DRUG:	BHV-3000 (rimegepant)
STUDY NUMBER(S):	BHV3000-301
PROTOCOL(S) TITLE:	BHV3000-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy, Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine
IND NUMBER:	109886
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ORIGINAL PROTOCOL DATE:	April 12, 2017
VERSION NUMBER:	V 4.0 (Incorporates Administrative Letter 3)
VERSION DATE:	23-January-2018

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: BHV3000-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy, Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine

Study No: BHV3000-301

Original Protocol Date: 12 April 2017

Protocol Version No: V4.0

Protocol Version Date: 23 January 2018

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Signature Approval	Date
PPD		

SUMMARY OF CHANGES[1]

Change	Page(s) Affected	Summary
1. **6.2.4.1 Safety Laboratory Testing**	52	Requirements for addressing elevated CPK results have been revised: ***Currently written:*** **Blood chemistry/electrolyte**: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CPK (**with local lab fractionation, if elevated);** ***Should be written:*** **Blood chemistry/electrolyte**: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CPK **(with local lab fractionation, if central lab CK result is > 1.5 x ULN);**

[1] If higher than v1.0

Change	**Page(s) Affected**	**Summary**
2. **8.1.2 Collection and Reporting Serious Adverse Events**	60	The time period for reporting on-study SAEs has been updated as follows: ***Currently written:*** Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur **during the screening period and within 30 days of discontinuation of dosing.** The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures. ***Should be written:*** Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur **during the screening period and throughout the course of the study up to and including the End of Treatment Visit.** The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures.

Change	**Page(s) Affected**	**Summary**
3. **9.3 Populations for Analysis**	63	The definition of the mITT population was adjusted to correspond with recent instructions from the FDA. The mITT population had been defined as all treated subjects. It is now defined as all treated subjects with a migraine of moderate to severe intensity and who provide at least one evaluable, post-baseline efficacy data point.
4. **9.4.1 Primary Endpoints(s)**	64	The analysis of the MBS had previously been stratified by use of prophylactic medication and MBS. It is now stratified only by use of of prophylactic medication. The discussion of sensitivity analyses has been moved to statistical analysis plan.
5. **9.4.2 Secondary Endpoints**	64	The hierarchical testing order for the secondary endpoints has been changed.
6. **9.4.3 Analysis of Safety**	64, 65	Eliminated the phrase “and clinically relevant abnormalities” from the reporting of AEs.
7. **Minor administrative corrections**	Misc.	In addition to the changes detailed above, several minor administrative edits have been made throughout the document

BHV-3000-301

BHV3000-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy, Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine Confidentiality and Investigator Statement

The information contained in this protocol and all other information relevant to BHV-3000 (rimegepant) are the confidential and proprietary information of Biohaven Pharmaceutical Holding Company Limited, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Biohaven Pharmaceutical Company Limited.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Biohaven Pharmaceutical Holding Company Limited or specified designees. I will discuss the material with them to ensure that they are fully informed about Biohaven and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3000-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy, Trial of BHV-3000 (rimegepant) for the Acute Treatment of Migraine
Rationale:	Rimegepant is being developed for the treatment of migraine, with a specific focus on acute treatment. Effectiveness against migraine was demonstrated in a Phase 2b double-blind, randomized, placebo-controlled, dose-ranging study where rimegepant at 75 mg showed efficacy on all four traditional endpoints: pain, nausea, photophobia and phonophobia. The data from this study will allow characterization of the relative safety, and efficacy of tablets of rimegepant versus placebo in the treatment of moderate or severe migraine measuring freedom from pain and freedom from most bothersome symptom (nausea, photophobia or phonophobia) reported at the onset of the treated migraine. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom in patients with an acute migraine will also be obtained.
Target Population:	The study will recruit male and female patients 18 years of age and older with at least a one-year history of migraines (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition beta version[1], including an age of onset prior to 50, migraine attacks that last about 4 - 72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1415 patients will be screened to randomize 1200 patients (approximately 600 per arm). If, however, the targeted number of treated subjects (see Section 9.2 Sample Size) is reached first, the study may be closed. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).
Objectives:	This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. The study drug will be

	rimegepant presented in a 75 mg tablet or matching placebo. The study will randomize approximately 1200 patients. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no). A patient whose usual migraine attack results in headache pain of moderate or severe intensity and who is otherwise found acceptable for entry into this trial based on inclusion and exclusion criteria will first participate in the screening phase (3 - 28 day period). Patients on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry. After randomization, the patient will be dispensed a single dose of the double-blind study medication that will be taken at the time a migraine attack reaches moderate or severe pain intensity (described below) on the numeric rating scale (NRS) as indicated in the electronic diary (eDiary). The patient will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe pain intensity and only after they have identified their most bothersome migraine-associated symptom (phonophobia, photophobia or nausea). The patient will complete an eDiary for up to forty-eight hours after taking study medication. The patient will telephone the study center immediately if a severe or serious adverse event occurs. Patients will record efficacy data in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to ***and*** at time of taking study medication. The patient should record all headache intensity leading up to dosing, but should not dose with study medication until the headache reaches moderate or severe pain intensity. Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Patients will also complete the migraine-specific quality-of-life

	questionnaire and preference of medication (PoM) scale 24 hours after dosing. Patients who experience reduction of headache pain to a mild intensity or pain free intensity level will be considered to have achieved pain relief. The patient who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been completed on the eDiary) will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen (up to 1000 mgs/day) naproxen (or any other type of nonsteroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. If at the end of 48-hours after dosing with study medication (but before the End of Treatment Visit) patients are in need of migraine relief, they may take their prescribed standard of care medications, including triptans if not contraindicated, provided all of the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the patient will be permitted to take the same rescue therapy as outlined above. In all circumstances, the patient will always continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication. Patients will return to the study site within 7 days of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a patient has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, he or she will be withdrawn from the trial and instructed to return the unused study medication and eDiary to the study center.

STUDY SCHEMATIC

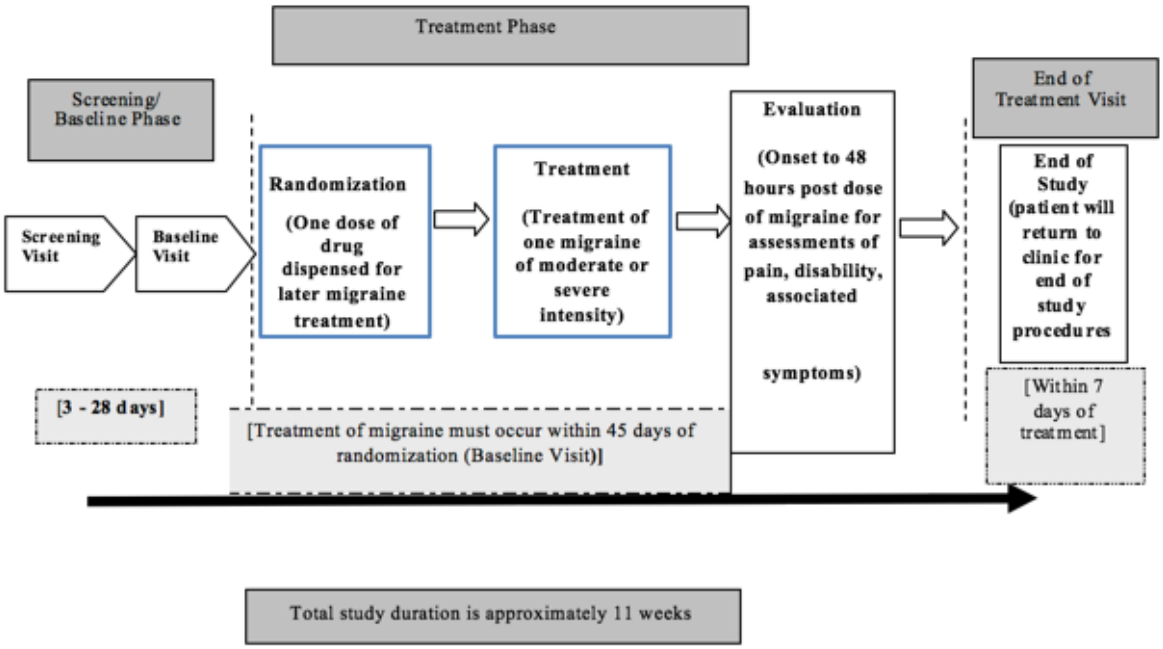


TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Concentration
CGRP	Calcitonin gene-related peptide
CONMED	Concomitant Medication
CV	Coefficient of Variation
DILI	Drug induced liver injury
DSMC	Data and Safety Monitoring Committee
DSM V	Diagnostic and Statistical manual of mental Disorders Fifth edition
ECG	Electrocardiogram
EC	Ethics Committee
eCRF	Electronic case report forms
EDC	Electronic Data Capture
eDiary	Electronic Diary
ePRO	Electronic Patient Reported Outcome
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
IB	Investigator's Brochure

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IHS	International Headache Society
Iv	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
kg	Kilogram
kBq	Kilobecquerel
mg	Milligram
Min	Minute
MBq	Megabecquerel
MBS	Most bothersome Symptom
MQoLQ	Migraine-Specific Quality-of-Life Questionnaire
msecs	Milliseconds
MTD	Maximum tolerated dose
PK	Pharmacokinetic
Qd	Once Daily
QTc	Interval between Q-wave and T-wave in the cardiac cycle
SAE	Serious Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Therapeutic Area Background

BHV-3000 (rimegepant, /rih-MEJ-eh-pant/) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of migraine. A comprehensive and durable efficacy profile for rimegepant was demonstrated in an 821 patient Phase 2b double-blind, randomized, placebo controlled, dose-ranging trial where migraine sufferers received either placebo, sumatriptan (100 mg) or rimegepant (10, 25, 75, 150, 300 or 600 mg) (Study CN170003)[2]. A dose of 75 mg was selected as the optimal dose for Phase 3 clinical trials, given that larger doses showed a similar efficacy profile and there was negligible benefit identified with higher doses. Rimegepant at 75 mg showed statistically significant comprehensive efficacy across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable as evidenced by the presence of pain freedom and pain relief which persisted through 24 hr and 48 hr showing significant difference from placebo on the corresponding 2-24 and 2-48 hr pain endpoints.

1.2 CGRP's Role in Migraine

The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology. For example, research and clinical studies have shown: serum levels of CGRP are elevated during migraine attacks, infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers, and treatment with anti-migraine drugs normalize CGRP levels. Additionally, multiple clinical studies show that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors, are effective in aborting migraine attacks.

Treatment with a CGRP receptor antagonist is believed to relieve migraine through the following possible mechanisms:

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

- **Decreasing Artery Dilation:** By blocking the CGRP receptors located in smooth muscle cells within vessel walls, CGRP receptor antagonists would inhibit the

pathologic dilation of intracranial arteries without the unwanted effect of active vasoconstriction.

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

1.3 Product Development Background

Details of the clinical and preclinical studies are provided in the most current investigator brochure. A summary of the relevant date to the study are presented below.

1.3.1 Non-clinical Pharmacology

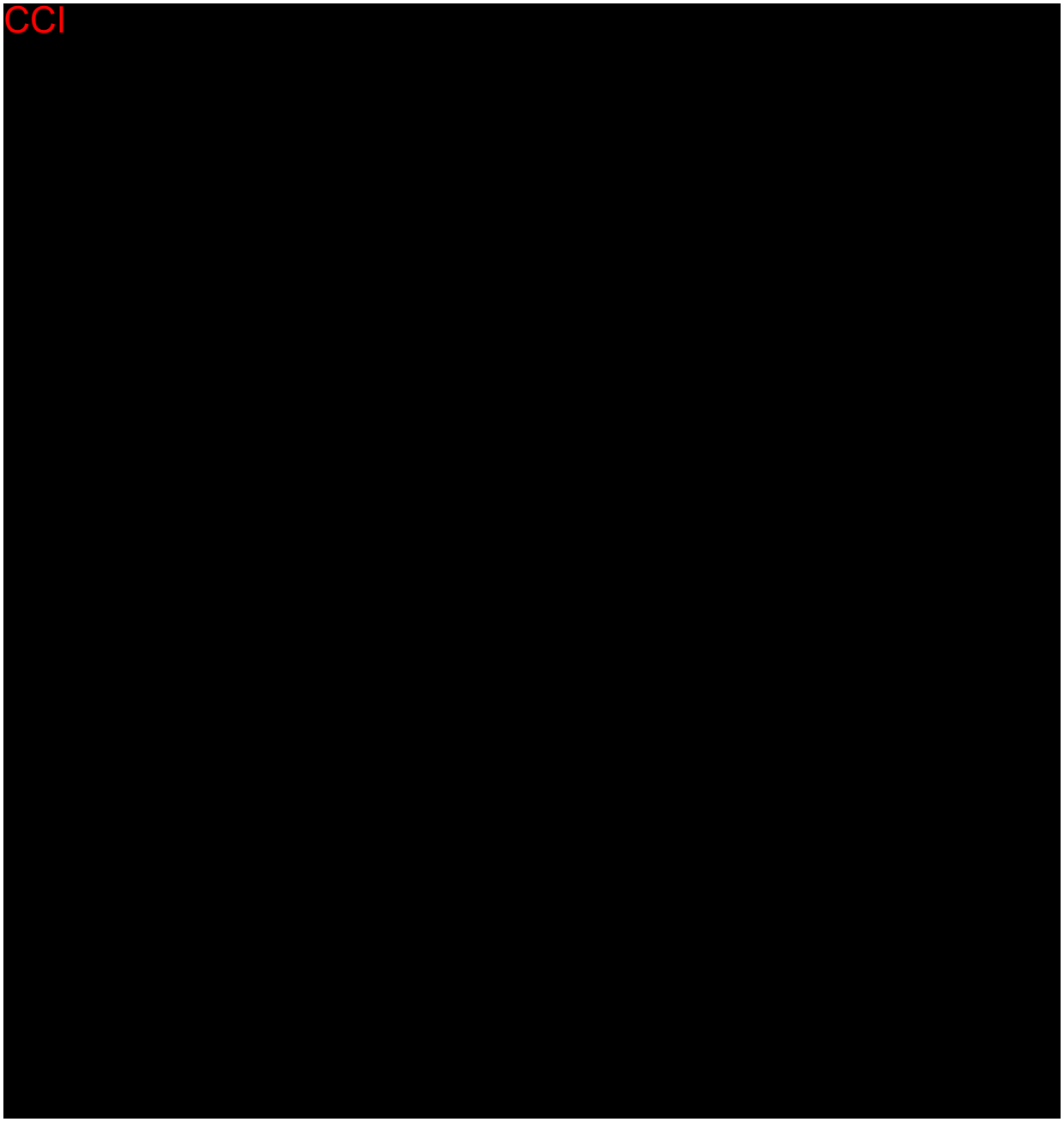
1.3.1.1 Nonclinical Pharmacokinetics and Pharmacodynamics

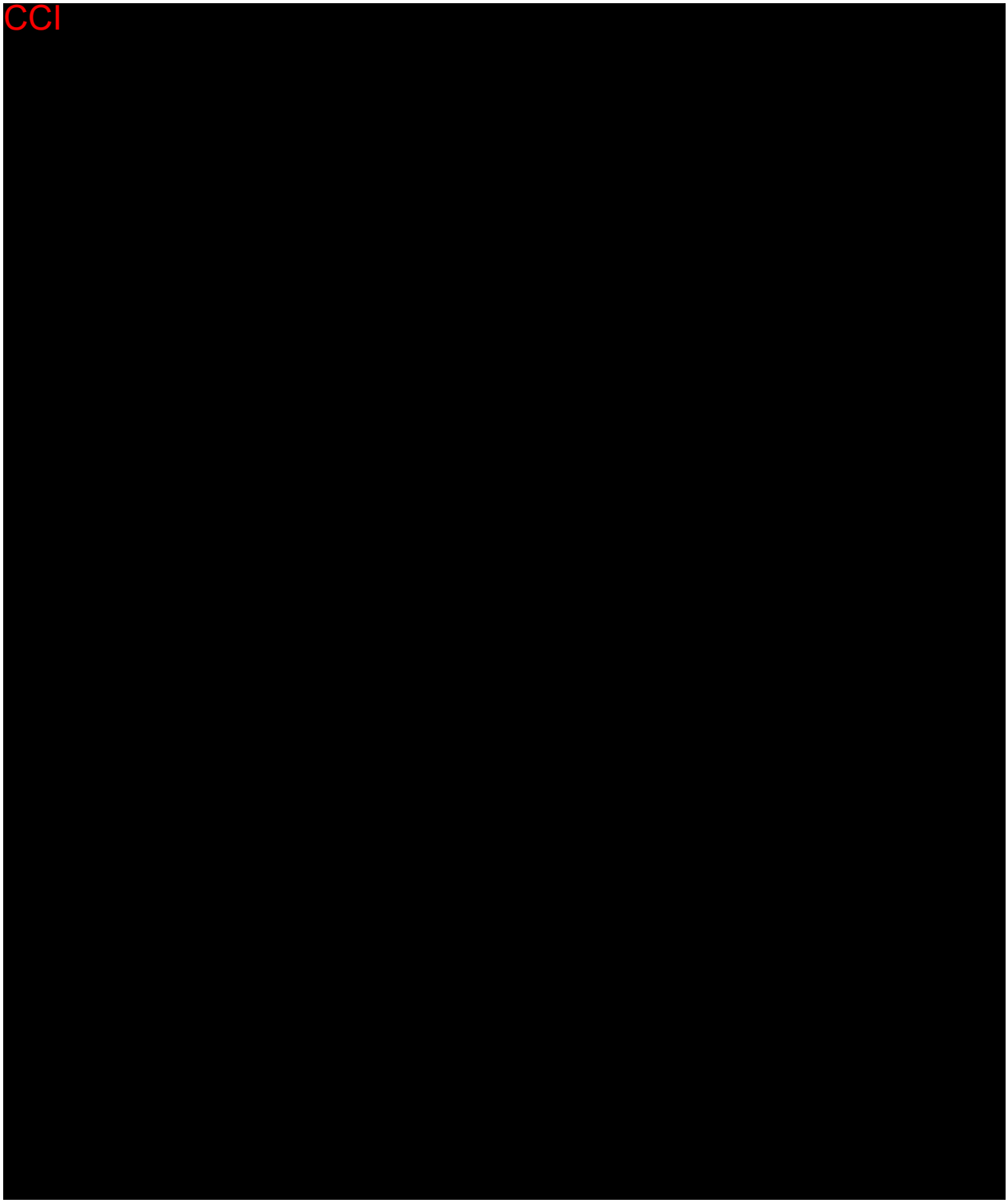
A series of in vitro and in vivo pharmacokinetic (PK) and metabolism studies were conducted with rimegepant in rats, dogs, and monkeys. In addition, rimegepant was compared with two different triptans to assess potential to contract coronary vessels. While sumatriptan and zolmitriptan exhibited progressive contraction of human coronary vessels at increasing concentrations, the CGRP receptor antagonist compounds leading up to identification of rimegepant did not induce any changes in the baseline tension in human coronary vessels even at very high (10 uM) concentrations. Rimegepant was tested using the identical protocols in dog coronary artery (when viable human tissues were not available) and no vessel contraction was observed, in contrast to the triptans which again showed progressive concentration-dependent constriction. These data provide direct evidence that rimegepant acts without the undesirable effect of active vasoconstriction associated with treatment by 'triptans'. Please refer to the most current version of the Investigator Brochure for further details.

1.3.1.2 Nonclinical Toxicology

The nonclinical toxicity of rimegepant was comprehensively evaluated in a series of single- and repeat-dose oral toxicity, genetic toxicity, phototoxicity, and safety pharmacology studies. Rimegepant is not genotoxic or phototoxic and has a low potential for off-target receptor interactions or adverse effects on the cardiovascular, respiratory, and central nervous (CNS) systems. Please refer to the most current version of the Investigator Brochure for further details.

1.3.2 Clinical Experience

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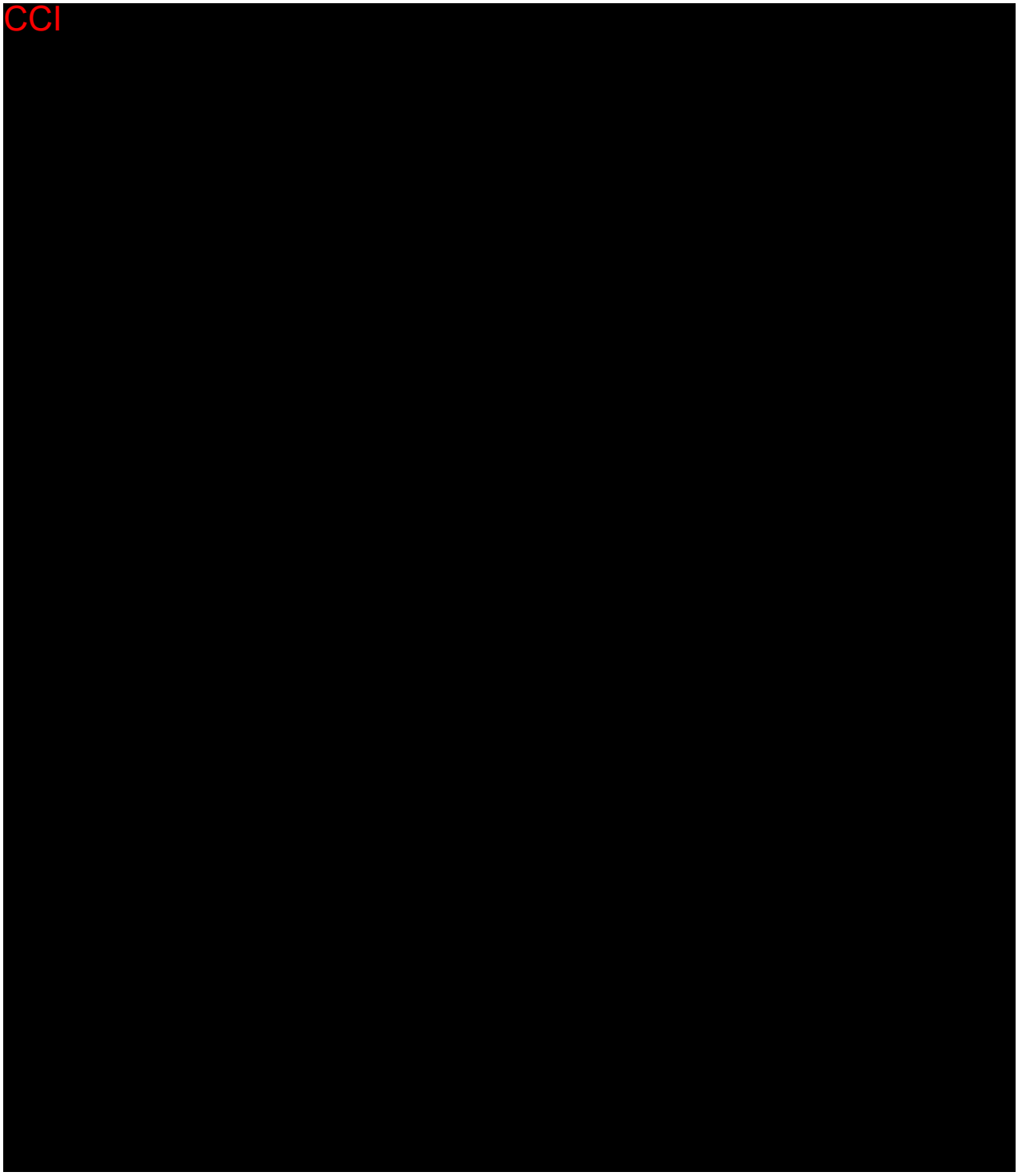

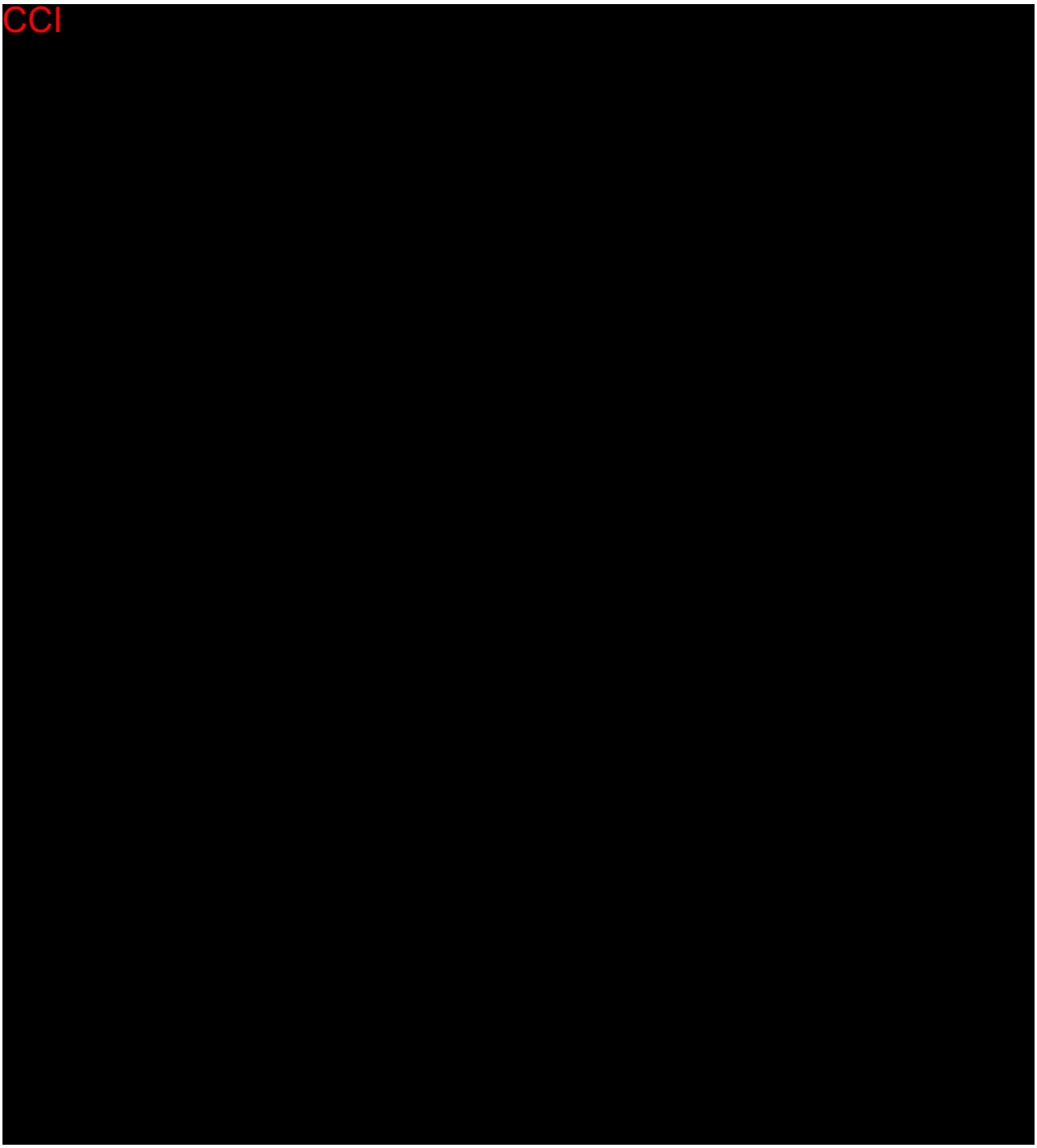
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1.3.2.8 RCT Dose-ranging trial of rimegepant for acute migraine (CN170003)

Study CN170003 [3] was a double-blind, randomized, placebo-controlled, dose-ranging trial of rimegepant for the acute treatment of migraine. The primary objective was to evaluate the efficacy of rimegepant compared with placebo in the acute treatment of migraine as measured by pain freedom (head pain intensity level reported as "no pain") at 2 hours post-dose using a four point rating scale (no pain, mild pain, moderate pain, severe pain) while identifying an optimal dose to support the Phase 3 clinical trials. Subjects were randomized to receive placebo, sumatriptan 100 mg or rimegepant (10 mg, 25 mg, 75 mg, 150 mg, 300 mg, or 600 mg). Randomization made use of an adaptive design, whereby one quarter of subjects were assigned placebo and one-eighth were

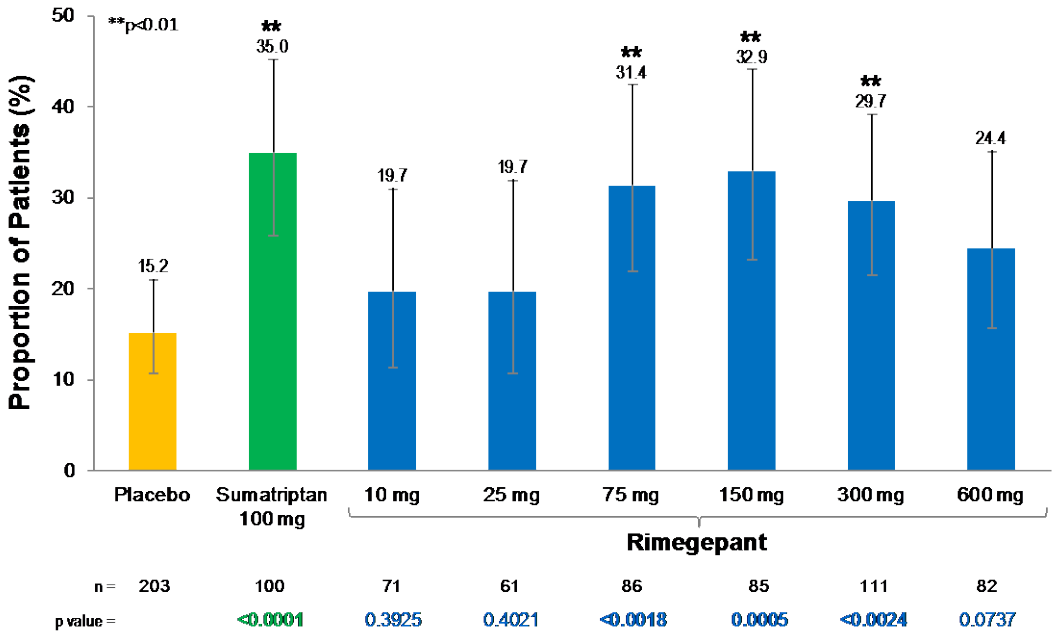
assigned sumatriptan; the remainder were assigned to one of six rimegepant groups based on a Bayesian analysis of the observed response rates. Subjects were instructed to treat one migraine of moderate or severe pain intensity and then return to the clinic within 7 days.

A total of 885 subjects were randomized and 812 completed the study.

A broad and durable efficacy profile for rimegepant was demonstrated to be fully present at 75 mg [2]. This dose was selected as the optimal dose to support Phase 3 clinical trials, given that larger doses showed a similar efficacy profile and there was negligible benefit identified with larger doses, consistent with previously published migraine studies characterizing the dose-response profiles of acute treatments for migraine [8].

Rimegepant at 75 mg showed statistically significant efficacy(Figure 1) across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hr following a single oral dose of 75 mg, patients who previously were experiencing moderate-to-severe migraine pain had no-pain (31.4% $p < 0.0018$) or mild-to-no-pain (72.1% = < 0.0007) as compared to placebo (15.2% and 51.2%, respectively).

Figure 1. Phase 2b Primary Endpoint: Rimegepant Pain Freedom at 2 hours Post Dose (+/- 95% Confidence)



In conclusion, Study CN170003[3] demonstrated that rimegepant is superior to placebo in the acute treatment of migraines. The selection of 75 mg rimegepant as the Phase 3 dose is based on reliably demonstrated efficacy on the key primary outcome measure, Pain Freedom at 2 hours (31.4% vs 15.3% placebo; p = 0.0018).

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1.3.4 Clinical Adverse Event Profile

To date, 7 clinical studies have been completed in healthy volunteers and migraineurs that inform PK, metabolic interactions, safety, tolerability and efficacy. In total, the current data suggests a favorable benefit-risk profile for rimegepant in the acute treatment of migraine attacks. Efficacy was established in Study CN170003, and the overall database suggests a favorable safety profile. Clinical experience with rimegepant has also allowed the characterization of safety and tolerability at substantial multiples of the intended therapeutic exposure and intended frequency of use. Rimegepant has been assessed in single doses up to 1500 mg and in multiple doses from 75 mg to 600 mg with 14-days of dosing (including 300 mg twice daily), where the higher doses yielded exposures more than 60 times greater in AUC and 30 times higher in Cmax as compared to the mean therapeutic exposure of a single 75 mg dose. These high exposure multiples were generally well tolerated and safe.

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Rimegepant appears to be 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 Investigators Brochure for a summary of the clinical safety profile.

The primary identified AE of interest is potential change in liver functions tests. Investigators must carefully monitor routine liver functions tests (ALT, AST, total bilirubin, and ALP) and potentially liver related symptoms and signs. Clinicians should also monitor changes in hematology and other laboratory measures. Please refer to the current Investigators Brochure for further information regarding the clinical safety profile of rimegepant.

1.4 Study Rationale

Migraine is a chronic and debilitating disorder characterized by recurrent attacks lasting four to 72 hours with multiple symptoms, including typically one-sided, pulsating headaches of moderate or severe pain intensity that are associated with nausea or vomiting, and/or sensitivity to sound (phonophobia) and sensitivity to light (photophobia). The World Health Organization's (WHO) Global Burden of Disease Study ranks migraine as the third most prevalent disease worldwide [9] and the Global Burden of Disease Survey 2010 rates migraine as the seventh highest specific cause of disability worldwide. Annually, migraines affect approximately 15% of the adult population in the United States [10], comprising approximately 33 million adults. Approximately 62% of migraineurs have one or more attack per month, and approximately 25% have one or more per week[11]. Approximately 80% of individuals are unable to work or function normally during a migraine attack, with 53% reporting severe impairment and/or requiring bedrest [12, 13]. Comorbid conditions associated with migraine include depression, anxiety and cardiovascular disease [14] .

While there are multiple classes of medications for the acute treatment of migraine, considerable unmet need remains, as evidenced by migraines being the seventh leading cause of disability worldwide [9]. In part, this burden is attributed to limitations of current standard-of-care pharmacotherapies, which are contraindicated for use in over 2.6 million American migraine sufferers with known cardiovascular disease as well as many others with multiple cardiovascular (CV) risk factors. The US Prescribing Information (USPI) for triptans includes warnings and precautions for migraine patients with risk factors for cardiovascular disease and states that high risk patients, including those with

increased age, diabetes, hypertension, smoking, obesity or a strong family history of coronary artery disease, should be evaluated prior to receiving the first dose of a triptan. Triptans are contraindicated in patients with a history of ischemic heart disease, coronary artery vasospasm, history of stroke, peripheral vascular disease or uncontrolled hypertension. Even in patients who have a negative cardiovascular evaluation, product labeling for triptans recommends that consideration be given to administration of the first dose in a medically-supervised setting and performing an electrocardiogram immediately following administration. Additionally, periodic cardiovascular evaluation should be considered for long-term users of triptans who have cardiovascular risk factors. According to a recent study published in the journal Headache, an estimated 2.6 million migraine sufferers in the United States have a cardiovascular event, condition or procedure that limits the potential of triptans as a treatment option. Thus, there remains a significant unmet medical need for a novel migraine-specific medication that does not increase the risk of cardiovascular liability.

Biohaven is developing a small molecule CGRP receptor antagonist, rimegepant, for the acute treatment of migraine that will address such cardiovascular limitations. Clinical and nonclinical studies show that rimegepant is not associated with adverse vasoconstrictive properties that are thought to cause the serious cardiovascular adverse events of the triptan class and does not share a mechanism with other agents of cardiovascular concern such as non-steroidal anti-inflammatories (NSAIDs) and ergotamine derivatives. A completed Phase 2 trial [3] demonstrated the efficacy of rimegepant in the acute treatment of migraine, with and without aura, at doses of 75 mg and above. Doses above 75 mg were not associated with clinically significant differences in efficacy and therefore 75 mg is the selected dose for Phase 3.

The randomized controlled study proposed herein will further assess the efficacy and safety of rimegepant (75 mg) for the acute treatment of migraine. As such, this study serves the broader objectives of the rimegepant clinical development program: to demonstrate the safety, tolerability, and efficacy of rimegepant in the acute treatment of migraine with or without aura in adults.

1.4.1 Study Design Rationale

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. The study drug will be rimegepant formulated in a 75 mg tablet or a matching placebo. The patient will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity.

The study will randomize approximately 1200 patients. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

This study design is utilized to confirm the efficacy and safety profiles observed in the Phase 2b study with rimegepant. Incorporation of placebo and use of appropriate rescue medications will permit enrollment of patients with a broad range of comorbidities, including cardiovascular conditions, representative of the potential treatment population.

1.4.2 Dose Selection Rationale

Study CN170003 was a double-blind, randomized, placebo-controlled, dose-ranging trial of rimegepant for the acute treatment of migraine [2]. The primary objective was to evaluate the efficacy of rimegepant compared with placebo in the acute treatment of migraine as measured by pain freedom (head pain intensity level reported as "no pain") at 2 hours post-dose using a four point rating scale (no pain, mild pain, moderate pain, severe pain) while identifying an optimal dose to support the Phase 3 clinical trials. Subjects were randomized to receive placebo, sumatriptan 100 mg or rimegepant (10, 25, 75, 150, 300, or 600 mg). Randomization made use of an adaptive design, whereby one quarter of subjects were assigned placebo and one-eighth were assigned sumatriptan; the remainder were assigned to one of the six rimegepant groups based on a Bayesian analysis of the observed response rates. Subjects were instructed to treat one migraine of moderate or severe pain intensity and return to the clinic within 7 days.

A total of 885 subjects were randomized and 812 completed the study. Key entry criteria were very similar to those chosen for this clinical trial.

A comprehensive and durable efficacy profile for rimegepant was demonstrated to be fully present at 75 mg but not at lower doses (i.e., 10 mg or 25 mg). This dose was selected as the optimal dose to support Phase 3 clinical trials, given that larger doses (150 mg, 300 mg, 600 mg) showed a similar efficacy profile and there was no pattern of added benefit in dosing higher, consistent with previously published migraine studies [8]. rimegepant at 75 mg showed statistically significant broad efficacy across all four traditional endpoints at 2 hr (pain, nausea, photophobia and phonophobia) which was durable and persisted through 24 hr. At 2 hr following a single oral dose of 75 mg, patients who previously were experiencing moderate-to-severe migraine pain had no-pain (31.4% $p = 0.0018$) or mild-to-no-pain (72.1%) as compared to placebo (15.3% and 51.2%, respectively). For the 75 mg dose at 2 hr, patients also showed significant freedom from nausea (67.4%, $p = 0.0074$) freedom from phonophobia (52.3%, $p = 0.0001$) and freedom from photophobia (41.9%, $p = 0.0023$) vs. placebo (51.2%, 28.1%

and 24.1%, respectively). The lasting nature of these beneficial anti-migraine effects were evidenced by a comparatively similar efficacy profile in the 2-24 hr measures, where rimegepant at 75 mg produced significant 2-24 hr sustained pain freedom (27.9%, $p < 0.0001$) and 2-24 hr sustained pain relief (69.8%, $p < 0.0001$) vs. placebo (7.4% and 42.4%, respectively).

1.4.3 Other Rationale related to the compound/study

Prior to initiation of Phase 3, a Phase 1 crossover study to assess the safety, tolerability and pharmacokinetics of a single dose of the rimegepant tablet in healthy volunteers will be conducted to ensure PK comparability with the previously studied capsule (rimegepant free-base). The Investigator Brochure will be updated to include these study results when available.

1.5 Research Hypothesis

Rimegepant (75mg tablet) will have efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile suitable for use by a broad patient population.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the efficacy of rimegepant (75 mg tablet) compared with placebo in the acute treatment of migraine as measured by **pain freedom** and by **freedom from the most bothersome symptom** (MBS), associated with migraine, at two hours post dose.

2.2 Secondary

- To evaluate rimegepant (75 mg tablet) compared to placebo on **freedom from photophobia** at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on **freedom from phonophobia** at 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on **pain relief at** 2 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on **freedom from nausea** at 2 hours post-dose
- To evaluate rimegepant (75 mg tablet) compared to placebo on the **probability of requiring rescue medication** within 24 hours of initial treatment.
- To evaluate rimegepant (75 mg tablet) compared to placebo on **sustained pain freedom** from 2 to 24 hours post-dose
- To evaluate rimegepant (75 mg tablet) compared to placebo on **sustained pain relief** from 2- 24 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo on **sustained pain freedom** from 2- 48 hours post-dose..
- To evaluate rimegepant (75 mg tablet) compared to placebo on **sustained pain relief** from 2- 48 hours post-dose.
- To evaluate rimegepant (75 mg tablet) compared to placebo for the incidence of **pain relapse** from 2 to 48 hours post-dose

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the patients ability function at a "normal" level at 2 hrs post dose according to the **Functional Disability** scale.

2.3 Exploratory

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the patients ability to work or function at 24 hrs post dose according to the Functional Disability scale.

- To evaluate rimegepant (75 mg tablet) compared to placebo on **pain relief at** 90 minutes post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on **pain relief at** 60 minutes post-dose.

- To evaluate rimegepant (75 mg tablet) compared to placebo on **pain relief at** 30 minutes post-dose.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the **Migraine Preference of Medication (PoM)**

- To evaluate rimegepant (75 mg tablet) relative to placebo for pain relief on the 4 point scale at all scheduled time points post dose

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the **Migraine Quality of Life** (MQoLQ)

- To evaluate the **tolerability and safety** of rimegepant (75 mg tablet) in the acute treatment of migraine as measured by the frequency of adverse events of at least moderate intensity, serious adverse events; and clinically relevant laboratory abnormalities.

- To evaluate the effect of rimegepant (75 mg tablet) relative to placebo on the **Sheehan Suicidality Tracking Scale**.

3 STUDY ENDPOINTS

3.1 Primary

Pain freedom will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on a 4 point Likert scale (0=none, 1=mild, 2=moderate, 3=severe).

Freedom from the most bothersome symptom (MBS) will be assessed using the number of evaluable subjects that report the absence of their MBS at 2 hours post-dose. The MBS (nausea, phonophobia or photophobia) will measured using a binary scale (0=absent, 1=present).

3.2 Secondary

- **Freedom from Photophobia** will be assessed by tabulating the number of subjects that report the absence of photophobia at 2 hours post-dose in the subset of subjects that reported the presence of photophobia at headache baseline.

- **Freedom from Phonophobia** will be assessed by tabulating the number of subjects that report the absence of phonophobia at 2 hours post-dose in the subset of subjects that reported the presence of phonophobia at headache baseline.

- **Pain Relief** (aka "headache response"), at 2 hours post-dose, will be assessed using the number of evaluable subjects that report a pain level of moderate or severe (responses of 2 or 3 on the 4 point Likert scale) at baseline and then report a pain level of none or mild (response of 0 or 1) at two hours post-dose.

- **Freedom from Nausea** will be assessed by tabulating the number of subjects that report the absence of nausea at 2 hours post-dose in the subset of subjects that reported the presence of nausea at headache baseline.

- The probability of **requiring rescue medication** will be assessed using the number of subjects that take rescue medication within 24 after administration of study medication (BHV3000 or placebo).

- **Sustained pain freedom**, from 2 to 24 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest.

- **Sustained pain relief**, from 2 to 24 hours will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.

- **Sustained pain freedom**, from 2 to 48 hours, will be assessed using the number of subjects that do not experience any headache pain through the time period of interest

- **Sustained pain relief** from 2 to 48 hours, will be assessed using the number of subjects that do not use any rescue medications, and do not experience any moderate or severe headache pain through the time period of interest.

- **Pain relapse** will be assessed using the number of subjects that are pain free at 2 hours post-dose and then have a headache of any severity (response of 1, 2 or 3 on the 4 point scale) within 48 hours after administration of study medication (BHV3000 or placebo).

- The proportion of subjects able to function normally, at 2 hours, will be assessed using the number of subjects that self-report as "normal" on the **functional disability** scale.

3.3 Measures of Interest

Safety and Other assessments:

- Adverse Events

- ECG assessments

- Vital Sign and Physical Measurements

- Routine Laboratory Tests

- Sheehan Suicidality Tracking Scale (S-SST)

- Preference of Medication (PoM)

- Assessment of Migraine Pain and Symptoms

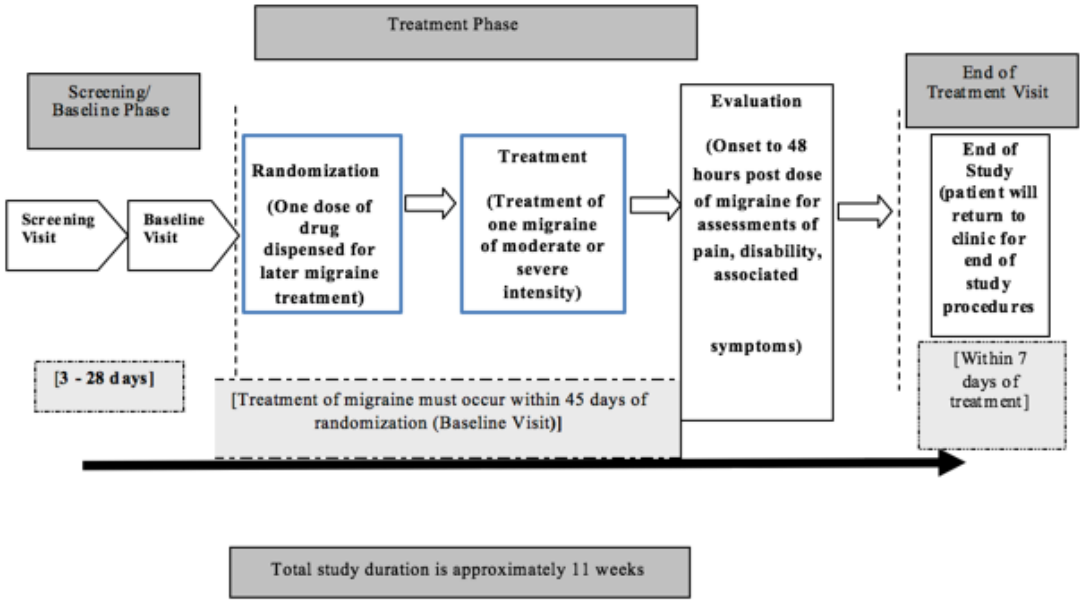
- Migraine Specified Quality of Life Questionnaire (MQoLQ)

4 STUDY PLAN

4.1 Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the treatment of moderate or severe migraine. Participants will be dispensed one dose of study medication consisting of a rimegepant 75 mg tablet or a matching placebo. The total duration of the study will be approximately 11 weeks. This includes a 3-28 day Screening Period, an Acute Phase that can last up to 45 days or until the patient has a migraine that reaches moderate or severe intensity, followed by an End of Treatment Visit 7 days after the administration of the study medication.

4.2 Study Schematic



4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit (3-28 days)[1]	Baseline Visit (Randomization)[1]	Onset of moderate or severe migraine[2]	During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose	During Treatment 2, 3, 4, 6, 8 hours Post- Dose	During Treatment 24 hours Post-Dose	During Treatment 48 hours Post- Dose	End of Treatment Visit
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Prophylactic Migraine Medication/ Concomitant Medication[3]	X	X						X
Assessment of Migraine History (Signs and symptoms) paper source[14]	X							
Safety Assessments								
Physical Examination	X							X
Vital Signs/Physical Measurements[4]	X	X						X
Clinical Safety Laboratory Testing[5]	X							X

Procedure	**Screening Visit (3-28 days)[1]**	**Baseline Visit (Randomization)[1]**	**Onset of moderate or severe migraine[2]**	**During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose**	**During Treatment 2, 3, 4, 6, 8 hours Post- Dose**	**During Treatment 24 hours Post-Dose**	**During Treatment 48 hours Post- Dose**	**End of Treatment Visit**
ECG	X							X
Pregnancy Test[6]	X	X	X					X
Adverse Event and Serious Adverse Event Assessment[7]	X	X	X	X	X	X	X	X
Sheehan Suicidality Tracking Scale[8]	X	X						X
Clinical Drug Supplies/Study Supplies								
Randomize[9]		X						
Dispense Study Medication		X						
Administer 1 dose of study medication[10]			X					
Return unused study medication								X
eDiary returned/reviewed for completeness[11]								X
Efficacy Assessments[12]								
Assessment of migraine pain[13]			X	X	X	X	X	

Procedure	**Screening Visit (3-28 days)[1]**	**Baseline Visit (Randomization)[1]**	**Onset of moderate or severe migraine[2]**	**During Treatment 15, 30, 45, 60 and 90 minutes Post-Dose**	**During Treatment 2, 3, 4, 6, 8 hours Post- Dose**	**During Treatment 24 hours Post-Dose**	**During Treatment 48 hours Post- Dose**	**End of Treatment Visit**
Assessment of Migraine Symptoms (photophobia, phonophobia, and nausea - eDiary)[13]			X	X	X	X	X	
Functional Disability Scale[13]			X	X	X	X	X	
MQoLQ (Migraine Specified Quality of Life Questionnaire)[13]						X		
Preference of Medication[13]						X		

[1] **Screening/Baseline Phase** will be 3 - 28 days. The **Baseline Visit** may be scheduled but should only occur ***after*** all screening procedures are complete, patient meets inclusion/exclusion criteria, and lab test results have been received by the site.

[2] Patients will use eDiary to answer questions about their migraine symptoms upon experiencing a moderate/severe migraine headache. The patient will administer pre-dispensed study drug if 1) the headache remains moderate or severe; 2) the patient has completed all required migraine assessment questions in the eDiary, including their current most bothersome migraine symptom, and 3) the patient has not already taken prohibited medications (see protocol section 5.4).

[3] Patients should keep track of their concomitant medications throughout the study and report them to the study personnel at the End of Treatment Visit. Any medication taken for recurrent headache should be documented. Use of concomitant medications after randomization, including rescue medications, will be recorded by the patient on a paper diary and reported to the site.

[4] Height will only be captured at the Screening Visit. Weight body temperature, respiratory rate, blood pressure and heart rate will be collected at all time points where indicated. Sitting arterial systolic and diastolic blood pressure and pulse rate will be measured.

[5] All Screening Visit laboratory test results must be received prior to Baseline Visit.

[6] A serum pregnancy test will be completed at Screening and End of Treatment Visits as part of the standard laboratory tests (if appropriate). Confirmatory urine pregnancy test for WOCBP should be completed on site at Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion. Home pregnancy test will be provided to WOCBP after completion of baseline visit.

[7] SAEs are reported from the time of informed consent and non-serious AEs are reported from baseline. All ongoing non-serious AEs and SAEs will be followed to resolution or until investigator deems there will be no further status change. SAE and AE's that occur during the treatment period should be reported to the site.

[8] This scale will be clinician administered, completed on site, and will be in paper. The source document will be provided by Biohaven. The assessment period for completing the scale will be 30 days prior to Screening, and since the last visit for the remainder of the study.

[9] Patients will be randomized in the IWRS system at the Baseline Visit (Randomization Day 01)

[10] Patient should be instructed that the dose should be taken once the migraine attack reaches moderate or severe pain.

[11] Site staff to review and confirm entries with patients and confirm all data points are transferred to the system and reset eDiary for future patient use, PRIOR to the patient leaving the clinic.

[12] ± Windows for timeframe around efficacy assessments (15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 24 and 48 hours) will be automated and captured in the eDiary.

[13] These scales will be captured in the eDiary. Patients will also be asked about their most bothersome symptom at the time of reporting and treating a qualifying migraine.

[14] Paper source document will be used to capture Migraine History. Patients will also be asked about their typical most bothersome symptom when having a migraine.

4.3.1 Screening Phase (3-28 days)

It is estimated that approximately 1415 patients will be screened to allow 1200 patients to be randomized at the Baseline visit. All patients who are screened into the study will be entered into the IWRS system. After obtaining informed consent, patients will undergo all screening procedures as detailed in Table 1. After all screening procedures are complete, patients will return 3-28 days from signing informed consent to be randomized at the Baseline visit if they meet all eligibility criteria. Patients on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to randomization.

4.3.2 Acute (Randomization) Phase (45 days)

If the patient meets all eligibility criteria they will be randomized at the Baseline Visit via the IWRS system. The patients will be provided with an eDiary. The study personnel will instruct the patient on the proper use of the eDiary and ensure proper understanding and use of the tool, prior to the patient leaving the office.

After randomization via the IWRS system, the patient will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. This study medication is to be taken when a migraine attack reaches moderate or severe intensity on the numeric rating scale (NRS) as indicated in the eDiary. The patient will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity **after they answer eDiary questions about their current pain and symptoms and identify their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea)**. The patient will complete an eDiary for up to forty-eight hours after taking study medication. The patient will telephone the study center immediately if a severe or serious adverse event occurs.

Patients will record efficacy data in their eDiary. This includes the following: onset time of headache, intensity of the headache prior to ***and*** at time of taking study medication. The patient should record all headache intensity leading up to dosing, but should not dose with study medication until the headache reaches moderate or severe intensity. Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings. Patients will also identify their currently most bothersome symptom before taking study medication. Patients will record the date and time study therapy was taken in their eDiary. Patients will also complete the migraine-specific quality-of-life questionnaire (MQoLQ) and preference of medication (PoM) 24 hours after

dosing. Patients who have headache pain reduced to a mild intensity or pain free intensity level will be considered to have achieved pain relief.

After dosing with study medication, all other headache medication is prohibited during the 2 hours post dose. However, a patient who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been completed on the eDiary) will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) naproxen (or any other type of nonsteroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. However, if needed, after 48-hours of administering the one dose of study medication (and before returning for the End of Treatment Visit) patients may take their prescribed standard of care medications for treatment of migraine, including triptans if not contraindicated, **provided all of the assessments have been completed on the eDiary**. Exclusionary rescue medication such as, opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) are not allowed on this study. Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the patient will be permitted to take the same rescue therapy as outlined above. In all circumstances, the patient will continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication.

4.3.3 Extension Phase

Not Applicable

4.3.4 End of Treatment (7 days after Treatment)

Patients will return to the study site within 7 days of study treatment (+2 days) for review of the eDiary assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a patient has NOT experienced a migraine headache of sufficient severity within 45 days after randomization, he or she will be withdrawn from the trial and instructed to return unused study medication and eDiary to the study center.

4.4 Post Study Access to Therapy (if applicable)

At the end of the study the sponsor will not continue to supply study drug to patients/investigators. The investigator should ensure that the subject receives the appropriate standard of care to treat the condition under study. Alternatively, patients may be eligible to receive study drug by participation in a rimegepant Long Term Safety study requiring approval by responsible health authorities and ethics committees.

5 POPULATION

Individuals entered in this trial will be patients who suffer from migraines. The treatment setting for these patients may include clinics, institutions or private office practices. Patients may be recruited through a variety of sources, including referral from physicians and other health care professionals.

5.1 Number of Subjects

It is anticipated that 1415 patients will need to be screened in order to randomize approximately 1200 patients. If, however, the minimum number of treated subjects is reached first, the study may be closed. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. It is anticipated that enrollment will occur at approximately 50 sites in the United States over a period of approximately 3 months during this trial.

5.2 Inclusion Criteria

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

2. Target Population

    Patient has at least 1 year history of migraines (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, beta version[1], including the following:

    a) Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age
    b) Migraine attacks, on average, lasting about 4 - 72 hours if untreated
    c) Not more than 8 attacks of moderate or severe intensity per month within last 3 months
    d) Patients must be able to distinguish migraine attacks from tension/cluster headaches.
    e) Consistent migraine headaches of at least 2 migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period
    f) Less than 15 days with headache (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and maintains this requirement during the Screening Period
    g) Patients on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.
    h) Patients with contraindications for use of triptans may be included provided they

meet all other study entry criteria.

3. Age and Reproductive Status
    a) Male and Female patients ≥ 18 years and older
    b) Women of childbearing potential (WOCBP) and non-sterile men must be using two acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 5.5 for the definition of WOCBP. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months prior to study participation
    c) No clinically significant abnormality identified on the medical or laboratory evaluation. A subject with a clinical abnormality or laboratory parameters outside the reference range may be included only if the investigator considers that the finding is not clinically significant and will not introduce additional risk factors and will not interfere with the study procedures
    d) At the Baseline Visit prior to dispensing Investigational Study Medication, WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
    e) Women must not be breastfeeding

5.3 Exclusion Criteria

1. Disease Target Exclusion
    a) Patient has a history of basilar migraine or hemiplegic migraine

2. Medical History and Concurrent Diseases
    a) Patient history of HIV disease
    b) Patient history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Patients with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS),Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during the 6 months prior to screening.
    c) Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however patients can be included who have stable hypertension and/or diabetes for 3 months prior to being enrolled)
    d) Patient has a current diagnosis of major depression, other pain syndromes, psychiatric conditions (e.g., schizophrenia), dementia, or significant neurological disorders (other than migraine) that, in the Investigator's opinion, might interfere with study assessments
    e) Patient has a history of gastric, or small intestinal surgery, or has a disease that causes malabsorption

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

g) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or patients who have met DSM-V criteria[15] for any significant substance use disorder within the past 12 months from the date of the screening visit

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

i) Detectable levels of cocaine, amphetamine, and phencyclidine (PCP) in the drug screen are exclusionary. Patients who are positive for amphetamines on the urine drug screen may have their urine samples evaluated for further analysis at the investigator's discretion to rule out a false positive result.

ii) Detectable levels of marijuana in the drug screen are not exclusionary, if in the investigator's documented opinion the patient does not meet DSM-V criteria[15] for substance use disorder, in the investigator's documented opinion, the positive test does not signal a clinical condition that would impact the safety of the patient or interpretation of the study results.

3. Allergies and Adverse Drug Reactions

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

4. Sex and Reproductive Status

a) Females of child-bearing potential who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for 56 days after the study.

b) Women who are pregnant or breastfeeding. Women with a positive pregnancy test on enrollment or prior to study drug administration

5. ECG and Laboratory Test Findings

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

b) Corrected QT interval > 470 msec (QTc by method of Frederica), during the Screening/Baseline Phase

c) Left Bundle Branch block

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

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

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

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

h) AST (SGOT) or ALT (SGPT) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period.)

6. Other Exclusion Criteria
   a) Prisoners or subjects who are involuntarily incarcerated
   b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
   c) Exposure to non-biological investigational agents (other than rimegepant) within the 30 days prior to Baseline visit.
   d) Exposure to biological investigational agents within the 90 days prior to Baseline visit.
   e) Score of >0 on the Sheehan Suicidality Tracking Scale for the period of 30 days prior to Screening and during the study.

7. Please see Section 5.4 for Prohibited medications and Section 5.4.1 for allowable Rescue Medications

5.4 Prohibited Concomitant Medication

The below medications are prohibited prior to randomization and during the course of this study or as specified.

1. St. John's Wort should not be taken 14 days prior to randomization and throughout the study.
2. Butterbur root or extracts should not be taken 14 days prior to randomization and throughout the study.
3. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months
4. History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 months
5. Use of narcotic medication, such as barbiturates, heroin, opium in the form of morphine and codeine, oxycodone and hydrocodone for at least 2 days prior to randomization.
6. Use of acetaminophen or acetaminophen containing products at daily dosing levels greater than 1000mg/day for at least two days prior to randomization.
7. Use of marijuana is prohibited during the study.

Patients on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to studyentry.

5.4.1 Rescue Medications

After dosing with study medication, all other headache medication is prohibited during the 2 hours post dose. However, a patient who does not experience relief of their migraine headache at the end of two hours after dosing with study medication (and after the two hour assessments have been completed on the eDiary), will be permitted to use the following rescue medication: aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. However, if needed, after 48-hours of administering the one dose of study medication (and before coming in for the End of Treatment Visit) patients may take their prescribed standard of care medications for treatment of migraine (including triptans if not contraindicated, **provided all of the assessments have been completed on the eDiary.** Similarly, if the migraine is relieved by study medication at 2 hours after dosing but then recurs to a moderate or severe intensity level between two and forty-eight hours, the patient will be permitted to take the same rescue therapy as outlined above. In all circumstances, the patient will always continue to complete his or her eDiary for up to forty-eight hours after consuming the study medication. Use of concomitant medication after randomization, including rescue medication, will be recorded by the patient on a paper diary and reported to the site. The site will record medications that were taken within 14 days of dosing with study medication (or until the End of Treatment Visit).

5.5 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as:

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

2. Woman with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL or

   NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year

3. Woman on hormone replacement therapy (HRT)

Women of childbearing potential (WOCBP) and men must be using two acceptable methods of contraception to avoid pregnancy throughout the study and for up to 56 days after the last dose

of investigational product in such a manner that risk of pregnancy is minimized. It is required that all WOCBP use two methods of contraception for the duration of the study (i.e. beginning before treatment with the 1 dose of study medication to 56 days after dosing). The two methods should include one barrier method (ex. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include oral contraceptives or another barrier method (Note an Intra Uterine Device is considered one method).

Women who suspect that they have become or may have become pregnant despite using proper birth control methods, should use the home pregnancy test provided at Baseline Visit. Home pregnancy test should be administered prior to taking Investigational Study Drug. Patient should not take Investigational Study Drug if they are pregnant and patient should immediately contact Study Investigator.

5.6 Other Restrictions and Precautions (if applicable)

Not Applicable

5.7 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 your IRB/EC. There will be no protocol exceptions granted by the Sponsor for Inclusion/Exclusion criteria.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

- Investigator File/Regulatory Binder
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant and Rescue Medication Logs (take home for patient)
- Investigator Brochure
- Interactive Web-based Response System (IWRS)
- Electronic Case Report Form (eCRF) instructions
- Electronic Diary (eDiary): 1 will be given to each randomized patient
- Instructions for the ePRO device and access to the portal
- Laboratory Kits and Laboratory Manual
- Home Pregnancy Test
- ECG Machine and Instructions
- Serious Adverse Event (SAE) forms
- Pregnancy Surveillance Forms

All sites will use an Electronic Data Capture (EDC) tool to submit study data to Sponsors CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including responses to queries) will be submitted to the CRO using eCRFs. Electronic Patient Reported Outcomes (ePRO) will be used for all patient-rated scales and will be captured on an eDiary. Any assessment completed by the patient in the eDiary will be transferred from the site/patient to the vendor and from the vendor to the CRO and/or sponsor. No additional source documents are required for scales and assessments completed by the patient in eDiary.

Safety laboratory, plasma, serum, instructions for all specimens collected will be provided by a designated central laboratory. ECG equipment, supplies, instructions and training materials will be supplied by a centralized ECG vendor.

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

Body weight and height will be recorded at the scheduled visits as outlined in Table 1.

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at all scheduled visits as outlined in Table 1. A central ECG service will be utilized for all ECGs and the investigator will determine if any abnormalities are clinically significant or not.

6.2.3 Physical Exam

Patients will undergo a routine physical examination during the Screening Phase and at all scheduled visits as outlined in Table 1.

6.2.4 Laboratory Assessments

6.2.4.1 Safety Laboratory Testing

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

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

Blood chemistry/electrolyte: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CPK (with local lab fractionation, if central lab CK result is > 1.5 x ULN);

Lipid panel: Cholesterol, LDL, HDL, triglycerides (Screening Only).

Estimated glomerular filtration rate: eGFR using the estimated MDRD formula will be calculated and reported by the central lab at each visit that clinical laboratory tests are collected as outlined in Table 1.

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

Urine Drug Screen: For drugs of abuse

6.2.4.2 Pregnancy Testing

Pregnancy tests will be conducted (serum, urine, or home pregnancy test), if appropriate prior to randomization, and as outlined in Table 1.

6.2.5 Sheehan Suicide Tracking Scale

The Sheehan STS is a prospective, patient self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors[16, 17]. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. The subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor.

6.3 Efficacy Assessments

6.3.1 Pain

Subjects are given an eDiary to record their migraine pain score, on a 4-point numeric rating [no pain, mild pain, moderate pain, severe pain] at the time points indicated in Table 1.

6.3.2 Nausea, Phonophobia and Photophobia

The migraine associated symptoms of photophobia, phonophobia and nausea are measured on a two point scale (present or absent), using the eDiary, at the time points listed in Table 1. If a subject reports the presence of a symptom, the subject is then asked to rate the severity of the symptom on a four point scale (none, mild, moderate or serve). All assessment is done using the eDiary.

The subjects are also asked to identify their most bothersome symptom on the eDiary (nausea, phonophobia or photophobia) at the onset of the migraine to be treated. The most bothersome symptom must be identified before the subject takes study medication.

6.3.3 Rescue Medication

The subject's use of rescue medication is recorded by the subject in a paper diary.

6.3.4 Functional Disability

Impact of treatment on functional disability will be assessed using a single-question scale. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions. This is done in the eDiary, at the times indicated in Table 1, using a 4 point numeric rating scale: Normal Function, Mild Impairment, Severe Impairment, Required Bedrest.

6.3.5 Migraine Quality of Life Questionnaire

Impact of treatment on subject-reported quality of life will be assessed using The Migraine Quality of Life Questionnaire (MQoLQ). The MQoLQ is a 15-item instrument that has been validated in migraine patients to measure the short-term impact of treatment (within 24-hours) on seven migraine-specific domains: work, social function, energy, vitality, feelings, concerns, and migraine symptoms. The eDiary is used to evaluate the Migraine Quality of Life Questionnaire at 24 hours post-dose (see Table 1).

6.3.6 Migraine Preference of Medicine

The Preference of Medication Scale (PoMs) is a brief scale that captures the subjects' perception of whether the medication they are taking has had a greater benefit compared with previous medications to treat their pain. The eDiary is used to evaluate the Preference of Medication Scale at 24 hours post-dose (see Table 1).

6.4 Early Discontinuation from the Study

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

All subjects who discontinue should comply with protocol specified End of Treatment procedures as outlined in Table 1. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

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

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

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

The rimegepant tablet and the matching placebo appear identical visually, via touch, smell and taste.

7.1.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: Not applicable for this study.

7.1.3 Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.2 Dose and Administration

7.2.1 Method of Assigning Patient Identification

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned an unique sequential 4-digit subject number beginning with 0001, 0002, 0003, etc. for identification

throughout the study through an IWRS system. This subject number must not be reused for any other participant in the study. The physician/coordinator must contact the IWRS to enroll each subject into a centralized database at the time of signing consent.

After completion of all screening evaluations all eligible subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

Randomization schedules will be generated and kept by CCI in a secure network folder with access limited to only unblinded team members. Each subject who is qualified for treatment will be randomized via the IWRS randomization option. Patients will maintain their subject number assigned at screening throughout the trial. The IWRS will provide the double-blind treatment assignments.

The randomization will trigger a bottle number for the randomized treatment type. The drug will be dispensed at the time of randomization.

7.2.2 Selection and Timing of Dose and Administration

Study medication (one 75mg tablet) will be in a bottle. There are no dose adjustments in this study and patients will receive one dose to treat one migraine headache of moderate or severe intensity within the 45 days of randomization (Baseline Visit). Patients will be administered the study medication at randomization (Baseline Visit) and will take ***the tablet*** from the bottle at the time of moderate or severe migraine headache onset after answering questions regarding their migraine symptoms on the eDiary. The tablet should swallowed with water.

7.2.3 Dose Modifications

There will be no dose adjustments in this study.

7.3 Blinding and Unblinding

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

Before breaking the blind of an individual patient's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the patient'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 patient is receiving active product without the need for unblinding.

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

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Accountability and compliance verification should be documented in the patient's study records.

Patients have to be counseled on the importance of taking the study drug as directed when a migraine occurs and reaches moderate or severe intensity. If the patient does not have a migraine or take their study medication within 45 days of the Baseline Visit, they should return to the clinic for their End of Study Visit and return their study medication.

7.5 Destruction and Return of Study Drug

If the study drug (those supplied by the sponsor or sourced by the investigator) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible BHV Study monitor or the sponsor's designee unless this is against institutional policy.

All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 ADVERSE EVENTS

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

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

There are two types of adverse events, Serious Adverse Events (SAE) and Non-Serious Adverse Events (AEs).

8.1 SERIOUS ADVERSE EVENT

8.1.1 Definition of Serious Adverse Event (SAE)

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received rimegepant
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse
    - Potential drug-induced liver injury

Definition of Terms

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more severe form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

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

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

1. A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening);

2. Elective surgery, planned prior to signing consent;

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

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

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

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

8.1.2 Collection and Reporting Serious Adverse Events

Following the patient’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur

during the screening period and throughout the course of the study up to and including the End of Treatment Visit. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures.

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

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

SAEs, whether related or not related to study drug must be reported to BHV (or designee) within 24 hours of the site's knowledge of the event. SAEs must be recorded in the EDC system on the AE and SAE electronic Case Report Form (eCRF. If the site cannot access the EDC to report the SAE within the required timeframe, the SAE should be reported using paper forms, which should be faxed to CCI [redacted]

The minimum information required for an initial SAE report is:

Sender of report (Site number, Investigator name)

Subject identification (subject number)

Protocol number

SAE term (if an SAE is being reported)

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BHV (or designee) using the same procedure used for the transmission of the initial SAE.

All SAEs should be followed to resolution or stabilization.

8.1.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered excessive as determined by the investigator. All occurrences of overdose (suspected or confirmed and irrespective of whether or not it involved rimegepant or placebo) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

8.1.4 Pregnancy

If following the baseline visit, it is subsequently discovered that a study patient, or the female partner of a male study patient, is pregnant or may have been pregnant at the time of the investigational product exposure, including during at least 6 half-lives after the product administration, the investigational product will be permanently discontinued in an appropriate manner (i.e., dose tapering if necessary for patient safety). Protocol-required procedures for the study discontinued and the follow-up must be performed on the patient unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the Biohaven (or designee) Medical Monitor of the event and complete and forward the Pregnancy Form to Biohaven (or designee) within 24 hours and in accordance with SAE reporting procedures as described in Section 8.1.2. The pregnancy should be reported using paper forms, which should be faxed to CCI [redacted]

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Report Form, as appropriate.

8.1.5 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

3. No other immediately apparent possible causes of AT 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.

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

8.2 Non-serious Adverse Events

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

8.2.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the Baseline visit. Non-serious AE information should also be collected from any observational period intended to establish a baseline status for a patient.

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

8.2.2 Laboratory Test Abnormalities

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

1. Any laboratory test result that is clinically significant or meets the definition of an SAE;

2. Any laboratory abnormality that required the patient to have the study drug discontinued or interrupted;

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

9 STATISTICS

9.1 General Procedures

Categorical variables are tabulated with counts and percentages. Continuous variables are summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

For the calculation of descriptive statistics of observed data, subjects must have a baseline value to be evaluable for endpoints based on values and changes from baseline over time.

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; interruptions of study therapy; non-study medications; adverse events; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

9.2 Sample Size

If approximately 90% of the 600 subjects randomized to each treatment arm have a migraine in the allotted time period, there will be approximately 550 treated subjects per group.

Based on approximations from the Phase IIb study, 550 subjects provides more than 95% power to detect a difference between rimegepant and placebo on the subject's self-reported most bothersome symptom. Also, based on the Phase IIb study, 550 subjects provides more than 95% power to detect a difference in freedom from pain at 2 hours. Having at least 95% power on each co-primary endpoint provides at least 90% power to detect a difference on both endpoints jointly.

9.3 Populations for Analysis

- Enrolled subjects: Patients who sign an informed consent form and are assigned a subject identification number.

- Randomized subjects: Enrolled subjects who receive a randomization treatment assignment from the IWRS (rimegepant or placebo).

- Treated subjects: Enrolled subjects who take study therapy (rimegepant or placebo).

- Modified Intent to Treat (mITT) subjects: randomized subjects that take study therapy, have a migraine of moderate or severe baseline intensity, and provide at least one evaluable, post-baseline, efficacy data point.

9.4 Statistical Methods

9.4.1 Primary Endpoint(s)

BHV-3000 (rimegepant) is tested for superiority to placebo, at an alpha=0.05 level, on both pain freedom at 2 hours post-dose and freedom the most bothersome symptom at 2 hours post-dose. Both endpoints are evaluated using Cochran-Mantel Haenszel tests. The test for pain is stratified by the use of prophylactic migraine medication (yes or no). The test for the most bothersome symptom is also stratified by the use of prophylactic migraine medication (yes or no). These tests are conducted using the mITT subjects, with missing data at two hours imputed to be failure (i.e., Non-Completers = Failure; NC=F). Sensitivity analyses are described in the Statistical Analysis Plan (SAP).

9.4.2 Secondary Endpoint(s)

If the primary endpoint tests are both significant, then the secondary endpoints are evaluated using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at p=0.05. These secondary endpoints will be tested in the following order:

1. Photophobia freedom at 2 hours
2. Phonophobia Freedom at 2 hours
3. Pain Relief at 2 hours
4. Nausea Freedom at 2 hours
5. Probability of requiring rescue medication within 24 hours
6. Sustained pain freedom from 2 to 24 hours
7. Sustained Pain Relief from 2 to 24
8. Sustained Pain Freedom 2 to 48 hours
9. Sustained Pain Relief from 2 to 48 hours
10. Pain relapse from 2 to 48 hours
11. Proportion of patients able to work or function normally at 2 hours.

9.4.3 Analysis of Safety

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the

latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs are presented by system organ class and preferred term, ordered by the overall frequency of events. If a subject had an adverse event with different intensities over time, then only the greatest intensity is reported.

AEs are tabulated in all treated subjects. SAEs occurring in subjects enrolled but not treated are listed. Deaths are listed for enrolled subjects without regard to onset.

The frequencies of the following safety events are summarized by treatment regimen, and overall, for treated subjects: SAEs; all AEs, non-serious AEs, AEs by intensity; and AEs by relatedness..

Graphical and tabular displays of liver function test results are provided.

9.4.4 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics are made for: subjects randomized but not treated; subjects randomized and treated; and overall. A separate set of tabulations are made for subjects enrolled but not randomized.

9.5 Interim Analysis

There is a final analysis after the last subject has his/her last visit. No interim analyses are anticipated.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any 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, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to Biohaven (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the stud or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients 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., lose of medical licensure, debarment).

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data Safety Monitoring Committee (DMC). The study medication rimegepant has been found to be well tolerated in previous clinical studies. Safety will be closely monitored via the sites and procedures for unblinding in cases of emergency will be followed.

10.3 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favorable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the Investigator site and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Principal investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

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

10.4 Informed Consent

Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, 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.

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

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must read and sign a written informed consent form. This signed informed consent form will be reviewed and approved by an IRB/IEC, revisions to the protocol and informed consent form will be reviewed and approved by the IRB/IEC, a copy retained in the Study Master File, and the date and time the subject signed the form will be entered in his or her CRF. The subject will be provided with a copy of his or her signed and dated informed consent form.

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

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

The rights, safety, and well-being of study patients are the most important considerations and should prevail over interests of science and society.

10.5 Case Report Forms

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

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

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

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

10.6 Records Management and Retention

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

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

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

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

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

1. amount of study drug received and placed in storage area

2. label ID number or batch number or Kit number as specified for the protocol

3. amount dispensed to and returned from each patient

4. amount transferred to another area or site for dispensing or storage if applicable

5. amount of drug lost or wasted

6. amount destroyed at the site if applicable

7. amount returned to sponsor, if applicable

8. retain sampled for bioavailability/bioequivalence, if applicable

9. record of dates and initials of personnel responsible for IM dispensing and accountability

10.7 Source Documentation

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

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

10.8 Study Files and Record Retention

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

11 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Biohaven. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

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. Biohaven will submit protocol amendments to the appropriate regulatory authorities for approval.

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

12 STUDY REPORT AND PUBLICATIONS

Biohaven is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

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

13 STUDY DISCONTINUATION

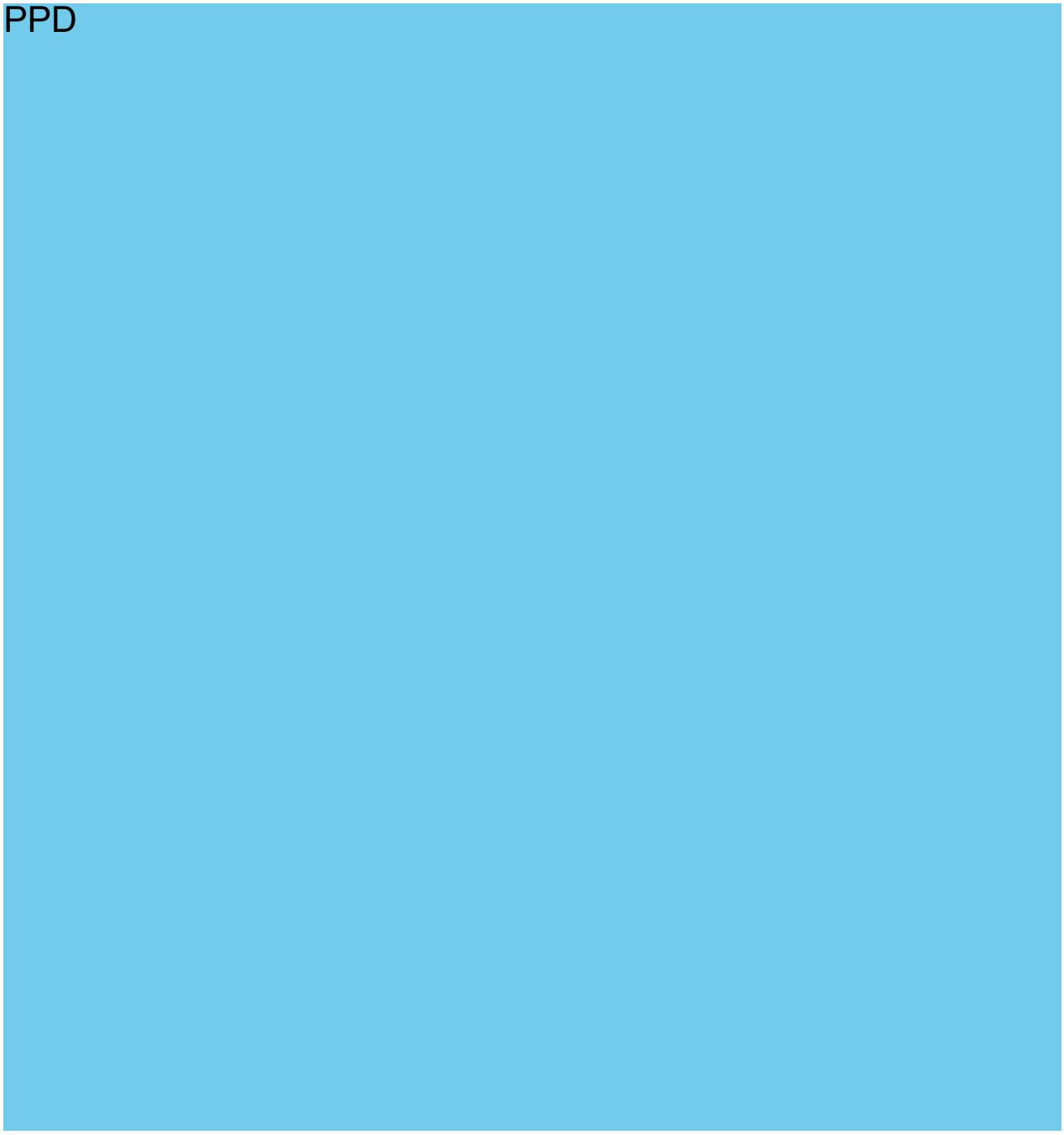
Both Biohaven and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, Biohaven or a specified designee will inform the appropriate regulatory authorities of the termination of the study if needed and the reasons for its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

14 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from Biohaven. However, authorized regulatory officials, IRB/IEC personnel, Biohaven and its authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by initials, subject numbers only. Only if required by law, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

APPENDICES



APPENDIX II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles

for

Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for

review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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