing of Dose and Administration 64
8.2.3. Dose Modifications 64
8.2.4. Dose Interruptions 64
8.3. Blinding and Unblinding 65
8.4. Treatment Compliance 65
8.5. Destruction and Return of Study intervention 66
8.6. Prior and Concomitant Therapy 66
8.6.1. Prohibited and Restricted Concomitant Therapy 67
8.6.2. Acute Headache Medications 68
9. ADVERSE EVENTS 69
9.1. Serious Adverse Events 71
9.1.1. Definition of Serious Adverse Event (SAE) 71
9.1.2. Collection and Reporting Serious Adverse Events 73
9.2. Non-serious Adverse Events 74
9.2.1. Collection and Reporting of Non-Serious Adverse Events 74

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

9.2.2. Laboratory Test Abnormalities....74
9.3. Overdose....74
9.4. Potential Drug Induced Liver Injury (DILI)....75
9.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure....76
9.5.1. Exposure During Pregnancy....76
9.5.2. Exposure During Breastfeeding....78
9.5.3. Occupational Exposure....79
9.6. Lack of Efficacy....79
9.7. Medication Errors....79
10. STATISTICS CONSIDERATIONS....79
10.1. Sample Size....79
10.2. Analysis Sets....80
10.3. Statistical Methods....80
10.3.1. Primary Endpoint....81
10.3.2. Secondary Endpoints....81
10.3.3. Type 1 Error Control....83
10.4. Schedule of Analyses....83
11. ETHICS AND RESPONSIBILITIES....83
11.1. Good Clinical Practice....83
11.2. Data and Safety Monitoring Committee....84
11.3. Institutional Review Board/Independent Ethics Committee....84
11.4. Informed Consent....84
11.5. Case Report Forms....85
11.6. Data Protection....85
11.7. Dissemination of Clinical Study Data....86
11.8. Sponsor's Medically Qualified Individual....87
12. RECORDS MANAGEMENT....87
12.1. Source Documentation....88
12.2. Use of Medical Records....89
12.3. Study Files and Record Retention....89
12.4. Study report and publications....90

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

13. AMENDMENTS 90
14. STUDY DISCONTINUATION 90
15. APPENDICES 91
15.1. APPENDIX 1 – Definition of Migraine Days 91
15.2. APPENDIX 2 – Categories of Migraine Prevention Medications 93
15.3. APPENDIX 3 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive) 95
15.4. APPENDIX 4 - Liver Safety: Suggested Actions and Follow Up Assessments and Study Intervention Rechallenge Guidelines 97
15.5. Appendix 5 - Contraceptive and Barrier Guidance 99
15.5.1. Male Participant Reproductive Inclusion Criteria 99
15.5.2. Female Participant Reproductive Inclusion Criteria 99
15.5.3. Woman of Childbearing Potential 99
15.5.4. Contraceptive Methods 100
15.6. Appendix 6 - ECG Findings of Potential Clinical Concern 102
16. REFERENCES 104

LIST OF TABLES

Table 1. Schedule of Assessments – Observation Phase and Double-blind Treatment Phase 41
Table 2. Schedule of Assessments – Open-label Extension Phase and Follow-up Week 4 Visit 45

LIST OF FIGURES

Figure 1. Study Schema 25

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting-enzyme
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blockers
AST	aspartate aminotransferase
AV	atrioventricular
bpm	beats per minute
BUN	blood urea nitrogen
C-SSRS	Columbia-suicide severity rating scale
CGRP	calcitonin gene-related peptide
CI	confidence interval
CK	creatine kinase
CLR	calcitonin receptor-like receptor
CRF	case report form
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
DBT	double-blind treatment
DILI	drug-induced liver injury
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSU	drug safety unit
ECG	electrocardiogram
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
EOD	every other day
EOT	end of treatment
EQ-5D-5L	EuroQol 5-dimensional questionnaire
EQ VAS	EuroQol visual analogue scale
eTMF	electronic Trial Master File
EU	European Union
EudraCT	European clinical trials database
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Abbreviation	Definition
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAV	Hepatitis A Virus
HbA1c	Hemoglobin A1c
HBc IgM	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HDL-C	high density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
HRT	hormone replacement therapy
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
ICHD-3	International Classification of Headache Disorders, 3rd edition
IEC	Institutional Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator Site File
IWRS	Interactive Web-based Response System
LBBB	left bundle branch block
LDL-C	low density lipoprotein cholesterol
LDH	lactate dehydrogenase
LFT	liver function test
MDD	major depressive disorder
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MQI	medically qualified individual
MSQoL	Migraine-Specific Quality-of-Life Questionnaire
N/A	not applicable
NOAEL	no observed adverse effect level
NSAIDs	nonsteroidal anti-inflammatory drugs
ODT	orally disintegrating tablet
OLE	open-label Extension

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Abbreviation	Definition
OP	observation phase
OTC	over the counter
PCP	phencyclidine
P-gp	P-glycoprotein
PK	pharmacokinetics
PRN	pro re nata (as required)
PSSA	Pfizer SAE Submission Assistant
PVC	premature ventricular contraction
QD	once daily
RAMP1	receptor activity-modifying protein 1
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOP	standard operating procedure
SRSD	Single Reference Safety Document
T bili	total bilirubin
THC	tetrahydrocannabinol
UK	United Kingdom
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cells
WOCBP	Women of Childbearing Potential

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1. PROTOCOL SUMMARY

1.1. Synopsis

Title: An Interventional, Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Chinese Participants

Brief Title: A Study to Learn About the Safety and Efficacy of Rimegepant to Prevent Migraine in Chinese Participants.

Regulatory Agency Identification Number(s):

US IND Number:	N/A
EudraCT/EU CT Number:	N/A
ClinicalTrials.gov ID:	NCT05810038
Pediatric Investigational Plan Number:	N/A
Protocol Number:	BHV3000-319 (C4951019)
Phase:	3

Rationale: Rimegepant has been approved for both the acute treatment of migraine and the preventive treatment for episodic migraine by the United States (US) Food and Drug Administration (FDA). Similar approvals have recently been granted in the European Union (EU) and United Kingdom (UK). The purpose of the current study is to provide confirmatory evidence of the efficacy and safety of rimegepant for migraine prevention in Chinese participants.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To compare the efficacy of Rimegepant to placebo as a preventive treatment for migraine, as measured by the mean reduction from the Observation Phase (OP) in the number of migraine days per month over the entire Double-blind Treatment (DBT) Phase.	Mean change from the OP in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).	The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
Secondary:	**Secondary:**	**Secondary:**
• To compare the efficacy of rimegepant to placebo on the	• Percentage of participants with ≥50% reduction from	• The estimand is the treatment effect of

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Objectives	Endpoints	Estimands
proportion of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase.	OP in the number of moderate to severe migraine days per month over the entire DBT Phase.	rimegepant relative to placebo in terms of the difference in percentage of participants with ≥50% reduction from the OP in the number of moderate to severe migraine days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
• To compare the efficacy of rimegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.	• Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase.	• The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
• To compare the efficacy of rimegepant to placebo on the mean reduction from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.	• Mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase.	• The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.

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Objectives	Endpoints	Estimands
• To compare the change from baseline in the Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQoL v2.1) role function - restrictive domain score at Week 12 of the DBT Phase between rimegepant and placebo.	• Change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase.	• The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in change from baseline in the MSQoL role function-restrictive domain score at Week 12 of the DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
• To compare the efficacy of rimegepant to placebo on the mean number of acute migraine medication days per month over the entire DBT Phase.	• Mean number of acute migraine medication days per month over the entire DBT Phase.	• The estimand is the treatment effect of rimegepant relative to placebo in terms of the difference in mean number of acute migraine medication days per month over the entire DBT Phase among all randomized participants with migraine who took study intervention without regard to the use of prophylactic medications. Data collected after study intervention discontinuation will be excluded.
• To evaluate the safety and tolerability of rimegepant during the DBT and Open-label Extension (OLE) Phases.	• Number and percentage of participants with adverse events (AEs) by severity, serious adverse events (SAEs), AEs leading to study intervention discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the DBT Phase and OLE Phase.	• Not applicable.
• To evaluate the frequency of ALT or AST > 3×ULN concurrent with total bilirubin > 2×ULN in	• Number and percentage of participants with ALT or AST > 3×ULN concurrent with total bilirubin > 2×ULN	• Not applicable.

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Objectives	Endpoints	Estimands
participants treated with rimegepant during the DBT and OLE Phases.	on treatment during the DBT and OLE Phases.	
• To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to study intervention discontinuation in participants treated with rimegepant during the DBT and OLE Phases.	• Number and percentage of participants with hepatic-related AEs and hepatic-related AEs leading to study intervention discontinuation on treatment treated with remigepant during the DBT Phase and OLE Phase.	• Not applicable.

Overall Design:

This is a 12-week multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant in migraine prevention in Chinese participants followed by a 12-week Open-label Extension Phase.

The Observation Phase will include the Screening Visit. Upon completion of the Screening Visit, participants will be provided an electronic diary (eDiary) to be used daily to report headache (including migraine and non-migraine) occurrence, pain features, and associated symptoms during the Observation Phase. Participants will record all concomitant medications, including acute standard of care headache medications (both prescribed and over the counter [OTC]) they take in a concomitant medication paper diary. To be eligible for the study, participants must report having had 4 to 18 migraine attacks of moderate to severe intensity per month (4-week period) within the 3 months prior to the Screening Visit, and at least 6 migraine days and no more than 18 headache days during the Observation Phase. After completing the Observation Phase, participants will return to the study site with both diaries for the Baseline (Randomization) Visit. At the Baseline Visit, eligibility for continued study participation will be assessed before randomization occurs and before study intervention is dispensed. Eligible participants will be randomized 1:1 to 2 treatment groups: rimegepant 75 mg ODT dosed EOD (n=392) or matching placebo EOD (n=392). Randomization will be stratified by the number of migraine days during the Observation Phase (<8, ≥8). During the 12-week Double-blind Treatment Phase, participants will be instructed that they must take 1 tablet of blinded study intervention (rimegepant 75 mg or placebo) every other calendar day. If participants have a headache during the Double-blind Treatment Phase, if needed, they may treat the headache with their permitted standard of care headache medication and continue to take study intervention on their scheduled dosing days.

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

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Participants will continue to use the eDiary daily to report headache occurrence and pain features during the Double-blind Treatment and Open-label Extension Phases. Participants are required to report each dose of study intervention taken in a study intervention paper diary throughout the entire study. Participants are also required to record any concomitant medications, including acute standard of care headache medications (both prescribed and OTC) taken in a concomitant medication paper diary throughout the entire study.

At select study visits, participants will complete or will be administered the MSQoL v2.1, the migraine disability assessment (MIDAS) and EuroQol 5-dimensional questionnaire (EQ-5D-5L) and the Columbia-Suicide Severity Rating Scale (C-SSRS). Additional assessments and visit schedule are outlined in the procedural table in Section 4.3.

Study visits will occur at the following time points: Screening during the Observation Phase; Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12 during the Double-blind Treatment Phase; Week 14, Week 16, Week 20, and Week 24/ End of Treatment (EOT) during the Open-label Extension Phase. Participants will return to the study site at the end of Week 24 for the EOT visit. Participants who discontinue Double-blind Treatment Phase, or do not enter or complete the Open-label Extension Phase, will also return to the site for the EOT visit at the time of study intervention discontinuation. There is a Follow-up Week 4 Visit approximately 28 days after the EOT visit. All randomized participants should complete the Follow-up Week 4 Visit, regardless of completing either treatment phase.

To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Laboratory results that meet predefined LFT abnormality criteria as potential DILI events should be reported as a serious adverse event (SAE). See Section 9.4 Potential DILI.

Number of Participants: Approximately 1426 participants will be screened to randomize up to approximately 784 participants to rimegepant or matching placebo group. It is estimated that approximately up to 728 participants will enter into an Open-label Extension Phase.

Study Population:

Key Inclusion Criteria

- Chinese male and female participants ≥18 years
- Target population: participants with 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, including the following:
    - Age of onset of migraines prior to 50 years of age.
    - Migraine attack, lasting 4 to 72 hours on average if untreated.
    - Per participant report, 4 to 18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit.

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- Six or more migraine days during the Observation Phase per eDiary.
- Not more than 18 headache days during the Observation Phase per eDiary.
- Ability to distinguish migraine attacks from tension/cluster headaches.
- Participants with contraindications for use of triptans may be included provided they meet all other study entry criteria.

- Participants must complete at least 24 eDiary reports during the Observation Phase, and must be able to read, understand and complete the study questionnaires and eDiary per investigator's judgement.

Key Exclusion Criteria

- Target Disease Exclusion
  - History of basilar migraine or hemiplegic migraine
- Clinically significant/unstable disease(s), or laboratory parameters outside the reference range that are considered clinically significant by investigators.
- No therapeutic response with >2 of the 9 medication categories of preventive treatment of migraine (see Section15.2) after an adequate therapeutic trial in the past 3 years per investigator's judgement.
- Prohibited Medications (Not all prohibited medications are listed here, for details please see Section 8.6.1)
  - CGRP monoclonal antibodies or onabotulinumtoxinA (Botox®) taken within 6 months (24 weeks) prior to the Screening Visit. Other medications with demonstrated efficacy for the prevention of migraine taken within 30 days prior to the Screening Visit (ie, topiramate, flunarizine, and atogepant; for the full list please see Section 15.2)
  - Medication accepted for treatment of acute migraine (see Section 8.6.2) for a non-migraine indication taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.
  - Ergotamine taken ≥10 days per month on a regular basis for ≥3 months (≥12 weeks) in the year prior to the Screening Visit.
  - Analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.
    - Prohibited medication or device used during the Observation Phase (see Section 8.6.1)

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Study Arms and Duration: All participants will participate in a 28-day Observation Phase (+3 days). After completion of the OP, on Day 1 (Randomization), participants will start the DBT phase and are to be assigned to 1 of the 2 study arms to receive either rimegepant or matching placebo. The DBT period lasts 12 weeks. At the end of DBT Phase eligible participants will start the optional 12-week OLE. If a participant early terminates from the trial, they will complete the End of Treatment procedures.

Study Intervention(s)		
Intervention Name	Rimegepant (PF-07899801)	Matching Placebo
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Dose Formulation	ODT	ODT
Unit Dose Strength(s)	75 mg.	0 mg
Route of Administration	Oral	Oral
Study Arm(s) Double Blind Treatment Phase		
Arm Title	Active	Control
Arm Type	Experimental	Placebo
The participants will be instructed that they must take ***one (1) ODT every other day (EOD), regardless of whether they have a migraine on that day or not.***	Rimegepant EOD Dosing	Matching placebo EOD Dosing
Study Arm(s) Open Label Treatment Phase		
Arm Title	Active	
Arm Type	Experimental	
Participants who complete the DBT Phase Week 12 visit will be screened for eligibility to continue to OLE. The participants will be instructed that they must take ***one (1) 75 mg ODT EOD, regardless of whether they have a migraine on that day or not. If participants have a migraine on the day that they are not scheduled to take a dose of study intervention, if needed, they may take a study intervention dose to treat a migraine on that calendar day. Dosing during OLE then, may be EOD or up to once a day (QD) as needed.***	Rimegepant EOD Dosing	

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Statistical Methods:

The study will randomize approximately 392 study participants per treatment group (784 participants in total). Based on data from migraine prevention study BHV3000-305 conducted in the U.S., we estimate that this will result in approximately 364 participants per treatment group (728 participants in total) in the double-blind treatment migraine analysis set.

Assuming rimegepant provides roughly a 0.8-day advantage over placebo on the primary endpoint, and a common standard deviation of 3.6 days, then the study will have roughly 85% power on the primary endpoint at a 2-sided alpha level of 0.05. Estimates are based on data from study BHV3000-305; the advantage over placebo on the primary endpoint was estimated from a model, whereas the common standard deviation was estimated from the observed data.

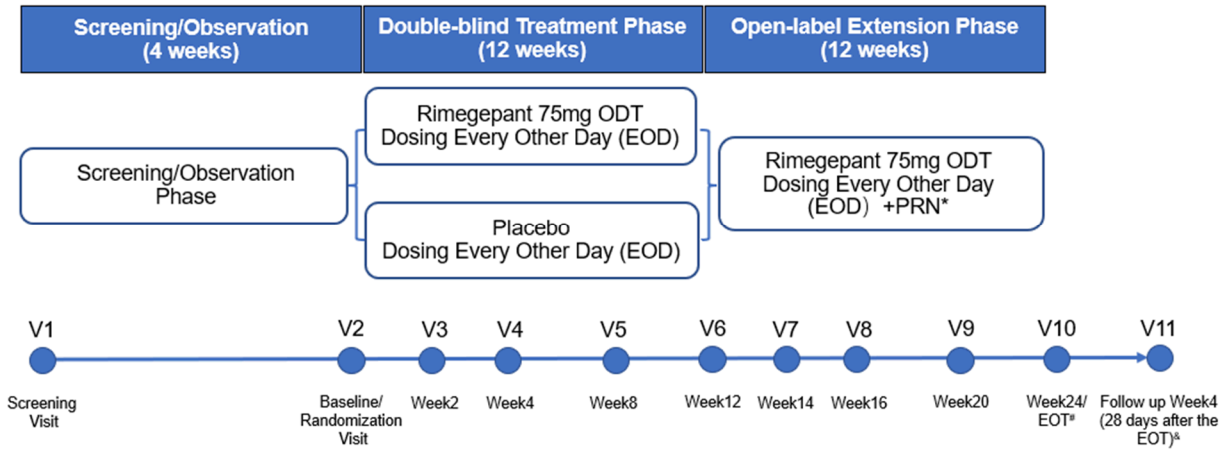
The primary endpoint will be assessed for the double-blind treatment migraine analysis set using a linear mixed effects model with repeated measures that will include the following variables: change from the Observation Phase in the number of migraine days per month as the dependent variable; number of migraine days per month in the Observation Phase as a covariate; and fixed effects for treatment group, randomization stratum, month, and month-by-treatment group interaction.

Categorical data will be summarized using Mantel-Haenszel risk estimation stratified by randomization stratum. Missing data will be imputed as non-response (ie, failure). The stratified difference estimate (rimegepant – placebo), SE, p-value, and 95% CI will be reported.

The frequencies of safety endpoints will be assessed descriptively as the number and percentage of participants with events/findings separately.

1.2. Study Schematic

Figure 1. Study Schema



090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

*During the Open-label Extension Phase, participants will be instructed that they must take 1 rimegepant 75 mg ODT every other calendar day. If participants have a migraine attack on the day that they are not scheduled to dose with rimegepant, they may take 1 rimegepant 75 mg ODT on that calendar day to treat a migraine. Therefore, during the Open-label Extension Phase, participants can take a maximum of 1 rimegepant 75 mg ODT per calendar day up to 12 weeks.

Participants will return to the study site at the end of Week 24 for the EOT visit. Participants who do not complete the Double-blind Treatment Phase, or do not complete the Open-label Extension Phase, will complete the EOT visit.

& There is a Follow-up Week 4 Visit approximately 28 days after the EOT visit. For the participants who complete the EOT Visit, and the participants who complete the Double-blind Treatment Phase (Week12 visit) but do not enter the Open-label Extension Phase should complete the Follow-up Week 4 Visit.

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2. INTRODUCTION AND RATIONALE

2.1. Background

Migraine is a disabling neurological disorder that affects over 1 billion people worldwide and induces huge burden on patients, their families and society[1,2]. The estimated 1-year prevalence of migraine ranges from 7.9% to 14.3% in China[3-5], however, only half of them (52.9%) had consulted a doctor specifically for headache and only 2.7% of people with migraine had taken preventive medication according to a clinic-based study in China[6], which indicate a huge unmet medical need for migraine preventive treatment in China.

Rimegepant is a small molecule oral calcitonin gene-related peptide (CGRP) antagonist and the only CGPR targeted medication approved for both the acute treatment of migraine and the preventive treatment for episodic migraine by the US FDA[7]. Similar approvals have recently been granted in the European Union and United Kingdom. The efficacy for acute treatment was confirmed in 3 US Phase 3 trials and 1 regional Phase 3 trial that was conducted in China and South Korea. All 4 trials demonstrated that rimegepant 75 mg was superior to placebo for freedom from pain and freedom from the most bothersome symptom at 2 hours post-dose.

Additionally, in a double-blind, placebo-controlled US Phase 2/3 prevention study, rimegepant 75 mg dosed EOD demonstrated superiority to placebo on the primary endpoint of mean reduction from the Observation Phase in the number of migraine days per month in the last month (Weeks 9 to 12) of the Double-blind Treatment Phase[8]. This study demonstrated that the optimal dose for acute treatment is effective when dosed EOD for preventive treatment[8].

This Phase 3 study is being conducted to evaluate the efficacy, safety and tolerability of rimegepant 75 mg ODT dosed EOD versus matching placebo dosed EOD in the preventive treatment of migraine in Chinese participants.

2.2. The role of CGRP and CGRP receptor in migraine

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

CGRP is an endogenous 37 amino acid peptide contained within pain-signaling nociceptive afferents, and it is thought to play a causal role in migraine[9,10]. Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine[11]; 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief[11,12]; 3) intravenous CGRP infusion produces lasting pain in non-migraineurs and migraineurs[10,13].

The CGRP receptor is a G protein-coupled receptor of the B-type consisting of CLR and RAMP1[14,15]. CGRP receptors are widely expressed in both central and peripheral nervous system sites that have been implicated in migraine pathophysiology[14,15]. Treatment with a CGRP receptor antagonist is believed to relieve migraine through the following possible mechanisms[16]:

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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

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

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

With the potential to address important unmet needs (efficacy without medication overuse headache, no contraindications or warnings in patients with cardiovascular disease), rimegepant offers a novel therapeutic strategy for both acute and preventive treatment of migraine.

2.3. Product Development Background

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

2.3.1. Clinical Experience

As of January 2022, more than 8500 participants have participated in Phase 1 studies in healthy participants or Phase 2 and 3 studies in participants with migraine.

A total of 24 Phase 1 studies have contributed to the characterization of the biopharmaceutics and clinical pharmacology of rimegepant. These studies were conducted in approximately 828 participants including healthy participants (N=694), participants in specific populations (e.g., elderly, hepatic impairment and renal impairment; N=86), and participants with migraine (N=48). In these Phase 1 studies, approximately 782 participants were administered at least 1 dose of rimegepant.

In Phase 2 and 3 studies, more than 4900 participants received clinical dose of rimegepant 75 mg. Overall, approximately 2525 unique participants received rimegepant in single dose studies: these included 2439 participants in the 4 pivotal Phase 3, single-dose, placebo-controlled, acute treatment studies (ie, BHV3000-301[17], BHV3000-302[18], BHV3000-303[19], BHV3000-310[20]), and 86 participants in the Phase 2b dose-ranging study CN170003[21]. Safety data are also available for the 2471 participants who received rimegepant 75 mg in the Phase 2/3 multiple dose studies (BHV3000-201[22] and BHV3000-305[23]). In the pivotal migraine prevention study (BHV3000-305) [23], the median time on double-blind or open-label rimegepant treatment was 51.6 weeks. Four hundred sixteen participants (62.0%) received rimegepant for at least 1 year, and 203 participants (30.3%) received rimegepant for at least 15 months. In the supportive long-term safety study

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

(BHV3000-201) [22], a total of 1154 participants received rimegepant 75 mg for at least 6 months, and 368 participants received rimegepant for at least 1 year.

In addition, a multicenter, open-label, long-term safety study of rimegepant for the acute treatment of migraine in Chinese participants is currently ongoing in China (BHV3000-318[24]). This study aims to provide long-term safety data of rimegepant 75 mg administered as needed (PRN use, up to 1 tablet per day) for 52 weeks in Chinese participants with moderate to severe migraine. Approximately 240 participants are planned to be enrolled. The First Patient First Visit was achieved on 19 May 2022, results are not available yet.

2.3.2. Clinical Adverse Event Profile

Rimegepant is generally safe and well tolerated in humans when given as single oral doses up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. Please refer to the current version of Investigators Brochure for a summary of the clinical safety profile.

2.4. Study Rationale

The efficacy of rimegepant for the acute treatment of migraine in adults have been confirmed in 3 US Phase 3 registrational trials and 1 regional Phase 3 registrational trial that was conducted in China and South Korea. All 4 trials demonstrated that rimegepant 75 mg was superior to placebo for freedom from pain and freedom from the most bothersome symptom at 2 hours post-dose. The safety profile in the Phase 2/3 BHV3000-201 long-term open-label study suggests that rimegepant is well tolerated with a favorable safety profile with up to daily dosing for as long as 1 year in participants with migraine. Above data suggest that rimegepant may have an important role in the treatment of migraine.

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

Rimegepant has been approved for both the acute treatment of migraine and the preventive treatment for episodic migraine by the US FDA[7]. Similar approvals have recently been granted in the EU and UK. The purpose of the current study is to provide confirmatory evidence of the efficacy of rimegepant for migraine prevention in Chinese participants with migraine.

2.4.1. Study Design Rationale

This is a 12-week multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of rimegepant 75 mg ODT taken every other day for the prevention of migraine with a 12-week Open-label Extension Phase. Approximately 784 participants with migraine will be randomized and assigned treatment in the Double-blind Treatment Phase of the study. It is estimated that approximately up to 728 participants will enter into the Open-label Extension Phase of the study.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

At the Baseline (Randomization) Visit, eligible participants will be randomized 1:1 to 2 treatment groups: rimegepant 75 mg ODT dosed EOD (n=392) or matching placebo EOD (n=392). Randomization will be stratified by the number of migraine days during the Observation Phase (<8, ≥8). During the Double-blind Treatment Phase, participants will be instructed that they must take 1 ODT of blinded study intervention (rimegepant 75 mg or matching placebo) dosed EOD. If participants have a headache (including migraine and non-migraine) attack during the Double-blind Treatment Phase, if needed, they may treat the headache with their permitted acute standard of care headache medication (see Section 8.6.2) and continue to take study intervention on their scheduled dosing days.

During the Open-label Extension Phase of the study, participants will be instructed that they must take 1 rimegepant 75 mg ODT every other calendar day. However, if participants have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 rimegepant 75 mg ODT on that calendar day to treat the migraine. Therefore, during the Open-label Extension Phase, participants can take a maximum of 1 tablet of rimegepant 75 mg ODT per calendar day up to 12 weeks.

2.4.2. Dose Selection Rationale

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine[21]. The 4 Phase 3 studies BHV3000-301, BHV3000-302, BHV3000-303 and BHV3000-310 confirmed the efficacy of rimegepant 75 mg acute treatment using the current registrational endpoints for acute treatment of migraine. Likewise, the prevention study, BHV3000-305, confirmed that rimegepant 75 mg dosed EOD is an effective dose for the preventive treatment of episodic migraine in adults.

The BHV3000-118 was a Phase 1, randomized, placebo-controlled, single and multiple-dose, double-blind study to evaluate the PK and safety of rimegepant ODT in healthy adult Chinese participants[25]. A total of 16 participants (12 rimegepant and 4 placebo) were enrolled and received a single dose of rimegepant 75 mg ODT or placebo on Day 1, followed by multiple doses of rimegepant 75 mg ODT or placebo daily for 5 days (Days 3-7). Results show that administration of rimegepant 75 mg ODT was safe and well-tolerated following single and multiple doses. Furthermore, Chinese and Japanese ethnicities were tested as a covariate in the population PK model, results suggested ethnicity was not a clinically relevant factor, indicating no dose or dose frequency adjustment is required in Chinese participants. The BHV3000-310 study also confirmed rimegepant 75 mg ODT was effective in the acute treatment of migraine in Chinese participants. For more details, please refer to the current version of IB.

2.4.3. Research Hypothesis

Rimegepant 75 mg, administered as EOD, is a safe and effective treatment for the prevention of migraine in Chinese participants.

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2.4.4. Benefit Risk Assessment

Rimegepant represents an advancement in migraine therapeutics, providing the first CGRP antagonist to demonstrate benefit for both the acute treatment and prophylaxis of 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.

Broad and sustained efficacy of rimegepant 75 mg was demonstrated in 3 previously completed Phase 3 studies (BHV3000-301, BHV3000-302 andBHV3000-303). 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. 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 one 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.

Across rimegepant clinical development program, low frequency of events of hypersensitivity (including urticaria, angioedema, anaphylactic reaction and rash) were observed. No AEs representing serious cutaneous manifestation of hypersensitivity (e.g., Stevens-Johnson syndrome) were observed.

Across the rimegepant clinical development program, no cases of Hy's Law were identified, and there was no signal of DILI due to rimegepant when administered up to once daily PRN for up to 52 weeks of treatment.

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.

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There are no adequate data on the developmental risk associated with the use of rimegepant in pregnant women. Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of EFD nonclinical toxicity studies with rimegepant. Contraception method is required, and measures will be taken to limit the risk of pregnancy in the female population of childbearing potential enrolled (See Section 15.5.4). The potential risk of exposure to rimegepant in a sexual partner of a male participants in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.

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 The US 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 or cerebrovascular 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 Investigator Brochure, which is the SRSD for this study.

Investigators are to monitor changes in hematology, chemistry, and other laboratory measures (see Section 9.4). In addition, Investigators are required to monitor all reported AEs, changes on physical examination, ECG, and emergent lab abnormalities, etc. (see Table 1).

3. OBJECTIVES, ENDPOINTS, ESTIMANDS

3.1. Study Objectives

3.1.1. Primary Objective(s)

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

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3.1.2. Secondary Objective(s)

1. To compare the efficacy of rimegepant to placebo on the proportion of participants with ≥50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase.

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

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

4. To compare the change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

5. To compare the efficacy of rimegepant to placebo on the mean number of acute migraine medication days per month over the entire Double-blind Treatment Phase.

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

7. To evaluate the frequency of ALT or AST >3×ULN concurrent with total bilirubin >2×ULN in participants treated with rimegepant during the Double-blind Treatment and Open-label Extension Phases.

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

3.1.3. Exploratory Objective(s)

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

2. To compare the efficacy of rimegepant to placebo on the proportions of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire Double-blind Treatment Phase.

3. To compare the efficacy of rimegepant to placebo on the mean reduction from the Observation Phase in the number of migraine days per week and number of headache

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days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase.

4. To compare the efficacy of rimegepant to placebo on the proportions of participants with ≥50% reduction from the Observation Phase in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase.

5. To compare the efficacy of rimegepant to placebo on the proportions of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the Double-blind Treatment Phase.

6. To compare the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication days per month in each month and over the entire Double-blind Treatment Phase.

7. To evaluate the mean reductions from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire Open-label Extension Phase.

8. To evaluate the proportions of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire Open-label Extension Phase.

9. To evaluate the mean numbers of acute migraine medication days per month and acute migraine-specific medication days per month in each month and over the entire Open-label Extension Phase.

10. To compare the mean changes from baseline in the MSQoL preventive role function and emotional function domain scores at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

11. To compare the mean changes from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the Double-blind Treatment Phase between rimegepant and placebo.

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

13. To evaluate the mean changes from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the Open-label Extension Phase.

3.2. Study Endpoints

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

AEs are determined from CRFs.

MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores are derived from CRFs.

Grade 3 to 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria.

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoint(s)

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

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

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

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

5. Mean number of acute migraine medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).

6. Number and percentage of participants with AEs by severity, SAEs, AEs leading to study intervention discontinuation and grade 3 to 4 laboratory test abnormalities on treatment during the Double-blind Treatment Phase and Open-label Extension Phase.

7. Number and percentage of participants with AST or ALT elevations >3×ULN concurrent (ie, on the same laboratory collection date) with total bilirubin elevations >2×ULN on treatment during the Double-blind Treatment Phase and Open-label Extension Phase.

8. Number and percentage of participants with hepatic-related AEs by intensity, and hepatic-related AEs leading to study intervention discontinuation on treatment during the Double-blind Treatment Phase and Open-label Extension Phase.

3.2.3. Exploratory Endpoint(s)

1. Mean change from the Observation Phase in the number of migraine days per month by intensity (total; moderate or severe) and number of headache days by intensity (total; moderate or severe) in each month and the entire Double-blind Treatment Phase (Weeks 1 to 12).

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2. Proportion of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month by intensity (total; moderate or severe) and number of headache days per month by intensity (total; moderate or severe) in each month and the entire Double-blind Treatment Phase (Weeks 1 to 12).

3. Mean change from the Observation Phase in the number of migraine days per week by intensity (total; moderate or severe) and number of headache days per week by intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase (Weeks 1 to 4).

4. Proportion of participants with ≥50% reduction from the Observation Phase in the number of migraine days per week by intensity (total; moderate or severe) and number of headache days per week by intensity (total; moderate or severe) in each week of the first 4 weeks of the Double-blind Treatment Phase (Weeks 1 to 4).

5. Proportions of participants with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the Double-blind Treatment Phase (Days 1 to 7).

6. Mean number of acute migraine-specific medication days per month in each month and the entire Double-blind Treatment Phase.

7. Mean change from the Observation Phase in the number of migraine days per month by intensity (total; moderate or severe) and number of headache days per month by intensity (total; moderate or severe) in each month and the entire Open-label Extension Phase (Weeks 13 to 24).

8. Proportion of participants with ≥50% reduction, ≥75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month by intensity (total; moderate or severe) and number of headache days per month by intensity (total; moderate or severe) in each month and over the entire Open-label Extension Phase (Weeks 13 to 24).

9. Mean number of acute migraine medication days per month and acute migraine-specific medication days per month in each month and the entire Open-label Extension Phase (Weeks 13 to 24).

10. Mean changes from baseline in the MSQoL v2.1 preventive role function and emotional function domain scores at Week 12 of the Double-blind Treatment Phase.

11. Mean changes from baseline in the MIDAS total score, absenteeism and presenteeism scores at Week 12 of the Double-blind Treatment Phase.

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

13. Mean changes from baseline in the MSQoL domain scores, MIDAS scores, and EQ-5D-5L scores at Week 24 of the Open-label Extension Phase

3.3. Study Estimands

The tables that follow present the estimands corresponding to the primary and secondary objectives. Analysis sets are defined in Section 10.2.

Population

For all objectives, the population of interest is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval. Please refer to Sections 5.2 and 5.3 respectively for inclusion and exclusion criteria.

Intercurrent Events

Intercurrent events are those that occur after treatment initiation and either preclude observation of the endpoint or affect its interpretation. Study intervention discontinuation before the time point of interest defining the endpoint is considered an intercurrent event.

- For efficacy and safety objectives, study intervention discontinuation is handled with a "while-on-treatment strategy," i.e., response to treatment prior to the occurrence of the intercurrent event of interest, such that all observed values of the endpoint of interest are used prior to study intervention discontinuation.

- For all objectives, the use of prophylactic medications on or before the time point of interest is considered an intercurrent event and handled with a "treatment policy strategy", ie, such that all the observed values of the endpoint of interest are used. Note that the prophylactic medication is prohibited during the study. (see Section 8.6.1)

3.3.1. Primary Estimands

The estimands corresponding to the primary endpoint for this study are shown below.

Objective	**Reduction in the mean number of migraine days per month– Efficacy**
Variables	Change from Observation Phase in the mean number of migraine days per month on treatment over the Double-blind Treatment phase (Week 1 to 12)
Prop. Summary	Difference in means

3.3.2. Secondary Estimands

The estimands corresponding to the secondary endpoints for hierarchical testing in this study are shown below.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Objective	**Proportion of participants who have ≥50% reduction in migraine days per month – Efficacy**
Variables	Number and percentage of participants who have ≥50% reduction from Observation Phase in the mean number of moderate to severe migraine days per month on treatment over the Double-blind Treatment phase (Week 1 to 12)
Prop. Summary	Difference in percentages of responses
Objective	**Reduction in the mean number of migraine days per month – Efficacy**
Variable	Change from Observation Phase in the mean number of migraine days per month on treatment in the first 4 weeks of the Double-blind Treatment phase (Week 1 to 4)
Prop. Summary	Difference in means
Objective	**Reduction in the mean number of migraine days per month – Efficacy**
Variable	Change from Observation Phase in the mean number of migraine days per month on treatment in the last 4 weeks of the Double-blind Treatment phase (Week 9 to 12)
Prop. Summary	Difference in means
Objective	**MSQoL Restrictive Role Function - Efficacy**
Variable	Change from Baseline in the MSQoL role function- restrictive domain score at Week 12
Prop. Summary	Difference in means
Objective	**Mean number of acute migraine medication days per month– Efficacy**
Variable	Mean number of acute migraine medication days per month on treatment over the entire Double-blind Treatment phase (Week 1 to 12)
Prop. Summary	Difference in means

4. STUDY PLAN

4.1. Study Design and Duration

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

The Observation Phase will include the Screening Visit. Upon completion of the Screening Visit, participants will be provided an eDiary to be used daily to report headache occurrence, pain features, and associated symptoms during the Observation Phase. Participants will record all concomitant medications, including acute standard of care headache medications (both prescribed and OTC) they take in a concomitant medication paper diary. To be eligible

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for the study, participants must report having had 4 to 18 migraine attacks of moderate to severe intensity per month (4-week period) within the 3 months prior to the Screening Visit, and at least 6 migraine days and no more than 18 headache days during the Observation Phase. After completing the Observation Phase, participants will return to the study site with both diaries for the Baseline (Randomization) Visit.

At the Baseline Visit, eligibility for continued study participation will be assessed before randomization occurs and before study intervention is dispensed. Eligible participants will be randomized 1:1 to 2 treatment groups: rimegepant 75 mg ODT dosed EOD (n=392) or matching placebo EOD (n=392). Randomization will be stratified by the number of migraine days during the Observation Phase (<8, ≥8). During the 12-week Double-blind Treatment Phase, participants will be instructed that they must take 1 tablet of blinded study intervention (rimegepant 75 mg or placebo) every other calendar day. If participants have a headache during the Double-blind Treatment Phase, if needed, they may treat the headache with their permitted acute standard of care headache medication and continue to take study intervention on their scheduled dosing days.

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

Participants will continue to use the eDiary daily to report headache occurrence and pain features during the Double-blind Treatment and Open-label Extension Phases. Participants are required to report each dose of study intervention taken in a study intervention paper diary throughout the entire study. Participants are also required to record any concomitant medications, including acute headache medications (both prescribed and OTC) taken in a concomitant medication paper diary throughout the entire study.

At select study visits, participants will complete or will be administered the MSQoL v2.1, the MIDAS and EQ-5D-5L and the C-SSRS. Additional assessments and visit schedule are outlined in the procedural table in Section 4.3.

Study visits will occur at the following time points: Screening during the Observation Phase; Baseline (Randomization), Week 2, Week 4, Week 8, and Week 12 during the Double-blind Treatment Phase; Week 14, Week 16, Week 20, and Week 24/ EOT during the Open-label Extension Phase. Participants will return to the study site at the end of Week 24 for the EOT visit. Participants who discontinue Double-blind Treatment Phase, or do not enter or complete the Open-label Extension Phase, will also return to the site for the EOT visit at the time of study intervention discontinuation. There is a Follow-up Week 4 Visit approximately 28 days after the EOT visit. All randomized participants should complete the Follow-up Week 4 Visit, regardless of completing either treatment phase.

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To closely monitor for potential DILI, guidance on reporting potential DILI events is provided in the protocol. Laboratory results that meet predefined LFT abnormality criteria as potential DILI events should be reported as a SAE. See Section 9.4.

4.2. Study Schematic

Refer to Section 1.2.

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4.3. Schedule of Assessment

Table 1. Schedule of Assessments – Observation Phase and Double-blind Treatment Phase

	Observation Phase (28 days + 3 days)[10]	**Double-blind Treatment Phase**				
Procedure	**Screening Visit**	**Baseline** (Randomization) **Visit** (Day 1)	**Week 2** (Day 15 ±2 days)[11]	**Week 4** (Day 29 +3 days)	**Week 8** (Day 57 +3 days)	**Week 12**[12] (Day 85+3 days)
Eligibility Assessments						
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical History	X	X				
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X					
Concomitant medication paper diary[1]	X	X	X	X	X	X
Enroll participant/IWRS	X					
Randomize participant / IWRS[2]		X				
Safety Assessments						
Physical Examination	X	X				X
Vital Signs / Physical Measurements[3]	X	X		X	X	X
Hematology, Chemistry, eGFR	X	X		X	X	X
Liver Function Test (LFTs)	X	X	X	X	X	X
Lipid Panel	X	X				X

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Table 1. Schedule of Assessments – Observation Phase and Double-blind Treatment Phase

	Observation Phase (28 days + 3 days)[10]	**Double-blind Treatment Phase**				
Procedure	**Screening Visit**	**Baseline** (Randomization) **Visit** (Day 1)	**Week 2** (Day 15 ±2 days)[11]	**Week 4** (Day 29 +3 days)	**Week 8** (Day 57 +3 days)	**Week 12**[12] (Day 85+3 days)
ECG	X					X
Urinalysis		X				X
Urine Drug Screen for drugs of abuse	X					
FSH, if applicable, to determine WOCBP status	X					
Pregnancy Test	X (urine)	X (urine and Serum)		X (urine)	X (urine)	X (urine)
AE, SAE, and Concomitant Procedure assessment[4]	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X
Clinical Drug Supplies / Study Supplies						
Dispense study intervention[5]		X		X	X	X
Administer study intervention[6]		X	X	X	X	X
Electronic diary (eDiary) dispensed[7]	X					
Study intervention paper diary[6]		X	X	X	X	X
Return unused study intervention to site for compliance check			X	X	X	X

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Table 1. Schedule of Assessments – Observation Phase and Double-blind Treatment Phase

	Observation Phase (28 days + 3 days)[10]	**Double-blind Treatment Phase**				
Procedure	**Screening Visit**	**Baseline** (Randomization) **Visit** (Day 1)	**Week 2** (Day 15 ±2 days)[11]	**Week 4** (Day 29 +3 days)	**Week 8** (Day 57 +3 days)	**Week 12**[12] (Day 85+3 days)
eDiary returned / reviewed for completeness[8]		X	X	X	X	X
Other Assessments						
Daily report of migraine occurrence, migraine pain features and associated symptoms reported by participant in eDiary[9]	X (Observation Phase)	X	X	X	X	X
MSQoL v2.1		X				X
MIDAS		X				X
EQ-5D-5L		X				X

1 Concomitant medications, including acute standard of care headache medications (both prescribed and OTC) taken during Observation Phase and Double-blind Treatment Phase should be recorded in the participant's concomitant medication paper diary and reviewed by study personnel at each visit.

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

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

4 SAEs, AEs, and Concomitant Procedures must be reported after participant signs informed consent. SAEs and non-serious AEs should be reported from signing of consent through the Follow-up Week 4 Visit (4 weeks after the EOT visit).

5 Participants should finish a wallet of study intervention before starting a new wallet. Study intervention will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study intervention may be scheduled as needed. At the Week 12 Visit, open-label study intervention will be dispensed, and participants will be instructed not to begin taking rimegepant until confirmation from site staff pending lab results.

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Table 1. Schedule of Assessments – Observation Phase and Double-blind Treatment Phase

	Observation Phase (28 days + 3 days)[10]	**Double-blind Treatment Phase**				
Procedure	**Screening Visit**	**Baseline** (Randomization) **Visit** (Day 1)	**Week 2** (Day 15 ±2 days)[11]	**Week 4** (Day 29 +3 days)	**Week 8** (Day 57 +3 days)	**Week 12[12]** (Day 85+3 days)

6 Participants must take their study intervention every other day, regardless of whether they have a migraine. Participants must report each dose of study intervention taken in the study intervention paper diary. Dosing requirements and compliance should be discussed with participants at all visits.

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

8 Participants with less than 24 completed eDiary reports during the Observation Phase will not be considered for participation due to non-compliance with the eDiary. Participants in the Double-blind Treatment Phase who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the participant.

9 The participant will use the eDiary every day during the Observation Phase and Double-blind Treatment Phase to report migraine occurrence, migraine pain features, and associated symptoms.

10 The Observation Phase to determine eligibility is 28 days +3 days**.** The "+3" days window is included for scheduling purposes only.

11 While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return participants to the 14 or 28-day schedule if scheduling changes are made at any previous visit(s).

12 Participants who do not complete the Double-blind Treatment Phase or do not enter the Open-label Extension Phase should complete the End of Treatment Visit and the Follow-up Week 4 Visit (see Table 2).

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Table 2. Schedule of Assessments – Open-label Extension Phase and Follow-up Week 4 Visit

Procedure	**Phone visit**	**Week 14 (Day 99)** (± 3 days)[9]	**Week 16 (Day 113** (±3 days)	**Week 20 (Day 141)** (±3 days)	**Week 24 (Day 169)/ EOT** (±3 days)	**Follow-up Week 4 Visit** (28 days after EOT visit ± 2 days)
Confirm eligibility based on Week 12 Laboratory Results[1]	X					
Concomitant medication paper diary[2]		X	X	X	X[3]	X[3]
Safety Assessments						
Physical Examinations					X	
Vital Signs / Physical Measurements[4]			X	X	X	X
Hematology, Chemistry, eGFR			X		X	
Liver function tests (LFTs)		X	X	X	X	X
Lipid Panel					X	
ECG					X	
Urinalysis					X	
Pregnancy Test			X (urine)	X (urine)	X (urine)	X (serum)
AE, SAE, and Concomitant Procedure Assessment[5]		X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X
Clinical Drug Supplies / Study Supplies						
Dispense study intervention [1, 6]			X	X		
Administer study intervention[7]		X	X	X		

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Table 2. Schedule of Assessments – Open-label Extension Phase and Follow-up Week 4 Visit

Procedure	**Phone visit**	**Week 14 (Day 99)** (± 3 days)[9]	**Week 16 (Day 113** (±3 days)	**Week 20 (Day 141)** (±3 days)	**Week 24 (Day 169)/ EOT** (±3 days)	**Follow-up Week 4 Visit** (28 days after EOT visit ± 2 days)
Study intervention paper diary[7]		X	X	X	X	
Return unused study intervention to site for compliance check		X	X	X	X	
eDiary returned/reviewed for completeness		X	X	X	X	
Other Assessments						
Daily report of migraine occurrence, migraine pain features and associated symptoms reported by participant in eDiary[8]		X	X	X	X	
MSQoL v2.1					X	
MIDAS					X	
EQ-5D-5L					X	

1 Study eligibility must be confirmed by Week 12 laboratory results prior to first dose of study intervention in the Open-label Extension Phase, which is dispensed at the Week 12 visit. Sites must contact participant by phone to confirm study eligibility prior to participant taking first dose.

2 Concomitant medications, including acute standard of care headache medications (both prescribed and OTC), taken during the Open-label Extension Phase should be recorded in the participant's concomitant medication paper diary and reviewed by study personnel at each visit.

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

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

5 SAEs, AEs, and Concomitant Procedures must be reported after participant signs informed consent. SAEs and non-serious AEs should be reported from signing of informed consent through the Follow-up Week 4 Visit.

6 Participants should finish a wallet of study intervention before starting a new wallet. Study intervention will be dispensed at monthly (every 4 weeks) study visits, as needed. Unscheduled visits to dispense study intervention may be scheduled as needed.

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Table 2. Schedule of Assessments – Open-label Extension Phase and Follow-up Week 4 Visit

Procedure	**Phone visit**	**Week 14 (Day 99)** (± 3 days)[9]	**Week 16 (Day 113** (±3 days)	**Week 20 (Day 141)** (±3 days)	**Week 24 (Day 169)/ EOT** (±3 days)	**Follow-up Week 4 Visit** (28 days after EOT visit ± 2 days)

7 Participants must take their study intervention every other day, regardless of whether they have a migraine. If participants have a migraine on a day that they are not scheduled to take a study intervention, if needed, they may take a study intervention to treat a migraine on that calendar day. Therefore, participants can take a maximum of 1 ODT of study intervention per calendar day. Participants must report each dose of ODT taken in the study intervention paper diary. Dosing requirements and compliance should be discussed with participants at all visits.

8 The participant will be trained on the use of the eDiary. The participant will use the eDiary every day during the Open-label Extension Phase to report migraine occurrence, migraine pain features, and associated symptoms.

9 While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return participants to the 14 or 28-day schedule if scheduling changes are made at any previous visit(s).

4.3.1. Observation Phase

The Observation Phase will be 28 days + 3 days. Note that the "+3 days" window is included for scheduling purposes only. The Observation Phase will have 1 scheduled visit, Screening Visit, which should be completed in person.

4.3.1.1. Screening Visit

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

Once the eDiary device has been received, the participants will report headache occurrence, pain features and associated symptoms in the eDiary daily during the Observation Phase. If participants have a headache, they may treat the headache with permitted acute headche medications (see Section 8.6.2) as needed during the Observation Phase. Investigators should discuss with study participants in term of the type of acute headache medications they would use during the Observation Phase. Once aligned on the specific medication(s) they would use for acute headache treatment, it is not recommended to change the type of acute headache medication throughout the Observation Phase and Double-blind Treatment Phase. Participants will record all concomitant medications, including acute headache medications (both prescribed and OTC), taken during the entire Observation Phase in a concomitant medication paper diary.

If the participant meets study entry criteria (ie, inclusion/exclusion criteria), the participant will return to the study site for the Baseline Visit (Randomization). If the participant does not meet study entry criteria, the participant will be considered a screen failure and should be recorded as such in IWRS. The participant must return to the study site to return the eDiary.

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

The Double-blind Treatment Phase will be up to 12 weeks from the Baseline (Randomization) Visit through the Week 12, or from the Baseline (Randomization) to EOT Visit for participants who discontinue early at the Double-blind Treatment Phase.

4.3.2.1. Baseline (Randomization) Visit

Once completing the Observation Phase, participants will return to the study site for the Baseline (Randomization) Visit, which should be completed in person. Participants with fewer than 24 completed eDiary reports during the Observation Phase will not be considered for participation due to non-compliance with the eDiary. Participants who continue to meet all study entry criteria and have been compliant with the eDiary may enter the Double-blind Treatment Phase, pending review of additional laboratory test results. Because laboratory results from the Baseline Visit will be available after the participant may had been randomized and started treatment, there is the possibility that exclusionary laboratory results from the Baseline Visit may result in early discontinuation from the study.

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At the Baseline Visit, eligible participants will be randomized 1:1 to 2 treatment groups: rimegepant 75 mg ODT dosed EOD (n = 392) or matching placebo EOD (n = 392). Randomization will be stratified by the number of migraine days during the Observation Phase (<8, ≥8).

Participants should take the first dose of blinded study intervention the day of the Baseline Visit. During the Double-blind Treatment Phase, participants will be instructed that they must take 1 tablet of blinded study intervention every other calendar day, regardless of whether they have a migraine on that day or not. If participants have a headache during the Double-blind Treatment Phase, if needed, they may treat the headache with their permitted acute headache medication and continue to take study intervention on their scheduled dosing days.

4.3.2.2. Week 2, Week4 and Week 8 Visit

After the Baseline Visit, study visits will be approximately every 2 weeks during the first month, and then every 4 weeks until the Week 12 (Table 1).

During the Double-blind Treatment Phase, if a dose of study intervention for a given day is missed, lost, or otherwise unable to be taken, the participant should document that as a missed dose on the study intervention paper diary and should NOT take a dose of study intervention until the next scheduled dosing day in accordance with the planned EOD dosing schedule. Study intervention compliance will be reviewed at each visit using the study intervention paper diary, and participants will be dispensed additional study intervention as needed.

Participants will continue to report headache occurrence, pain features and associated symptoms in the eDiary every day during the Double-blind Treatment Phase. Participants will continue to record all concomitant medications, including acute headache medications (both prescribed and OTC), taken during the entire Double-blind Treatment Phase in a concomitant medication paper diary. At each visit, the eDiary will be reviewed by site staff for completeness and compliance. Concomitant medication use will also be reviewed and compared between the eDiary and concomitant medication paper diary entries, where applicable at each visit.

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

4.3.2.3. Week 12 Visit

Participants will return to the study site at the Week 12 Visit (Day 86 + 3 days) for review of the eDiary, assessment of medication compliance and assessment of tolerability and safety (including vital signs, laboratory tests and electrocardiography) (Table 1). Participants must return the unused study intervention to the study site. Participants in the Double-blind Treatment Phase who demonstrate poor compliance (less than 24 completed eDiary reports per month [a month is defined as 28 days in this study]) will be discussed with the Sponsor, corrective training will be completed by the site with the participant and may not be considered for the Open-label Treatment Phase.

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All randomized participants who discontinue early from the Double-blind Treatment Phase should complete the EOT visit at the time of study intervention discontinuation.

4.3.3. Open-label Extension Phase (12 weeks)

It is estimated that approximately up to 728 participants will be entered into the Open-label Extension Phase.

As indicated in Table 1, laboratory tests will be performed at the Week 12 visit (final visit of the Double-blind Treatment Phase). Participants who (1) complete the Double-blind Treatment Phase, (2) continue to meet all inclusion/exclusion criteria, and (3) have been compliant with the eDiary may enter the Open-label Extension Phase, pending review of laboratory test results.

Participants will be dispensed study intervention (rimegepant 75 mg) and must be instructed that they cannot take study intervention until laboratory results confirm study eligibility. Participants may be informed by Phone Visit; an office study visit is not required.

Participants will be instructed that they must take 1 tablet of rimegepant 75 mg ODT every other calendar day, regardless of whether they have a migraine on that day. If participants have a migraine on a day that they are not scheduled to dose with study intervention, they may take 1 tablet of rimegepant 75 mg ODT on that calendar day to treat a migraine. Therefore, if needed, participants can take a maximum of 1 tablet of rimegepant 75 mg ODT per calendar day for 12 weeks during the Open-label Extension Phase.

Participants will continue to use the eDiary daily to report headache occurrence, pain features and associated symptoms during the Open-label Extension Phase. Participants are required to report each dose of study intervention taken in a study intervention paper diary throughout the entire study. Participants are also required to record any concomitant medications, including the acute headache medications (both prescribed and OTC) taken in a concomitant medication paper diary throughout the entire study. At the beginning of the Open-label Extension Phase, investigators should discuss with study participants in term of the type of acute headache medications they would use during this phase. Please note that use if triptans is not allowed in the Open-label Extension Phase in this study. Once aligned on the specific medication(s) they would use for acute headache treatment, it is not recommended to change the type of acute headache medications throughout the Open-label Extension Phase.

Study visits will be approximately every 2 weeks during the first month and then every 4 weeks, until Week 24 (Table 2). At each visit, the eDiary and study intervention paper diary will be reviewed by site staff for completeness and compliance. Concomitant medication use will be reviewed and compared between the eDiary and concomitant medication paper diary entries, where applicable at each visit.

The MSQoL v2.1, MIDAS, EQ-5D-5L and C-SSRS will be completed, or administered by the investigator, at specified study visits (Table 2). Additional safety tests (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

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4.3.4. End of Treatment

For participants completing the study, the EOT visit occurs at the end of Week 24 (±3 days) (Week 24 Visit). For participants who do not complete the Double-blind Treatment Phase, or do not complete the Open-label Extension Phase will complete the EOT Visitstudy intervention. During the EOT visit, participants will return to the study site for review of the eDiary, study intervention paper diary and assessment of medication compliance, assessment of tolerability and safety (including vital signs, laboratory tests, and electrocardiography) (Table 2). Concomitant medication use will also be reviewed and compared between the eDiary and concomitant medication paper diary entries. Participants must return the unused study intervention and eDiary to the study site.

In cases where a Week 24/ EOT visit occurs remotely in order to be completed during the protocol required window and due to the public health emergencies, the participant should return to the site for the Follow-up Week 4 Visit (4 weeks from the scheduled Week 24/ EOT visit, ±2 days) to complete all procedures that were not able to be completed remotely. Procedures competed at the Week 24/ EOT Visit occurring remotely do not need to be repeated. Participants must return the unused study intervention and eDiary to the study site.

4.3.5. Follow-up Week 4 Visit

There is 1 scheduled visit occurs study intervention approximately 4 weeks after the Week 24/EOT visit (14 days +/- 2 days) to collect vital signs/physical measurements, assessment of AEs/SAEs, to have the LFTs, C-SSRS performed, and to have a serum pregnancy test performed (WOCBP). For the participants who complete the EOT Visit, and the participants who complete the Double-blind Treatment Phase (Week12 visit) but do not enter the Open-label Extension Phase will complete the Follow-up Week 4 Visit. Investigators should assess participants for AEs consistent with drug dependency or withdrawal effects and report as appropriate.

Participants must continue to track any concomitant medications and therefore must maintain the concomitant medication paper diary through the Follow-up Week 4 Visit. Participants will return the concomitant medications paper diary which should be reviewed 1 final time by site staff.

4.3.6. Public Health Emergencies Contingencies

Certain provisions may be implemented, in order to minimize potential hazards to study participants due to public health emergencies. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone, focusing on safety assessments during remote visits, performing safety labs via local labs instead of the central lab. However, investigators should contact the Sponsor first and any potential issues will be addressed on an individualized basis. With Sponsor's approval, shipping of study intervention directly to study participants by certified courier will be allowed. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on participant presentation.

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4.4. Post Study Access to Therapy

At the end of the study the Sponsor will not continue to supply study intervention to participants or investigators. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

5. STUDY POPULATION

Individuals entered in this study will be participants who suffer from migraines. Participants may be recruited from a variety of sources including referrals or professional recruitment agencies.

5.1. Number of Participants

Approximately 1426 participants will be screened to randomize approximately 784 participants (392 participants in each treatment group). It is estimated that approximately 728 participants will be entered into the Open-label Extension Phase.

5.2. Inclusion Criteria

1. Signed Written Informed Consent

    a. Written informed consent must be obtained from the participant in accordance with requirements of the study center's 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, including the following:

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

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

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

    d. Six or more migraine days during 28 days in the Observation Phase per eDiary

    e. Not more than 18 ***headache days*** during 28 days in the Observation Phase per eDiary

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

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

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3. Age and Reproductive Status

    a. Male and female participants ≥18 years

    b. Participant meets reproductive criteria. Refer to Appendix 5 for reproductive criteria for male (Section 15.5.1) and female (Section 15.5.2) participants.

4. Participants must complete at least 24 eDiary reports during the Observation Phase, and must be able to read, understand and complete the study questionnaires and eDiary per investigator's judgement.

5.3. Exclusion Criteria

1. Target Disease Exclusion

    a. Participant has a history of basilar migraine or hemiplegic migraine.

    b. Participants are excluded if they have had no therapeutic response with >2 of the 9 medication categories of preventive treatment of migraine (see Section 15.2) after an adequate therapeutic trial in the past 3 years per investigator's judgement.

2. Medical History and Concurrent Diseases

    a. Participant with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular or cerebrovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Participants with myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke or transient ischemic attack during the 6 months (24 weeks) prior to the Screening Visit.

    b. Uncontrolled hypertension or uncontrolled diabetes. However, participants can be included who have stable hypertension, hypercholesterolemia and/or diabetes and have been at a stable dose on treatments for at least 3 months (12 weeks) prior to the Screening Visit). Blood pressure greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary. This may be repeated once at Screening once at Baseline Visit to confirm reproducibility.

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

    d. Participant has a history or diagnosis of an active hepatic or biliary disorder.

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

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

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

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

i. Participant has a current or history of diagnosis of schizophrenia, bipolar disorder, or borderline personality disorder.

j. Participants with major depressive episode within the last 12 months, MDD or any anxiety disorder requiring more than 1 daily standard of care medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening Visit.

k. History of alcohol abuse and/or illicit drug use meeting DSM-5 criteria for substance use disorder within 6 months of the Screening Visit.

l. Participants who have tested positive at Screening Visit for cocaine, amphetamine, phencyclidine (PCP) and tetrahydrocannabinol (THC).

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

n. Body mass index $\geq$35.0 kg/m^2

3. Allergies and Adverse Drug Reactions

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

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4. Sex and Reproductive Status

    a. WOCBP who are unwilling or unable to use one acceptable method of contraception or abstinence to avoid pregnancy for the entire study period and for up to 28 days after last dose of study intervention.

    b. Women who are pregnant or breastfeeding.

    c. Women with a positive pregnancy test at Screening or prior to study intervention administration.

5. ECG and Laboratory Test Findings

    a. ECG abnormalities that, in the Investigator's opinion, makes the participant unsuitable for participation in the study (e.g. Corrected QT interval >470 msec).

    b. eGFR ≤30 mL/min/1.73m^2

    c. Serum total bilirubin >1.5× ULN (Only abnormal values with clinical justification ***may be repeated once for confirmation during the screening period)***). For Gilbert's syndrome, direct bilirubin >ULN is exclusionary.

    d. AST or ALT >2 × ULN (Only abnormal values with clinical justification ***may be repeated once for confirmation during the screening period)***..

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

    f. HbA1c ≥7.5 %

    g. Any other clinically significant abnormality identified on the medical or laboratory evaluation and is considered by investigator that it will introduce additional risk factors or interfere with the study procedures.

6. Prohibited Medications

    a. Medication for migraine prevention generally considered to have efficacy, regardless of indication (see Section 15.2):

        i. CGRP monoclonal antibodies taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study.

        ii. Botulinum toxin injections (e.g., Botox®) taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study.

        iii. Other medications with demonstrated efficacy for the prevention of migraine (ie, topiramate, flunarizine, and atogepant; for the full list please see Section 15.2) taken within 30 days prior to the Screening Visit and throughout the study.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

b. Medication accepted for treatment of acute migraine (see Section 8.6.2) for a non-migraine indication taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.

   - Ergotamine taken ≥10 days per month on a regular basis for ≥3 months (≥12 weeks) in the year prior to the Screening Visit.

   - Analgesics (e.g., NSAIDs or acetaminophen) taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.

c. Prohibited medication or therapy used during the Observation Phase (see Section 8.6.1)

7. 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. Participation in a clinical trial with a non-biologic investigational drug within 30 days prior to the Screening Visit.

   d. Participation in a clinical trial with a biological investigational agent such as monoclonal antibodies within 6 months (24 weeks) prior to the Screening Visit.

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

   f. Previous enrollment in any multiple dose BHV3000 (Rimegepant) study, such as BHV3000-318, regardless of the number of doses taken. Participants may be considered for the current study if they only participated in the acute treatment study (BHV3000-310). Participants who were considered screen failures in a past BHV3000 study may be considered after discussion with the Sponsor and written approval is received.

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

5.4. 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 15.5.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

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.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.5. Other Restrictions and Precautions (if applicable)

Not Applicable

5.6. Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion / exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by the IRB/EC of the study site. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.7. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for re-screening in select circumstances (e.g., previously pregnant, screening window too long, ineligibility was due to 1 of the eligibility criteria that may have changed due to medical intervention or 1 of the eligibility criteria modified in a protocol amendment). In some uncertain re-screening circumstances, the situation should be discussed with the Sponsor, with approval in writing from the Sponsor prior to re-screening if necessary. If a participant is approved for re-screening, a new participant number must be obtained from the appropriate study-related system. Re-screening will only be permitted 1 time.

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6. STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1. Study Materials

The Sponsor will provide investigational product which will include rimegepant (75 mg ODT) and matching placebo.

Sites will be provided with a Sponsor-approved protocol and any amendments. Regulatory binder, Investigator Brochure and IWRS Manual will also be provided. Instructions on all specimens collected will be provided by a central laboratory. Sponsor will also provide assessment questionnaires that will be used in the study to the sites.

Source document creation is the responsibility of the site. All sites will use an EDC tool to submit study data. Electronic Case Report Forms (eCRFs) will be prepared for all data collections. SAE data (including queries) will be submitted to the Sponsor's authorized pharmacovigilance team using SAE forms.

Study participants will be given an eDiary that will be used daily to report headache occurrence, pain features and associated symptoms. Study intervention paper diary and concomitant medication paper diary will also be provided to study participants.

The investigator will be required to have a centrifuge, a secure locked cabinet or similar (for drug storage) as well as appropriate containers and dry ice for shipment and storage of blood and plasma samples. Enough dry ice, when indicated, should be utilized to allow samples to arrive at their designated laboratory in a frozen state.

6.2. Safety Assessments

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

Vital signs, weight will be recorded at the scheduled visits as outlined in Table 1 and Table 2. Height will be recorded at Screening Visit only.

6.2.2. Physical Examination

Participants will undergo a complete physical examination (minimally including the head/eyes/ears/nose/throat, cardiovascular, respiratory, neurological, and gastrointestinal systems and otherwise directed by participant's signs and symptoms) at Screening Visit and and a directed physical exam at the scheduled visits as outlined in SOA. The directed physical exam should be guided by the participant's signs and symptoms.

6.2.3. Electrocardiogram (ECG)

A 12-lead ECG will be recorded during the Screening Visit and at specified scheduled visits as outlined in Table 1 and Table 2, and as medically necessary. The investigator will determine if any ECG abnormalities are clinically significant or not (see Section 15.6 Appendix 6).

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

6.2.4. Laboratory Assessments

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

6.2.4.1. Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 and Table 2. A central laboratory vendor will be utilized for this study. If possible, participants should be fasting for a minimum of 8 hours before laboratory tests. However, if a participant is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented. The safety laboratory testing includes the following:

1. **Hematology**: Hemoglobin, hematocrit, red blood cell count, white blood cell count (WBC) with differential (absolute and percentage of neutrophil, lymphocytes, monocytes, eosinophils, basophils), and platelets.

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

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

4. **LFTs**: AST, ALT, Alkaline Phosphatase and Bilirubin (Total with reflex to direct and indirect bilirubin). Additional tests may be obtained to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory manual.

   Reflex/add-on tests:

   If AST or ALT values ≥3×ULN or total bilirubin ≥2×ULN at any visit after the Baseline Visit, additional reflex or add-on tests may be performed that may include: CK, GGT, and anti-viral serologies. Participants may have to return to the study site to provide additional blood samples for these laboratory tests. See section on potential Drug Induced Liver Injury (Section 9.4).

   Additional laboratory tests may be required as per Section 15.4.

5. **Lipid panel:** Cholesterol, LDL-C, HDL-C, triglycerides

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

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

8. **FSH:** For female participants at screening only, to confirm postmenopausal status.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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

6.2.4.2. Pregnancy Testing

WOCBP will complete pregnancy tests (serum and / or urine) at specified study visits, prior to taking study intervention, and as outlined in Table 1 and Table 2. Serum pregnancy tests will be performed in the central lab, and urine pregnancy tests will be performed in local site.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment[26,27]. The C-SSRS "Baseline/Screening" version will be used at the Screening Visit and the "Since Last Visit" version will be used at subsequent visits in this study.

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

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

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

6.3. Efficacy Assessments

The eDiary will be used daily to record headache occurrence, pain features and associated symptoms throughout the study (from the Observation Phase to the Open-label Extension Phase).

Efficacy assessments will be derived from eDiary data and will include but not limit to the following: the number of migraine days by pain intensity (total; moderate or severe), number of headache days by pain intensity (total; moderate or severe) by study period.

6.4. Other Assessments

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

Impact of treatment on participant-reported quality of life will be assessed using the MSQoL v2.1. The MSQoL v2.1 is a 14-item instrument that has been validated in 3 domains: role function - restrictive, role function - preventive, and emotional function[28].

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

6.4.2. Migraine Disability Assessment (MIDAS) Questionnaire

MIDAS is a retrospective, participant-reported, 5-item questionnaire that measures headache-related disability as lost days due to headache from paid work or school, household work and non-work activities over a 3-month period[29].

6.4.3. EQ-5D-5L

EQ-5D-5L is a standardized measure of health status. The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ VAS[30]. It is designed for self-completion by respondents.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Participants MUST permanently discontinue investigational product for any of the following reasons:

- Any AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Pregnancy.
- Termination of the study by the Sponsor

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should complete the EOT Visit and Follow-up Week 4 Visit, as applicable. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

If safety or tolerability concern arises, in particular if not responsive to symptomatic management, double-blind study intervention may be stopped in an individual participant at the discretion of the investigator.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, further study follow-up, and/or future collection of additional information.

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7.2. Discontinuation/Withdrawal from the Study

7.2.1. Participant Discontinuation/Withdrawal from the Study

- Death.
- Lost to follow-up.
- Withdrawal of informed consent (participant's decision to withdraw for any reason).

7.2.1.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.2.1.2. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local applicative methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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8. STUDY INTERVENTION AND CONCOMITANT THERAPY

8.1. Description of Study intervention

8.1.1. Investigational Product

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

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

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

During the Double-blind Treatment Phase, investigational products are: rimegepant 75 mg ODT and the matching placebo ODT.

During the Open-label Extension Phase, investigational product is rimegepant 75 mg ODT.

8.1.2. Packaging, Shipment and Storage

Study intervention will be packaged in blistered packaging, which is heat sealed into a wallet.

The product storage responsible person should ensure that the study intervention is stored in accordance with the environmental conditions (temperature and light) as determined by the Sponsor. Please see the IB and IP Manual for specific conditions. If concerns regarding the quality or appearance of the study intervention arise, do not dispense the study intervention and contact the Sponsor/ Sponsor's designee immediately.

8.2. Dose and Administration

8.2.1. Method of Assigning Participant Identification

Immediately after written informed consent is obtained and before performing any study-related procedures, the site staff must obtain a participant identification by adding a new participant in the appropriate study-related system. In this study, an IWRS system will be utilized for obtaining participant identification. The participant number must not be reused for any other participant in the study. Participants will maintain their participant number assigned at Screening throughout the study except in cases of re-screening, where permitted, in which case a new participant number must be assigned.

At the Baseline Visit, eligible participants will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. **Randomization will be stratified by the number of migraine days during the Observation Phase (<8, ≥8). It is important to correctly enter the**

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

number of migraine days in the IWRS system. Once a participant is stratified in the IWRS, this cannot be changed and will be considered a protocol deviation if later found to be entered incorrectly.

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

8.2.2. Selection and Timing of Dose and Administration

Study intervention (rimegepant or matching placebo) will be assigned via the appropriate study-related system. There are no dose adjustments in this study and participants will receive rimegepant or placebo in drug wallets. Participants will be dispensed study intervention at the Baseline Visit, and the participants will be instructed that they must take ***one tablet of study intervention every other calendar day, regardless of whether they have a migraine on that day or not***. This is the scheduled dosing regimen for the Double-blind Treatment Phase and the Open-label Extension Phase. The ODT should be placed on top of or under the tongue until fully dissolved then swallowed. Participants should be instructed to use dry hands when handling the study intervention.

During the Open-label Extension Phase only, if a participant has a migraine on a non-scheduled dosing day, they may take 1 tablet of rimegepant 75 mg ODT as acute treatment for their migraine, if needed, with a maximum of 1 tablet of rimegepant 75 mg per calendar day. This regimen of scheduled dosing on every other calendar day and as needed study intervention dosing should be followed for up to 12 weeks in the Open-label Extension Phase.

Dosing should occur around the same time every other day for migraine prevention. It is recommended that participants dose EOD after completing the eDiary. However, it is more important that the participant consistently dose at approximately the same time EOD. The time of dosing should be consistent throughout the study for the EOD dosing days.

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

8.2.3. Dose Modifications

There will be no dose adjustments in this study.

8.2.4. Dose Interruptions

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

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8.3. Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. Study participants and the clinical study personnel involved in the collection, monitoring, revision, or evaluation of AEs, or personnel who could have an impact on the outcome of the study should be blinded with respect to the participant's treatment assignment (rimegepant or placebo).

The blinding state should not be broken except when medical emergency happens, and knowledge of the study drug treated would affect the treatment of the emergency. The emergent unblinding decision will be made on a case-by-case basis, at the discretion of the Principal Investigator in collaboration with the Sponsor Medical Monitor.

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

If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF. A bioanalytic scientist, pharmacokineticist, data monitoring committee member, IWRS randomization manager, pharmacovigilance representative, unblinded clinical supply manager may all be unblinded before data is more generally unblinded. Except as noted above, other members of the Sponsor research team will remain blinded.

A bioanalytic scientist, pharmacokineticist, data monitoring committee member, IWRS randomization manager, pharmacovigilance representative, unblinded clinical supply manager may all be unblinded before data is more generally unblinded. Except as noted above, other members of the Sponsor research team will remain blinded.

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

8.4. Treatment Compliance

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

Participants must be counseled on the importance of taking the study intervention as directed (see Section 8.2.2). Treatment compliance and review of study intervention doses through review of study intervention paper diary and returned study intervention wallet should be assessed by site staff at each study visit. Discrepancies between doses reported in the diary and review of returned study intervention wallet must be checked and documented in the

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

source record. Investigators should inform participants that involuntary termination from the study will occur in cases where non-compliance to study treatment or eDiary is identified. Study staff should contact a participant between the study visits if the participant demonstrates non-compliance with the eDiary and document the contact in the source, to identify potential lost to follow up participants as early as possible.

Investigators must monitor participants for possible cases of abuse of study intervention (participants taking study intervention for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should also assess study intervention accountability discrepancies (e.g., missing study intervention, loss of drug, or non-compliance cases in which more study intervention was used, as compared to expected). Investigators should obtain more information and explanation from participants when there are study intervention accountability discrepancies. See Section 9.3.

Cases of potential study intervention abuse or overdose (including cases of non-compliance with study intervention dosing instructions or participants who discontinue treatment without returning study intervention) should be documented in the source record and reported as an AE or SAE as appropriate. Dosing errors (e.g., accidentally taking 2 tablets of study intervention in 1 calendar day) should be reported as deviations.

8.5. Destruction and Return of Study intervention

All unused and/or partially used study intervention can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible study monitor or the Sponsor's designee. If it is site policy to destroy study intervention on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study interventions can only be destroyed after being inspected and reconciled by the responsible study monitor or the Sponsor's designee.

8.6. Prior and Concomitant Therapy

Participants in this study will be allowed to be on certain concomitant medications that have been prescribed. Attempts should be made not to alter the doses and regimens of the concomitant medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any changes must be captured in the CRF.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Section 15.5 Appendix 5).

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant medications at each visit.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

A concomitant medication paper diary will be provided to participants at the Screening Visit. Use of any concomitant medication will be recorded by the participant on a paper diary and returned to the site at the Baseline and EOT Visits.

8.6.1. Prohibited and Restricted Concomitant Therapy

All medications taken by participants at the Screening Visit until the Follow-up Week 4 Visit will be documented as concomitant medications including vaccinations.

The medications and therapy listed below are prohibited or restricted during the entire study, ie, starting at the Screening Visit and through the Follow-up Week 4 Visit, unless otherwise specified.

1. Medication for migraine prevention generally considered to have efficacy, regardless of indication (see Section 15.2 Appendix 2):

    a. CGRP monoclonal antibodies taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study.

    b. Botulinum toxin injections (e.g., Botox®) taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study.

    c. Other medications with demonstrated efficacy for the prevention of migraine (ie, topiramate, flunarizine, and atogepant; for the full list please see Section 15.2 Appendix 2) taken within 30 days prior to the Screening Visit and throughout the study, including small molecule CGRP antagonists other than rimegepant provided for the current study, like atogepant.

2. Traditional Chinese medicines that may be used for headache treatment (e.g., Tou Tong Ning Capsule, Tian Shu Capsule, Yang Xue Qing Nao Ke Li etc) taken within 5 half-lives prior to the Screening Visit and throughout the study.

3. Medication accepted for treatment of acute headache (see Section 8.6.2) for a non-headache indication taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.

4. Use of triptans is prohibited during the Open-label Extension phase.

5. St. John's Wort.

6. Butterbur root or extracts

7. Ergotamine taken ≥10 days per month on a regular basis for ≥3 months (≥12 weeks) in the year prior to the Screening Visit.

8. Analgesics (e.g., NSAIDs or acetaminophen) taken ≥15 days per month within 3 months (12 weeks) prior to the Screening Visit.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

9. Use of acetaminophen or acetaminophen containing products for non-headache indications after the Baseline Visit is prohibited. Any use of acetaminophen or acetaminophen containing products for non-headache indications during the Observation Phase must be stopped at least 2 days prior to the Baseline/Randomization Visit. Acetaminophen as an acute migraine medication as described in Section 8.6.2 is allowed during the Double-blind Treatment phase.

10. Atypical antipsychotics (e.g., risperidone, olanzapine, aripiprazole) and typical antipsychotics (e.g., haloperidol, fluphenazine).

11. Lamotrigine, valproic acid/valproate.

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

13. Marijuana and all forms of ingested or inhaled cannabidiol and THC-containing products.

14. Moderate to strong CYP3A4 inhibitors. If use of a moderate or strong CYP3A4 inhibitor is required, then dosing with study intervention should be stopped and should not start again until 14 days after the last dose of the moderate or strong CYP3A4 inhibitor. Please see Section 15.3 Appendix 3 for list of CYP3A4 inhibitors.

15. Moderate to strong CYP3A4 inducers. If use of a moderate or strong CYP3A4 inducer is required, then dosing with study intervention should be stopped and should not start again until 14 days after the last dose of the moderate or strong CYP3A4 inducer. Please see Section 15.3 Appendix 3 for list of CYP3A4 inducers.

16. Strong inhibitors of the P-gp transporter. If use of a strong inhibitor of the P-gp transporter is required, then dosing with study intervention should be stopped and should not start again until 14 days after the last dose of the strong inhibitors of the P-gp transporter. Please see Section 15.3 f Appendix 3 or list of P-gp transporter.

17. Acupuncture for the treatment of headache.

18. Use of any investigational agent other than rimegepant from the Screening Visit through the 4-Week Follow-up Safety Visit.

8.6.2. Acute Headache Medications

Participants may use their permitted medication if needed for acute treatment of a headache throughout the study. Use of acute headache medication throughout the study (from Screening Visit to the Follow-up Week 4 Visit) will be recorded by the participant in the concomitant medication paper diary and reported to the site. Acute headache medications that are permitted during the study include the following:

- triptans ***(triptans are prohibited during the Open-Label Extension Phase)***

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

- aspirin
- ibuprofen
- baclofen
- acetaminophen up to 1000 mg/day for a maximum of 2 consecutive days at a time (this includes Excedrin Migraine)
- naprosyn (or any other type of non-steroidal anti-inflammatory drug (NSAID))
- antiemetics (e.g. metoclopramide or promethazine)
- muscle relaxants

The above listed medications are the only medications allowed for acute headache treatment in the current study. Please note that ergotamine medication, lasmiditan and ubrogepant are not listed as permitted medications for acute migraine treatment in this study. However, use of these medications, if taken for migraine treatment, must be documented for the purposes of assessing migraine days and must be captured as a protocol deviation.

If a participant takes a tablet of study intervention and experiences a headache later that day, the participant may take their ***permitted acute migraine medication*** as described in this section of the protocol.

During the Open-label Extension Phase, participants are required to take 1 tablet of rimegepant 75 mg ODT every other day. If participants have a migraine on a day that they are not scheduled to dose with rimegepant, they may take 1 tablet of rimegepant 75 mg ODT on that calendar day to treat the migraine. ***The use of study intervention on non-scheduled dosing days is only permitted during the Open-label Extension Phase.***

Investigators should discuss with study participants in term of the type of acute headache medications they would use in the beginning of the Observation Phase and the Open-label Extension Phase, respectively. Once aligned on the specific medication(s) they would use for acute headache treatment, it is not recommended to change the type of acute headache medication throughout the Observation Phase and the Double-blind Treatment Phase. In the Open-label Extension Phase, use of triptans is prohibited. However, study intervention rimegepant can be used as an acute migraine medication on non-scheduled dosing days if a migraine is experienced on that day. Once aligned on the specific medication(s) they would use for acute headache treatment during the Open-label Extension Phase, it is not recommended to change the type of acute headache medication throughout the Open-label Extension Phase.

9. ADVERSE EVENTS

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a participant or clinical investigation participant administered an investigational (medicinal) product and that does not necessarily have a causal relationship

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

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

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

Recording of Adverse Events

All adverse events will be coded and described using the MedDRA. The adverse event record form should be truthfully filled in during the trial, including:

- Name of AE (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, unlikely related, and definitely unrelated), including the application for suspected procedures,
- Relevant measures taken for investigational drug,
- Event outcome,
- Whether it is an SAE (if yes, list the specific criteria for SAE),
- Medications and other interventions to correct AEs.

If possible, adverse events should be recorded according to the confirmed diagnosis. If a confirmed diagnosis cannot be recorded, separate signs and symptoms should be recorded separately. Each diagnosis/symptom should be recorded separately.

If the same adverse event occurs to the participant more than once, and the participant has recovered between adverse events, such adverse event shall be recorded separately according to the times of occurrence. If the severity of an adverse event changes during its occurrence, it should be re-recorded as a separate AE.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Assessment for Determining Relationship of AE to Study intervention:

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

1. Definitely related: occurrence of reaction is temporal relationship with administration, reaction is consistent with known reaction type of study intervention, and the reaction is improved after the discontinuation of study intervention.

2. Probably related: occurrence of reaction conforms to the temporal sequence of treatment, reaction conforms to the known principle of the treatment, cannot be explained by the participant's clinical status, psychological factors, concomitant medication or treatment, other environmental factors, etc., and the adverse event is improved after the discontinuation of study intervention.

3. Possibly related: occurrence of reaction has temporal relationship with administration, reaction is consistent with known reaction type of study intervention, and the participant's clinical status, psychological factors, concomitant drug or treatment and other environmental factors may also cause the reaction.

4. Unlikely related: The occurrence of reaction conforms to the temporal sequence of medication, reaction does not conform to the known reaction type of the investigational drug, and the participant's clinical status, psychological factors, concomitant medication or treatment, and other environmental factors may also cause the reaction.

5. Definitely unrelated: occurrence of the reaction does not follow a temporal sequence from administration of the drug, the reaction does not follow a known reaction pattern to the investigational drug, the participant's clinical state, psychological factors, concomitant medication or treatment, other environmental factors may cause the reaction, which is resolved after the disease state is improved or other treatment is stopped.

Definitely related, probably related and possibly related will be mapped into ‘related’ and unlikely related and definitely unrelated will be mapped into ‘unrelated’ via a binary method in the CRF, safety data base and clinical study report.

9.1. Serious Adverse Events

9.1.1. Definition of Serious Adverse Event (SAE)

An SAE is any event that meets any of the following criteria at any dose:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a participant who received rimegepant
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm.
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization.
    - Potential drug induced liver injury (see Section 9.4).
    - Abuse or Overdose of medication:
        - Potential study intervention abuse (including cases of excessive non-compliance with study intervention dosing instructions or participants who discontinue treatment without returning study intervention) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor participants for possible cases of abuse of study intervention (participants taking study intervention for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from participants when there are study intervention accountability discrepancies.
        - Potential study intervention overdose is defined in Section 9.3.

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

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

- A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening).
- Elective surgery planned prior to signing consent.
- Admissions as per protocol for a planned medical/surgical procedure.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

- Routine health assessment requiring admission (ie, routine colonoscopy).

- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (ie, lack of housing, care-giver respite, family circumstances).

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

Suspected unexpected serious adverse reaction refers to a suspected and unexpected serious adverse reaction whose nature, severity, frequency or consequence of clinical manifestations exceed those in the Investigator's Brochure of the investigational drug, package insert of the marketed drug or summary of product characteristics and other available information.

9.1.2. Collection and Reporting Serious Adverse Events

Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study intervention, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the Screening Phase and throughout the course of the study up to and including the Follow-up Week 4 Visit. The investigator should report any SAE occurring after this time period that is believed to be related to study intervention or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study intervention, overdose (see Section 9.3), potential drug induced liver injury (see Section 9.4) and exposures (see Section 9.5) must be reported within 24 hours of the investigator becoming aware of the event. For this study, SAEs will be captured through electronic data capture (EDC) and on the SAE form.

The investigator is responsible for submitting all applicable events to the IRB and/or the head of the institutional site as per the IRB's reporting requirements. Additionally, the investigator, or designated staff, is responsible for entering the SAE information into the CRF and/or system (ie, event term, start/stop dates, causality, and severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to Pfizer DSU either via the Pfizer SAE Submission Assistant (PSSA) tool or as a written description using the Pfizer CT SAE report form, that must be sent by facsimile (fax or eFax) to the Pfizer DSU at 1-866-997-8322.

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

The minimum information required for an initial SAE report is:

- Sender of report (Site number, Investigator name)
- Participant identification (participant number)
- Protocol number
- SAE term (if a SAE is being reported)

9.2. Non-serious Adverse Events

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

9.2.1. Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at signing of ICF through the 4-Weeks Follow up Safety Visit.

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

9.2.2. Laboratory Test Abnormalities

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

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

9.3. Overdose

There is limited clinical experience with overdose of rimegepant. Treatment of overdose with rimegepant should consist of general supportive measures. There is no known specific antidote for overdose with rimegepant. Single doses of 20-fold the 75 mg dose of rimegepant (ie, 1500 mg) have been administered without any untoward effects (CN170001).

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There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2.1.2).

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

4. Overdose is reportable to Pfizer Safety only when associated with an SAE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

Dosing errors should be reported as protocol deviations.

9.4. Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 9.1.2.

Potential drug induced liver injury is defined as:

5. ALT or AST elevation >3 times the ULN

6. AND

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

8. AND

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

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

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

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

If any potential DILI is identified and meets the criteria above, the Sponsor Medical Monitor (or designee) should immediately be contacted for further instruction and whether the participant must discontinue from the trial and appropriate follow up requirements.

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

9.5. 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 EDP, EDB, and occupational exposure.

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

9.5.1. 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 (ie, 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 (ie, X-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. The investigator must immediately notify the Pfizer (or designee) Medical Monitor and report the event by either using the PSSA tool and by completing an Exposure During Pregnancy (EDP) Supplemental Form following the SAE reporting procedures as described in Section 9.1.2.

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

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Any pregnancy that occurs in a female partner of a male study participant 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 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 non-participant 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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

Additional information regarding the EDP may be requested by the sponsor. Further follow up of birth outcomes will be handled on a case-by-case basis (e.g., follow up 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.

9.5.2. Exposure During Breastfeeding

An EDB occurs if:

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

- A female non participant 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 (e.g., vitamins) is administered in accordance with authorized use.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

9.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form or PSSA, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a 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.

9.6. Lack of Efficacy

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

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. **Lack of efficacy or failure of expected pharmacological action in an approved indication constitutes an SAE and should be reported to Pfizer Safety.**

9.7. Medication Errors

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

Medication errors are recorded and reported as follows:

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

10. STATISTICS CONSIDERATIONS

Complete details on the statistical methods for this study may be found in the SAP.

10.1. Sample Size

The study will randomize approximately 392 study participants per treatment group (784 participants in total). Based on data from migraine prevention study BHV3000-305 conducted in the US, we estimate that this will result in approximately 364 participants per treatment group (728 participants in total) in the double-blind treatment migraine analysis set (see Section 10.2).

Assuming rimegepant provides roughly a 0.8-day advantage over placebo on the primary endpoint, and a common standard deviation of 3.6 days, then the study will have roughly

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

85% power on the primary endpoint at an alpha level of 0.05. Estimates are based on data from study BHV3000-305; the advantage over placebo on the primary endpoint was estimated from a model, whereas the common standard deviation was estimated from the observed data.

10.2. Analysis Sets

The following analysis sets will be used in this study:Enrolled: Participants who sign an informed consent form and are assigned a participant identification number.

- Randomized: Participants in the enrolled analysis set who receive a randomized treatment assignment (rimegepant or placebo) from the IWRS.
- Double-blind treatment safety: Participants in the enrolled analysis set who take ≥1 dose of double-blind study intervention (rimegepant or placebo).
- Open-label rimegepant safety: Participants in the enrolled analysis set who take ≥1 dose of open-label rimegepant.
- Double-blind or open-label Rimegepant safety: Participants in the enrolled analysis set who take ≥1 dose of double-blind or open-label Rimegepant.
- Follow-up safety: Participants in the double-blind treatment safety analysis set whose last contact date is in the follow-up safety analysis period. The safety analysis period will be defined in SAP.
- Double-blind treatment efficacy: Participants in the randomized analysis set who are randomized only once and take ≥1 dose of double-blind study intervention (rimegepant or placebo).
- Double-blind treatment migraine: Participants in the double-blind treatment efficacy analysis set with ≥14 days of eDiary efficacy data (not necessarily consecutive) in the Observation Phase and ≥1 month (4-week interval) in the Double-blind Treatment Phase.
- Open-label efficacy: Participants in the double-blind treatment efficacy analysis set who take ≥1 dose of open-label Rimegepant.
- Open-label migraine: Participants in the Open-label efficacy analysis set with ≥14 days of eDiary efficacy data (not necessarily consecutive) in the Observation Phase and ≥1 month (4-week interval) in the Open-label Treatment Phase.

10.3. Statistical Methods

Results will be summarized by treatment group.

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10.3.1. Primary Endpoint

The primary endpoint is the mean change from the Observation Phase in the number of migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12). The primary null hypothesis is that rimegepant treatment is not different from placebo in the mean reduction from the Observation Phase in the number of migraine days per month across the Weeks 1 to 12 treatment period. The alternative hypothesis is that rimegepant has a different effect than placebo.

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

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

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

10.3.2. Secondary Endpoints

The proportion of participants with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed using Mantel-Haenszel risk estimation stratified by randomization stratum for the double-blind treatment migraine analysis set. Missing data will be imputed as non-response (i.e., failure). The stratified difference estimate (rimegepant-placebo), SE, p-value, and 95% CI will be reported for the entire Double-blind Treatment Phase (Weeks 1 to 12).

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

The mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase will be assessed for

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

the double-blind treatment migraine analysis set from the same model used for the primary endpoint.

The mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 will be analyzed for Double-blind Treatment efficacy analysis set using a linear mixed effect model that will include the following variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; and fixed effects for treatment group and randomization stratum. The Week 12 difference estimate (rimegepant – placebo), SE, p-value and 95% CI will be reported. The Huber-White "sandwich" estimator will be used for the estimation of SEs.

The mean number of acute migraine medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12) will be assessed for the double-blind treatment migraine analysis set using a model that is similar in structure to that used for the primary endpoint, except that the number of acute migraine medication days per month is the dependent variable.

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

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

The frequencies of the following safety endpoints will be tabulated on treatment: AEs by severity (CTCAE Grade 1 to 5, and total); AEs by relationship to study intervention (definitely related, probably related, possibly related, unlikely related, definitely unrelated); SAEs; AEs leading to study intervention discontinuation; hepatic-related

AEs by severity; hepatic-related AEs leading to study intervention discontinuation; laboratory test abnormalities by toxicity grade; and LFT elevations based on fold changes above ULN, including ALT or AST >3× ULN concurrent (on the same laboratory test collection date) with total bilirubin >2× ULN.

The investigators will determine the severity of AEs and the relationship of AEs to study therapy. The investigators' terms will be coded and grouped by system organ class using the latest version of the MedDRA available to the analyst. AEs will be presented by system organ class and preferred term. If a participant had an adverse event with different severities over time, then only the worst severity will be reported. In tables by relationship to study intervention, if a participant has an AE with different relationships over time, then the highest degree of relatedness to study intervention will be reported.

Laboratory test results will be graded according to numeric laboratory test criteria in the latest version of CTCAE. If a participant has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported. The frequency of unique participants with clinically significant laboratory test abnormalities will be tabulated based on Grade 3-4 clinical laboratory evaluations graded using CTCAE.

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10.3.3. Type 1 Error Control

Type 1 error will be controlled by the use of hierarchical testing. The significance of the primary endpoint will be evaluated at the 2-sided 0.05 level. If the primary endpoint is not significant, then any further tests on the following secondary endpoints will have p-values presented only for descriptive purposes. If the primary endpoint is significant, then the following secondary endpoints will be tested hierarchically at the 0.05 level in the following order:

- Proportion of participants with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).
- Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the Double-blind Treatment Phase.
- Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the Double-blind Treatment Phase.
- Mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the Double-blind Treatment Phase.
- Mean number of acute migraine medication days per month over the entire Double-blind Treatment Phase (Weeks 1 to 12).

10.4. Schedule of Analyses

The data from this study may be locked and analyzed at any point after the last study participant completes their last visit in the Double-blind Treatment Phase of the study, and adequate time has been allowed for follow-up. Analyses of the data may be conducted after the Double-blind Treatment Phase, and at any point in, or after, the Open-label Extension Phase.

11. ETHICS AND RESPONSIBILITIES

11.1. Good Clinical Practice

This study will be conducted in compliance with the protocol, GCP, GLP, International Conference on Harmonization guidelines, and all applicable regulations, any IRB/IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive IRB/IEC's approval/favorable opinion prior to initiation of the study.

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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

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

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

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

11.2. Data and Safety Monitoring Committee

This study will not make use of a Data Safety Monitoring Committee. Rimegepant has been found to be well tolerated in previous clinical studies and post-marketing in the US Safety will be closely monitored via the investigators, Sponsor/Sponsor's designee and an IRB/IEC.

11.3. Institutional Review Board/Independent Ethics Committee

All appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), IB and any other written information provided to study participants, will be provided to the IRB/IEC. The trial will not begin until the investigators have obtained the IRB/IEC favorable written approvals for the above-mentioned study documents.

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

11.4. Informed Consent

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

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

Before the potential participant has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the study participant, and the participant will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the participant must read, sign and date an IRB/IEC approved written informed consent form for study. The signed and dated ICF will be retained at the investigator's site, with a copy provided to the

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

study participant and date will be entered in his or her CRF or appropriate system. The IRB/IEC must review and approve all protocol versions and ICF versions and a copy of each version of the IRB/IEC approved protocol and ICF is to be retained in the Study Master file. Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and participants will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

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

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

The ICF form must also include a statement that the Sponsor and its representatives and regulatory authorities may have direct access to participant records.

11.5. Case Report Forms

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

Electronic CRFs will be prepared for all data collection fields when EDC is being used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator must retain a copy of the CRFs including records of changes and corrections. If EDC is being used, signatures will be obtained electronically and a copy of the electronic CRFs will be provided (or the data from the CRFs) for future reference.

11.6. 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.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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 subject data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

11.7. 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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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.

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.

11.8. Sponsor's Medically Qualified Individual

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

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

12. RECORDS MANAGEMENT

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

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

The Sponsor will notify the investigators when the study files for this study are no longer needed.

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

It is the responsibility of the investigator to ensure that the current disposition record of investigational product (may be supplied by the Sponsor) is maintained at each study site where the study intervention is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- Amount of study intervention received and placed in storage area.
- Label ID number or batch number or Kit number as specified for the protocol.
- Amount dispensed to and returned from each study participant.
- Amount transferred to another area or site for dispensing or storage if applicable.
- Amount of drug lost or wasted.
- Amount destroyed at the site if applicable.
- Amount returned to the Sponsor, if applicable.
- Retain samples for bioavailability/bioequivalence, if applicable.
- Record of dates and initials of personnel responsible for investigational product dispensing and accountability.

12.1. Source Documentation

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

12.2. Use of Medical Records

In certain situations, sponsor review of redacted copies of participant medical records if requested by Pfizer safety may be performed, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

12.3. Study Files and Record Retention

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

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

12.4. Study report and publications

The Sponsor (or specified designee) is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

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

13. AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the Sponsor (or specified designee). A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes. The Sponsor or specified designee will submit protocol amendments to the appropriate regulatory authorities for approval.

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

14. STUDY DISCONTINUATION

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

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15. APPENDICES

15.1. APPENDIX 1 – Definition of Migraine Days

Migraine Day: Any calendar day in which the participant experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache), as per participant eDiary. 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 (triptan, study intervention [Open-label Extension Phase only]) 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. Please note that ergotamine medication, lasmiditan and ubrogepant are not listed as permitted medications for acute migraine treatment in this study. However, use of these migraine-specific medications for headache treatment on a calendar day, must be documented and this calendar day will also be counted as a migraine day. The use of study intervention on non-scheduled dosing days is only permitted during the Open-label Extension Phase; dosing with study intervention on non-scheduled dosing days is not permitted during the Double-blind Treatment Phase.

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

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

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

- a headache of any duration for which acute headache treatment is administered.

Acute Migraine-specific Medication Day: Any calendar day during which the participant took a migraine-specific medication (triptan, study intervention [Open-label Extension Phase only]). The use of study intervention on non-scheduled dosing days is only permitted during the Open-label Extension Phase; **dosing with study intervention on non-scheduled dosing days is not permitted during the Double-blind Treatment Phase**. Please note that ergotamine medication, lasmiditan and ubrogepant are not listed as a permitted medication for acute migraine treatment in this study. However, use of these medication, if taken for headache treatment, must be documented for the purposes of assessing migraine days and acute migraine-specific medication day and must be captured as a protocol deviation.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

15.2. APPENDIX 2 – Categories of Migraine Prevention Medications

Medications for migraine prevention generally considered to have efficacy can be classified into the following categories:

- **Category 1**: Divalproex sodium, sodium valproate
- **Category 2**: Topiramate, carbamazepine, gabapentin
- **Category 3**: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- **Category 4**: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- **Category 5**: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- **Category 6**: Calcium channel blockers (for example: Flunarizine, verapamil, Nifedipine, Nimodipine)
- **Category 7**: ACE inhibitors/ARBs (Lisinopril, candesartan)
- **Category 8**: Neuromuscular blocker: (for example: onabotulinumtoxinA [Botox®])
- **Category 9**: CGRP antagonists (for example: Erenumab [Aimovig®], Fremanezumab [Ajovy®], Galcanezumab [Emgality®], Eptinezumab [Vyepti®], Rimegepant (Nurtec®), Atogepant [Qulipta™])

Note: Medications for migraine prevention generally considered to have efficacy are prohibited throughout the current study and a period of time prior to the Screening Visit:

i. CGRP monoclonal antibodies taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study is prohibited.

ii. Onabotulinumtoxin A (Botox®) taken within 6 months (24 weeks) prior to the Screening Visit and throughout the study is prohibited.

iii. Other medications with demonstrated efficacy for the prevention of migraine (medications listed as above in Category 1 to 7) taken within 30 days prior to the Screening Visit and throughout the study is prohibited.

Note: In addition, participants are excluded if they have had no therapeutic response with >2 of the 9 medication categories of preventive treatment of migraine after an adequate therapeutic trial in the past 3 years per investigator's judgement. Two trials with no therapeutic response within a category will be considered having no therapeutic response to that particular medication category.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

No therapeutic response is defined as no reduction in headache frequency, duration, or intensity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment. The following scenarios ***do not*** constitute lack of therapeutic response:

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

15.3. APPENDIX 3 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (Not all-inclusive)

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

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

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

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

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

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

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

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

Resources:

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

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

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

15.4. APPENDIX 4 - Liver Safety: Suggested Actions and Follow Up Assessments and Study Intervention Rechallenge Guidelines

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

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

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

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

- For participants with baseline AST OR ALT OR T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3× ULN; or ≥8× ULN (whichever is smaller).
    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1× ULN or if the value reaches ≥3× ULN (whichever is smaller).

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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

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

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

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15.5. Appendix 5 - Contraceptive and Barrier Guidance

15.5.1. 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.

15.5.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 2b (Age and Sex; Section 5.2) and specify the reproductive requirements for including female participants. Refer to Section 15.5.4 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 15.5.3).

  OR

- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study 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.

15.5.3. Woman of Childbearing Potential

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

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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.

15.5.4. Contraceptive Methods

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

The following contraceptive methods are appropriate for this study:

<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.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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).

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

15.6. Appendix 6 - ECG Findings of Potential Clinical Concern

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

• QTcF prolongation >500 ms.
• Absolute value of QTcF >450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex >120 ms).
• New-onset right bundle branch block (QRS complex >120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 second duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR 40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

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

090177e19e97cd17\Approved\Approved On: 15-Sep-2023 08:35 (GMT)

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