DRUG:	BHV-3000 (Rimegepant)
STUDY NUMBER(S):	BHV3000-202
PROTOCOL(S) TITLE:	BHV3000-202: Phase 2: A Double-Blind, Placebo Controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia
IND NUMBER:	CCI
SPONSOR:	Biohaven Pharmaceuticals Holding Company Limited
ORIGINAL PROTOCOL DATE:	16 January 2019
VERSION NUMBER:	V09
VERSION DATE:	08 Apr 2022

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Double Blind, Placebo controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia

Study No: BHV3000-202

Original Protocol Date: 16 January 2019

Protocol Version No: V09 (Amendment 08)

Protocol Version Date: 08 Apr 2022

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	Date
Author/Protocol Writer: PPD I confirm, QC completed for required elements	PPD	
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SUMMARY OF CHANGES

Version/Sections	Summary of Changes	Date
Version 9.0	Pg.10 and Section 3.5: Updated Study Schematic to include Open-label Extension Section 1.2.2: Updated Clinical Experience and removed outdated information from 1.2.2.1 – 1.2.2.7 Section 1.3.1 and 3.0: Added the Open-label Extension study design to section 1.3.1 and throughout section 3.0 Table 1& 2: Updated the Schedule of Assessments to include an Open-label Extension Phase and footnotes Section 3.5.3 Day-35 and added section 3.5.4 Open-label Extension Phase (Days 36-119) and 3.5.5. Follow-up Safety Visit Section 4.1: Number of subjects who can enter Open-label Extension. Section 5.4: Early Discontinuation who are not eligible to enter Open-label extension phase. Section 6.0: Study Drug/Medication Management to distinguish IP between Double-blind and Open-label, packaging, shipment, storage, administration, and treatment compliance. Section 9.5: Updated schedule of analyses which clarifies the final analysis of the Double-blind phase vs. the study/trial. Corrected inconsistencies and typographical errors throughout protocol	**08-Apr-2022**

BHV3000-202

BHV3000-202: A PHASE 2, DOUBLE-BLIND, PLACEBO CONTROLLED, CROSSOVER TRIAL OF BHV-3000 (RIMEGEPANT) FOR TREATMENT REFRACTORY TRIGEMINAL NEURALGIA

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 Pharmaceuticals, Inc., 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, Inc.

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 Pharmaceuticals, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about BHV-3000 (rimegepant) and the study.

_____	_____
Principal Investigator Name (printed)	Signature
_____	_____
Date	Site Number

STUDY SUMMARY

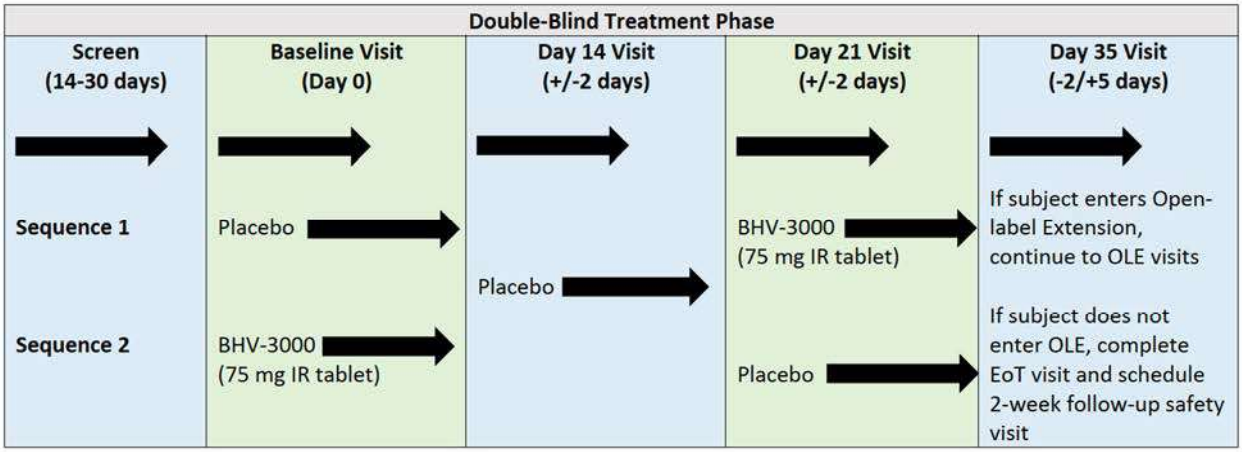
Title:	BHV3000-202: A Phase 2, Double-Blind, Placebo Controlled, Crossover Trial of BHV-3000 (Rimegepant) for Treatment Refractory Trigeminal Neuralgia
Rationale:	Trigeminal Neuralgia is a neuropathic pain disorder characterized by recurrent, paroxysmal, lancinating pain in the distribution of one or more branches of the trigeminal nerve. These episodic bouts of severe facial pain can last seconds to minutes, occur several times per day, and often result in significant disability. Although the exact mechanism of action remains unclear, antiepileptic drugs, most notably carbamazepine and oxcarbazepine, remain the first-line treatment for these patients. Nonetheless, the majority of patients have an incomplete response to current pharmacotherapy and resort to more invasive procedures, including rhizotomy and surgical decompression of the microvasculature surrounding the trigeminal nerve. While numerous treatment options exist, inadequate relief of pain and recurrence of symptoms are common, prompting the need for novel pharmacologic interventions.[1] Although the underlying mechanisms of classical Trigeminal Neuralgia have not been fully elucidated, imaging studies and surgical procedures clearly implicate vascular compression of the trigeminal nerve in the pathophysiology of the disease.[2] As a result of this nerve compression, subsequent axonal demyelination of the trigeminal nerve results in hyperexcitation and abnormal discharge of primary sensory neurons, ultimately contributing to the aberrant nociceptive transmission and neuropathic pain associated with this disorder.[1] The neuropeptide Calcitonin Gene-Related Peptide (CGRP) and its aberrant release from the trigeminal nerve has been clearly implicated in the pathophysiology of migraine headache. [3,4] In addition, CGRP is thought to play an important role in the development of neuronal sensitization and neuropathic pain and is a major mediator of pathologic vasodilatation of intracranial arteries. [3,4] Clinical studies have also shown increased levels of CGRP in the cerebrospinal fluid of patients with Trigeminal Neuralgia. [5] The proposed study is based on the evolving preclinical and clinical evidence suggesting a role for CGRP in the development of neuropathic pain syndromes and Trigeminal Neuralgia. BHV-3000 (rimegepant) is a small molecule CGRP receptor antagonist that is being developed for the potential treatment of Trigeminal Neuralgia. The data from this study will assess the safety and efficacy of rimegepant vs placebo in the treatment of Trigeminal Neuralgia.
Target Population:	The study will recruit male and female patients 18 years of age and older with a clinical diagnosis of classical or idiopathic Trigeminal

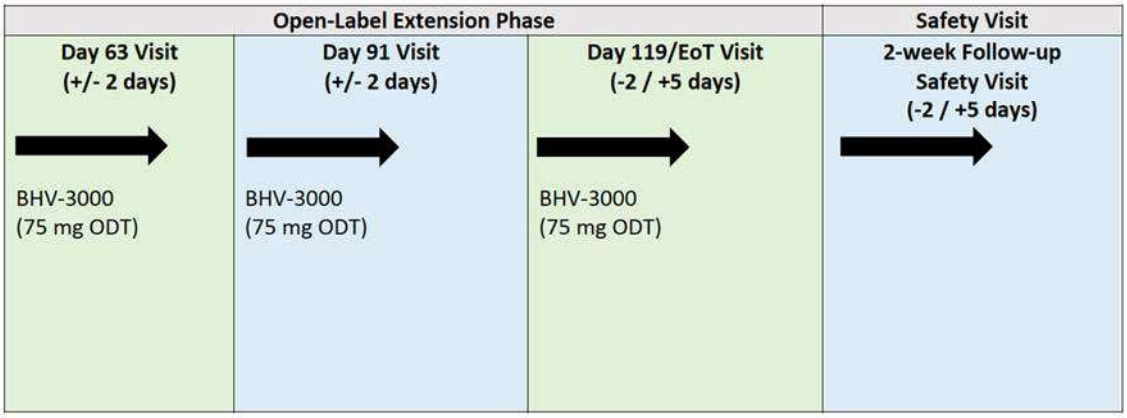
	Neuralgia based on the International Classification of Headache Disorders, 3rd edition, who have had an inadequate response, intolerance, or contraindication to current treatments and symptoms for at least three months. Additionally, patients must have neuroimaging to exclude a secondary cause of the neuralgia and a mean of ≥4 on the daily "average intensity", on an 11-point Numerical Pain Rating Scale (0-10) during the 14- 30 day screening period.
Number of Subjects:	Approximately 120 patients will be screened to randomize 60 patients in a 1:1 ratio into 2 treatment sequences receiving 75 mg rimegepant vs Placebo, using a 2-period, 2-sequence, crossover design.
Objectives:	The primary objective of the study is to evaluate the efficacy of rimegepant compared to placebo in providing symptomatic pain relief in patients with Trigeminal Neuralgia as measured by a reduction from baseline in the average daily Numeric Pain Rating Scale. The secondary objectives of the study will be: • To assess the safety and tolerability of rimegepant relative to placebo in patients with Trigeminal Neuralgia • To evaluate the efficacy of rimegepant vs placebo for improving physical function in Trigeminal Neuralgia patients as measured by the Penn Facial Pain Scale-Revised • To evaluate the efficacy of rimegepant vs placebo for improving functional disability in Trigeminal Neuralgia patients as measured by the Pain Disability Index • To evaluate the efficacy of rimegepant vs placebo on global functioning as measured by the Patient Global Impression of Change Scale. • To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief as captured by daily rating of worst pain episode as measured by the 11-point Numeric Pain Rating Scale • To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief of clinical importance as defined by a 2-point or greater reduction in the 11 point Numeric Pain Rating Scale 

	CCI [redacted]
Study Design:	BHV3000-202 is a phase 2, multi- center, double-blind, placebo controlled, crossover trial to assess the safety, tolerability, and efficacy of rimegepant in treating Trigeminal Neuralgia in patients who failed to respond adequately to or had intolerance or a contraindication to pharmacotherapy. Current inadequate response to therapy is defined by a daily pain score of greater than or equal to 4 on the "average intensity", on the 11 point Numerical Pain Rating Scale during the 14 days prior to baseline. A crossover design with a placebo washout period of 7 days between treatments will be used due to the limited number of subjects, with each patient serving as their own control. The study will be conducted at multiple centers. Prior to randomization, patients will enter a 14-30 day screening period during which they will complete daily self-reported assessments of pain intensity over a 24 hour period using an 11 point Numeric Pain Rating Scale, ranging from 0 (for no pain) to 10 (for the worst imaginable pain.) Throughout the study, patients will be allowed to remain on their current medication regimens, provided they are on a stable dose for a minimum of 4 weeks prior to randomization visit. Patients with a mean of ≥ 4 on the daily "average intensity" on the 11 point Numeric Pain Rating Scale, during the 14-30 day screening period, will be randomized to one of two treatment sequences to receive rimegepant 75 mg immediate release (IR) tablet administered orally vs placebo. Each sequence will include a 2 week treatment phase, with daily dosing of study drug/medication or placebo. This will be followed by a 7 day placebo washout period. After the placebo washout period, another 2 week treatment phase will follow, again with once daily dosing of study drug/medication or placebo. In the first sequence, patients will receive placebo for the first treatment period and rimegepant 75 mg IR tablet during the second treatment period. The second sequence will have rimegepant 75 mg IR tablet during the first 2 week treatment period, followed by placebo in the second treatment phase. For subjects, this design should seem like a "seamless" 5 week treatment phase. During each 2 week treatment phase and during the 7 day placebo washout period, patients will complete the 11 point Numeric Pain Rating Scale daily, as described above. In addition, patients will complete a paper diary daily to record efficacy data. The diary will include the daily recording of overall pain using the 11 point numeric pain rating scale, a recording of daily use of rescue medications, and a daily rating of worst pain episode using the 11 point Numeric Pain Rating Scale. This data will be entered into the CRF. Other secondary

	endpoints will be assessed at the beginning and end of each treatment period, including the Penn Facial Pain Scale (a 12-item activities of daily living scale designed to specifically assess the impact of Trigeminal Neuralgia symptoms on daily activities), the Pain Disability Index (which measures the degree to which chronic pain interferes with 7 categories of daily activities, measured on a 11 point scale ranging from 0 (no disability) to 10 (worst disability). The Patient Global Impression of Change (PGIC: a patient self-reported global index scale) will be assessed at the end of each treatment sequence. In addition, the Sheehan-Suicidality Tracking Scale (S-STS) will be administered as a safety measure at screening, as well as at every visit, as specified in the protocol. In addition, subjects completing the Double-Blind Phase of the study and who continue to meet inclusion/exclusion criteria may be offered up to 12 weeks of Open-Label Extension treatment, provided the Principal Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Open-Label Extension Phase will not be required to have a wash-out period of drug, but instead should continue dosing as specified in the Open-Label Extension Phase. All subjects will undergo a post study Follow-up Safety Visit 14 days after the final EOT Visit and last dose of study drug/medication administration. Subjects who discontinue from the study at any time during either the Double-Blind Phase or the Open-label Extension Phase are expected to complete the End of Treatment (day 119) Visit ***and*** the 2-Week Follow-up Safety Visit.
Primary Endpoint:	Improvement of Trigeminal Neuralgia symptoms as assessed by the Numeric Pain Rating Scale over the 2-week treatment period
Secondary Endpoints:	• The frequency of unique subjects with adverse events, serious adverse events, adverse events leading to discontinuation, Sheehan Suicidality Tracking Scale (S-STS) total score and clinically significant laboratory and ECG test abnormalities, from case report forms and clinical laboratory evaluations • Penn Facial Pain Scale-Revised (Penn-FPS-R) • Pain Disability Index • Patient Global Impression of Change Scale (PGI-C) • Measurement of worst pain in a 24-hour period using the Numeric Pain Rating Scale • Achievement of at least a 2-point reduction in average daily Numeric Pain Rating Scale score

STUDY SCHEMATIC





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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AAN	American Academy of Neurology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
CGRP	Calcitonin Gene-Related Peptide
CNS	Central Nervous System
CRF	Case Report Form
COVID-19	Coronavirus Disease 2019
DMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EFNS	European Federation of Neurological Societies
GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

INR	International Normalized Ratio
IRB	Institutional Review Board
IR	Immediate Release
iv	Intravenous
kg	Kilogram
L	Liters
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
NO	Nitric Oxide
NPRS	Numeric Pain Rating Scale
ODT	Orally Disintegrating Tablet
PGI-C	Patient Global Impression of Change Scale
Penn-FPS-R	Penn Facial Scale-Revised
CCI	[redacted]
po	By Mouth, Orally
QD	Once Daily
SAE	Serious Adverse Event
S-STS	Sheehan-Suicidality Tracking Scale
ULN	Upper Limit of Normal
WOCBP	Women of childbearing potential
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

The trigeminal nerve, or fifth cranial nerve, is the largest of the twelve cranial nerves and provides sensory innervation to the head and neck, as well as motor innervation to the muscles of mastication. The three major branches of the trigeminal nerve are the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves. Sensory innervation to the face is largely through these three branches. Trigeminal Neuralgia is a chronic facial pain syndrome characterized by paroxysmal, severe, lancinating episodes of pain in the distribution of one or more branches of the trigeminal nerve. It is estimated that trigeminal neuralgia has an overall incidence of approximately 4.3/100,000 in the general population, with a higher prevalence in women as compared to men, and is the most commonly diagnosed form of facial pain.[6] While trigeminal neuralgia remains an uncommon condition, the patient burden associated with this disorder is significant.[7] The persistent pain from trigeminal neuralgia is excruciating and frequently results in significant disability. Over the long term course of the disease, symptoms often become refractory to medical therapy and current treatment options remain suboptimal.[7]

Trigeminal neuralgia can be broadly divided into classical trigeminal neuralgia, which has no clear etiology other than neurovascular compression; idiopathic trigeminal neuralgia, which has no clear etiology; and secondary trigeminal neuralgia, which is caused by an underlying disease, including tumors, structural abnormalities at the base of the skull, and multiple sclerosis. Therefore, therapeutic regimens used to treat secondary TN are targeted at the identifiable underlying pathology. In the International Classification of Headache Disorders, third edition, secondary trigeminal neuralgia accounts for approximately 15% of cases of trigeminal neuralgia.[8] In the current study, patients with secondary trigeminal neuralgia will be excluded.

The diagnosis of classical and idiopathic trigeminal neuralgia rely largely on clinical symptomatology and physical exam. Imaging, especially MRI, is important to rule out any secondary cause of the disorder, which would prompt the diagnosis of *painful trigeminal neuropathy*. Imaging is also useful in confirming a diagnosis of classical trigeminal neuralgia when it reveals neurovascular compression of the trigeminal nerve. Patients generally present in the fiftieth decade or older with sudden, unilateral, excruciating, electric shock-like pain in the distribution of one or more branches of the trigeminal nerve, most commonly in the maxillary or mandibular branches. These episodes have an abrupt onset and termination, can last from a fraction of a second to a few minutes, and can be spontaneous or triggered by innocuous cutaneous stimuli, such as brushing teeth, chewing, laughing, or even air blown onto the face from an open window. Previously, trigeminal neuralgia was referred to as *tic douloureux*, as the sudden episodic pain can be associated with a concomitant facial spasm or grimace on the affected side. In between attacks, pain usually remits, and does not occur during sleep.

The International Classification of Headache Disorders, 3rd edition, (ICHD-3) has outlined the diagnostic criteria for trigeminal neuralgia. According to these criteria, a patient with trigeminal neuralgia must have a history of recurrent paroxysms of unilateral facial pain occurring in one or more divisions of the trigeminal nerve, most commonly in the second or third divisions, and with no radiation beyond the trigeminal distribution. **Additionally, the pain associated with these**

episodes must have the following characteristics: 1. Recurring as paroxysmal attacks lasting from a fraction of a second to 2 minutes, 2. Severe intensity of pain, 3. Sharp, shock-like, lancinating in quality. Pain may be precipitated by innocuous stimuli. On exam, there should be no evidence of a neurologic deficit. With severe attacks, there can be ipsilateral muscle spasms in the affected area. Ipsilateral autonomic symptoms can also sometimes be present.

The International Headache Society divides classical trigeminal neuralgia into two distinct forms, based on differences in clinical symptoms. The first, classical trigeminal neuralgia, purely paroxysmal, also previously called typical trigeminal neuralgia, is characterized primarily by sudden, episodic bouts of severe pain, with pain free periods in between these paroxysmal episodes. The second, classical trigeminal neuralgia with concomitant facial pain, also known as atypical trigeminal neuralgia, has a component of sharp, paroxysmal pain, but is distinguished by a predominance of persistent background facial pain on the affected side. This latter form of the disorder tends to be more refractory to current medical and surgical treatment options.[9] Idiopathic trigeminal neuralgia is divided similarly into these two forms of the disorder, namely idiopathic trigeminal neuralgia, purely paroxysmal and idiopathic trigeminal neuralgia with concomitant continuous pain. In order to simplify the nomenclature, this protocol will use the terms typical TN and atypical TN for these two subtypes of classical trigeminal neuralgia.

Although the exact pathophysiology of classical TN has not been fully elucidated, vascular compression of the trigeminal nerve root by aberrant blood vessels has been well described and is thought to play an integral role in the etiologic basis of the disease.[10-12] This compression, in turn, leads to morphological changes and sometimes atrophy of the nerve root. Accoding to the ICHD 3rd edition, when contact between a blood vessel and the trigeminal nerve and/or nerve root is found, but there is no evidence of atrophy or displacement of the nerve root, the condition is considered idiopathic.

Clinical Course and Current Treatment Options:

Classical trigeminal neuralgia usually presents over the age of 50, with an average age at onset of 63 years.[13] During the initial months, or even years, of the illness, the periods of pain are usually punctuated by pain-free intervals. However, over time, these periods of relapse have a tendency to become shorter and can eventually disappear entirely. The excruciating pain associated with this disorder has a profound impact on patient well-being, and may affect even the most basic functions of daily living, such as brushing teeth, washing the face, talking, chewing, laughing or yawning. This can ultimately result in significant weight loss, depression, anxiety, and sleep disorders.[14] A cross-sectional study of 82 patients with trigeminal neuralgia across six European countries found that one third of patients were prescribed medications for depression, anxiety, and sleep disturbances.[7] Trigeminal neuralgia has even been referred to in layman's terms as "the suicide disease," due to the crippling nature of these painful attacks.

Initial therapy with anticonvulsants, typically carbamazepine or oxcarbazepine, is generally effective in improving the symptoms of trigeminal neuralgia. However, over the long term, pharmacotherapy tends to become less effective, either due to the development of intolerable side effects or decreased efficacy. [15,16] Approximately half of patients resort to more invasive surgical interventions. [6] Although surgical interventions are often initially effective in relieving

symptoms, pain recurrence after one or more procedures is not uncommon. [1] Microvascular decompression of the nerve, which is the most invasive of these surgical interventions, provides the best long-term pain free outcome. [13,17]

Atypical trigeminal neuralgia tends to be more refractory to pharmacotherapy and neurosurgical interventions than typical TN.[9]

Medical Therapy:

According to the management guidelines for trigeminal neuralgia published jointly by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS), carbamazepine and oxcarbazepine are the first-line treatment options for trigeminal neuralgia. [18] These antiepileptic agents are thought to reduce neuronal excitability by blocking voltage-gated sodium channels. These agents are often initially very effective in reducing the frequency and intensity of paroxysmal pain symptoms associated with this condition. Over time, however, increasing doses are required in order to maintain efficacy. Although studies assessing long-term treatment outcomes are lacking, one systematic review of the literature estimated that greater than fifty percent of patients who initially respond to carbamazepine eventually, over 5 to 10 years, fail to respond adequately. [15] Another subset of patients discontinues carbamazepine treatment due to drug intolerance. [13] Side effects of carbamazepine and oxcarbazepine include drowsiness, dizziness, nausea, ataxia, diplopia, hyponatremia, hepatotoxicity, and, less commonly, toxic epidermal necrolysis, Stevens-Johnson Syndrome, aplastic anemia, and agranulocytosis. For patients who become treatment refractory to these medications due to lack of efficacy or drug-drug interaction, or for patients who cannot take these medications due to intolerable side effects or potential drug interactions with their current medications, the AAN-EFNS guidelines recommend that surgical options be considered. In the event that a patient either is resistant to surgery, or is not a surgical candidate for medical reasons, the guidelines suggest that baclofen, lamotrigine, or pimozide may be considered. A recent review of non-surgical treatment options concluded that there is not strong evidence in the literature to support the use of other available oral agents in the treatment of TN. [19]

- Carbamazepine is the only FDA-approved drug for the treatment of trigeminal neuralgia. Carbamazepine is administered in ascending doses. The starting dose is 100-200mg twice daily, and can be titrated up to a maximum dose of 1,800 mg/day.

- Oxcarbazepine shows similar efficacy and has a better safety profile than carbamazepine, but has not been as well-studied. [20] The starting dose is 300 mg twice daily and can be titrated up to a maximum dose of 2,700 mg/day.

Second-line medications include gabapentin, pregabalin, baclofen, lamotrigine, and pimozide. However, there is weak evidence in the literature to support these therapies. [21]

- Baclofen shows limited efficacy. The starting dose is 10 mg daily, which can be titrated as needed to control pain up to a dose of 60 to 80 mg per day.

- Lamotrigine showed some efficacy when used as adjuvant therapy with carbamazepine in patients who were unable to titrate to high enough doses of carbamazepine due to side effects. [19] Lamotrigine is started at 25 mg for two weeks and then increased to 50 mg daily for weeks 3 and 4. The suggested total dose is up to 400 mg daily in two divided doses.

- Pimozide is a dopamine receptor antagonist which is seldom used in the treatment of trigeminal neuralgia, as it is associated with serious side effects, which include extrapyramidal symptoms and cardiac arrhythmias. [21]

Alternative pharmacological treatments for classical trigeminal neuralgia include topiramate, levetiracetam, and botulinum neurotoxin type A. Further studies are needed to support a role for these agents in the treatment of trigeminal neuralgia.

Surgical Therapy:

Practice guidelines from the American Academy of Neurology (AAN) and European Federation of Neurological Societies (EFNS) suggest that surgical interventions may be considered for patients with trigeminal neuralgia refractory to first line medical therapy.[18] It is estimated that approximately half of all patients with trigeminal neuralgia eventually undergo a surgical procedure. [6,22] While there are a variety of neurosurgical options, microvascular decompression appears to offer the best long-term outcome. [13,18]

Neurosurgical interventions are as follows:

- Percutaneous Rhizotomy: In these procedures, a controlled lesion of the trigeminal ganglion or root is administered via a cannula passed through the foramen ovale. This selective ablation is performed either by radiofrequency ablation, percutaneous injection of glycerol, or balloon compression of the nerve. According to a systematic review of the literature in 2007 [17] complications of rhizotomies include sensory loss in approximately 50 percent of patients, dysesthesias in less than 6 percent, and corneal numbness in approximately 4 percent. With balloon compression of the trigeminal nerve, up to 50 percent of patients have transient weakness in the muscles of mastication. [17]

- Gamma knife surgery: In this technique, a beam of high dose radiation is focused at the trigeminal root. This procedure carries a risk of facial numbness and many patients do not achieve long term relief of symptoms. [18]

- Microvascular Decompression: Microvascular decompression is an open surgical procedure. Under microscopic visualization, the trigeminal nerve is exposed, the blood vessel compressing the nerve is moved in order to decompress the trigeminal nerve/nerve root. Complications include CSF leaks, infarcts, and hematomas. Also, in approximately 10 percent of patients, aseptic meningitis and ipsilateral hearing loss may occur. [18]

1.2 Product Development Background

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

1.2.1 Non-clinical Studies

1.2.1.2 Non-clinical 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.

1.2.2 Clinical Experience

Rimegepant (Nurtec® ODT, BHV-3000) is an oral, small molecule, calcitonin gene-related peptide (CGRP) receptor antagonist approved in the United States (US) for the acute treatment of migraine and the preventive treatment of episodic migraine in adults,[23] as well as in Israel and the United Arab Emirates (UAE), and Kuwait for the acute treatment of migraine. Rimegepant is currently in development for the acute and preventive treatment of migraine in pediatric subjects, as well as for the treatment of refractory trigeminal neuralgia, the acute treatment of chronic rhinosinusitis (CSR), and temporomandibular disorders (TMD). As of 27-Feb-2022, more than 8,600 unique subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine or refractory trigeminal neuralgia in the rimegepant clinical development program. It is estimated that approximately 5,780 unique subjects have been administered rimegepant (at any dose) across the Phase 1, Phase 2, and Phase 3 clinical studies. Collectively, the current data demonstrates a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine, as well as for the evaluation in trigeminal neuralgia.

Please refer to the most current version of the Investigator Brochure for further details. In total, the current data suggests a favorable benefit-risk profile for rimegepant.

1.2.3 Clinical Adverse Event Profile

Rimegepant has been studied up to the maximum dose of 1500 mg and multiple oral doses up to the maximum daily dose of 600 mg for 14 days. 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 function tests. Investigators must carefully monitor routine liver function 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.

1.3 Study Rationale

Trigeminal Neuralgia is a neuropathic pain disorder characterized by recurrent, paroxysmal, lancinating pain in the distribution of one or more branches of the trigeminal nerve. These episodic bouts of severe facial pain can last seconds to minutes, occur several times per day, and often result in significant disability. Although the exact mechanism of action remains unclear, antiepileptic drugs, most notably carbamazepine and oxcarbazepine, remain the first-line treatment for these patients. Nonetheless, the majority of patients have an incomplete response to current pharmacotherapy and resort to more invasive procedures, including rhizotomy and surgical decompression of the microvasculature surrounding the trigeminal nerve. While numerous treatment options exist, inadequate relief of pain and recurrence of symptoms are common, prompting the need for novel pharmacologic interventions.[1]

Although the underlying mechanisms of classical Trigeminal Neuralgia have not been fully elucidated, imaging studies and surgical procedures clearly implicate vascular compression of the trigeminal nerve in the pathophysiology of the disease. [2,10,12] Chronic nerve compression can lead to axonal demyelination and degeneration. Numerous studies, largely from biopsy specimens obtained during surgical decompression of the trigeminal nerve, have demonstrated subsequent demyelination of the trigeminal root and regional and trigeminal sensory axons, as well as trigeminal nerve atrophy.[24,25,26,27] As a result of this neuronal damage, studies suggest that these injured sensory neurons become hyperexcitable, leading to aberrant neuronal discharge, ultimately resulting in the painful paroxysms associated with trigeminal neuralgia.[28]

Within the central nervous system, the trigeminal neuronal network is an important nociceptive pathway, and stimulation of the trigeminal ganglion results in the release of the neurotransmitter calcitonin gene-related peptide (CGRP).[29,3] CGRP is an endogenous 37-amino acid peptide contained within pain-signaling nociceptive afferents, and this potent vasodilator is thought to play a causal role in migraine.[4,30] Aberrant release of CGRP from the trigeminal nerve has been clearly implicated in the pathophysiology of migraine headache [3,31] and has prompted the development of small molecule CGRP antagonists for the treatment of this disorder. [32] Further evidence has demonstrated that CGRP is upregulated in other neuropathic pain states and is thought to play an important role in the development of the central and peripheral sensitization associated with many chronic pain conditions.[3] Clinical studies have also shown increased levels of CGRP in the cerebrospinal fluid of patients with Trigeminal Neuralgia.[5] The proposed study is based on the evolving preclinical and clinical evidence suggesting a role for CGRP in the

development of neuropathic pain syndromes and Trigeminal Neuralgia. In addition, these studies provide evidence for a role for small molecule CGRP receptor antagonists in the treatment of other pain syndromes involving the trigeminal system, such as trigeminal neuralgia[32], and provides the basis of the rationale for the current study. BHV-3000 (rimegepant) is a small molecule CGRP receptor antagonist that is being developed for the potential treatment of Trigeminal Neuralgia.

1.3.1 Study Design Rationale

This is a phase 2, multi-center, double-blind, placebo-controlled, crossover trial to assess the safety, tolerability, and efficacy of BHV-3000 in treating Trigeminal Neuralgia. The study drug/medication will be rimegepant formulated in a 75 mg immediate release (IR) tablet or a matching placebo. The subjects will be instructed to take their study drug/medication, as an outpatient, daily during two 2-week treatment sequences (separated by a 7-day placebo washout period).

Approximately 120 patients will be screened to randomize 60 patients in a 1:1 ratio into 2 treatment sequences receiving 75 mg Rimegepant vs Placebo, using a 2-period, 2-sequence, crossover design. Patients with atypical TN and typical TN will be stratified equally into each of the two treatment sequences, with atypical TN patients not exceeding 50 percent of the subjects.

In addition, subjects completing the double-blind phase of the study and who continue to meet eligibility criteria may be offered up to 12 weeks of Open-Label Extension treatment, provided the Principal Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Open-Label Extension Phase will not be required to have a wash-out period of drug, but instead should continue dosing as specified in the Open-Label Extension Phase. During the Open-Label Extension phase, study drug/medication is rimegepant (BHV-3000) 75 mg orally disintegrating tablet (ODT) dosed daily.

All subjects will undergo a post study Follow-up Safety Visit 14 days after the final EOT Visit and last dose of study drug/medication administration. Subjects who discontinue from the study at any time during either the Double-Blind Phase or the Open-label Extension Phase are expected to complete the End of Treatment (day 119) Visit ***and*** the 2-Week Follow-up Safety Visit.

All randomized subjects should complete the 2-Week Follow-up Safety Visit (regardless of completing the Double-blind Treatment Phase), except those who are lost to follow-up, withdrew consent, or death.

1.3.2 Dose Selection Rationale

In three positive, double-blind, placebo-controlled BHV-3000 studies, a 75 mg dose of rimegepant was demonstrated to be effective for the treatment of migraine. Additionally, based on preliminary data from an ongoing long-term safety study, rimegepant has been well tolerated at the 75 mg dose and demonstrates a consistent favorable safety profile. Please refer to the current version of Investigators Brochure for a summary of the clinical safety profile.

1.4 Research Hypothesis

Rimegepant is superior to placebo in providing symptom relief for treatment-refractory patients with classical or idiopathic trigeminal neuralgia.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the efficacy of rimegepant compared to placebo in providing symptomatic pain relief in patients with refractory Trigeminal Neuralgia, defined as a reduction from baseline in the average daily Numeric Pain Rating Scale between the two-week treatment phases.

2.2 Secondary

- To assess the safety and tolerability of rimegepant relative to placebo in patients with Trigeminal Neuralgia
- To evaluate the efficacy of rimegepant vs placebo for improving physical function in Trigeminal Neuralgia patients as measured by the Penn Facial Pain Scale-Revised (Penn-FPS-R)
- To evaluate the efficacy of rimegepant vs placebo for improving functional disability in Trigeminal Neuralgia patients as measured by the Pain Disability Index
- To evaluate the efficacy of rimegepant vs placebo on global functioning as measured by the Patient Global Impression of Change Scale (PGI-C)
- To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief as captured by daily rating of worst pain episode as measured by the 11 point Numeric Pain Rating Scale
- To evaluate the efficacy of rimegepant vs placebo in providing symptomatic pain relief of clinical importance as defined by a 2-point or greater reduction in the 11 point Numeric Pain Rating Scale

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint is the change in average daily Numeric Pain Rating Scale from baseline to the end of the 2-week treatment phase of the study. Pain relief will be defined as an improvement (reduction) from baseline. The Numeric Pain Rating Scale is an 11-point numeric scale with pain intensity ratings ranging from 0 (for "no pain") to 10 (for the "worst pain imaginable").

3.2 Secondary

- The frequency of unique subjects with: serious adverse events; adverse events leading to discontinuation; adverse events judged to be related to study drug/medication; Sheehan Suicidality Tracking Scale (S-STS) total score, clinically significant ECG and laboratory abnormalities that are observed during the randomization phase of the study.
- Change in Penn Facial Pain Scale-Revised total score from baseline to the end of the randomization phase of the study.
- Change in Pain Disability Index total score from baseline to the end of the randomization phase of the study.
- Patient Global Impression of Change Scale at the end of the randomization phase of the study.
- Patient daily recording of worst pain episode in a day as measured using the 11-point Numeric Pain Rating Scale.
- Achievement of at least a 2-point reduction in average daily Numeric Pain Rating Scale score.

CCI

3.4 Study Design

BHV3000-202 is a phase 2, multi- center, double-blind, placebo controlled, crossover trial (with an open-label extension) to assess the safety, tolerability, and efficacy of BHV-3000 in treating Trigeminal Neuralgia in patients who failed to respond adequately to pharmacotherapy. Current inadequate response to therapy is defined by a daily pain score of greater than or equal to 4 for the "average intensity" on 11-point Numerical Pain Rating Scale during 14 days screening period. A crossover design with a placebo washout period of 7 days between treatments will be used due to the limited number of subjects, with each patient serving as their own control. In addition, subjects completing the double-blind phase of the study and who continue to meet

eligibility criteria, may be offered up to 12 weeks of Open-Label Extension treatment, provided the Principal Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Open-Label Extension Phase will not be required to have a wash-out period of drug, but instead should continue dosing as specified in the Open-Label Eextension Phase.

There is a [Post-Dose] Follow-up SafetyVisit 14 days after the final EOT Visit/last dose of study drug/medication administration. Subjects who discontinue from the study at any time during either the Double-Blind Phase or the Open-label Extension Phase are expected to complete the End of Treatment (day 119) Visit and the 2-Week Follow-up Safety Visit.

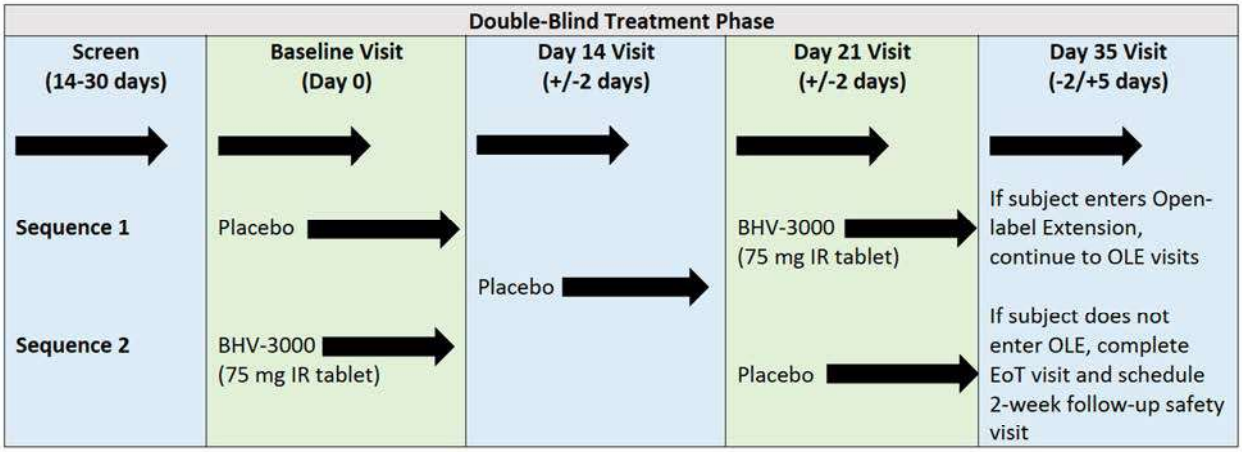
Subjects who have completed the Double-Blind Phase **prior to this amendment 08** may have an opportunity to return to the study to participate in the Open-Label Extension phase. Subjects will keep their original subject ID and will return to perform an unscheduled screening visit to re-confirm study eligibility. This OLE phase will ***not*** be permitted for those subjects who discontinued early from the Double-Blind Treatment Phase or were previously documented as a screen failure. Re-screen procedures will include all of the screening procedures except for neuro exam/neuroimaging and pain diaries.

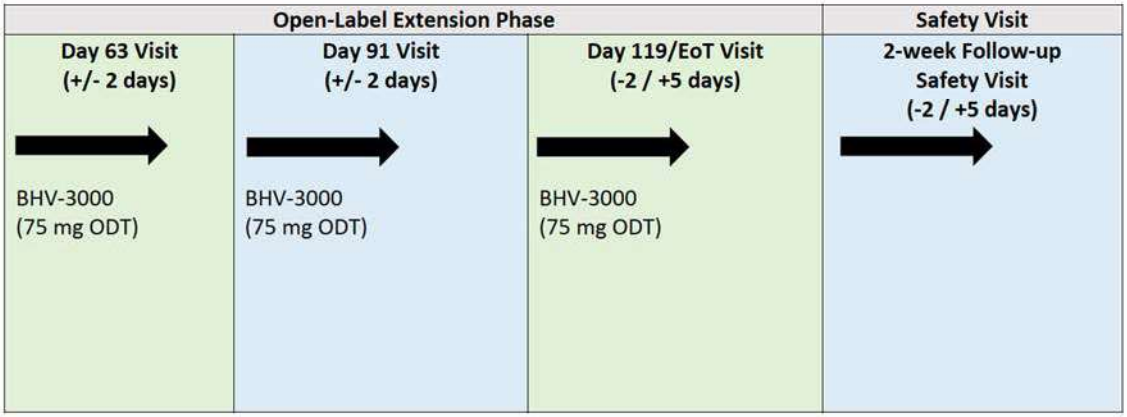
Subjects entering the Open-Label Extension Phase will have study drug/medication dispensed at Day 35 visit. The following visit will occur four weeks after Day 35 visit, starting with Day 63 visit. Thereafter, subjects will undergo visits every four weeks up through Day 119 of the OLE Phase as outlined in Table 2 (Open-label Schedule of Assessments). During the OLE Phase, subject will be instructed that they must take 1 tablet of rimegepant 75mg ODT medication daily, beginning at Day 36. If a dose of study drug/medication for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the study drug/medication wallet and should NOT take the following day's assigned dose until the next calendar.

All ***randomized*** subjects should complete the [Post-Dose] Follow-up SafetyVisit 14 days after the final EOT Visit. Subjects who discontinue from the study at any time during either the Double-Blind Phase or the Open-label Extension Phase are expected to complete the End of Treatment (day 119) Visit and the 2-Week Follow-up Safety Visit with the exception of those subjects who are lost to follow-up, withdrew consent, or death.

The study will be conducted at multiple centers.

3.5 Study Schematic





[a)]All ***randomized*** subjects should complete the 2 Week Follow-up Safety Visit at any time they either complete or discontinue from the study with the exception of those subjects who discontinue early from the the study due to withdrawal of consent by subject, are lost to follow-up or death

Table 1: Schedule of Assessments Double- Blind Phase

Procedure	Screening [o] Visit	Baseline (Randomization) (Day 1)[j]	Day 14 (+/- 2 days)	Day 21 (+/- 2 days)	Day 35 (-2/+5 days) [i]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed Consent	X				
Inclusion/Exclusion Criteria	X	X			
Medical History	X				
Neuroimaging [a]	X				
Neurologic Exam	X				
Concomitant Medications and Procedure Review [b]	X	X	X	X	X
Physical Exam	X				X
Vital signs/physical measurements [d]	X	X	X	X	X
Laboratory Assessments	X	X			X
Liver Function Tests	X	X	X		X
Serology (HBsAg, HCV, HIV)	X				
Pregnancy Test (Serum)	X	X			
Pregnancy Test (Urine)		X			X
Urine Drug Screen	X				X
12-Lead ECG	X	X	X		X
Serious Adverse Event Assessment [e]	X	X	X	X	X
Sheehan Suicidality Tracking Scale (S-STS)	X	X	X	X	X
Daily Average Pain (NPRS) [h]	X	X	X	X	X
Patient Global Impression Change Scale (PGI-C)			X	X	X

Procedure	Screening [o] Visit	Baseline (Randomization) (Day 1)[j]	Day 14 (+/- 2 days)	Day 21 (+/- 2 days)	Day 35 (-2/+5 days) [i]
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Pain Disability Index		X	X	X	X
Penn Facial Pain Scale-Revised		X	X	X	X
Record of Daily Rescue Medications		X	X	X	X
Daily Worst Pain (NPRS)	X	X	X	X	X
CCI					
Randomization [c] [g]		X			
Dispense Study Drug/Medication [l]		X	X	X	X[l]
Study Drug/Medication Accountability [f]		X	X	X	X
Paper Diaries Dispensed [m]	X	X			X[m]
Pain Paper Diary returned/reviewed for completeness		X	X	X	X

[a] Subjects must have at least one neuroimaging study (MRI) completed any time prior to randomization. For patients with a strong contraindication to MRI (eg, pacemaker), CT scan, preferably with CTA, will be allowed based on approval by the medical monitor.
[b] Concomitant medications, including standard of care Trigeminal Neuralgia medications, taken during the screening period and rescue medications taken during the double-blind treatment period and open-label extension should be recorded on the subject's paper diary and reviewed by study personnel at each visit.
[c] The actual baseline visit date should be used for IWRS enrollment date.
[d] Height measured at Screening Visit only. Weight, body temperature, respiration rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured.
[e] SAEs, AEs and concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the 14 day follow up safety visit. Non-serious AEs should be reported from the baseline visit to the safety follow up visit.
[f] Subjects must take their study drug/medication every day, regardless of whether or not they have Trigeminal Neuralgia pain. Subjects must report each tablet they take on the paper diary. Due to the COVID-19 Pandemic, study drug/medication may be shipped to a subject, with up to an 2-week supply. Proper documentation must be maintained in the subject's source records including shipping vendor, tracking number, confirmation of receipt by subject, and all other relevant information.
[g] Subjects with 2 or more missed daily paper pain diaries during the Screening Period should be considered for discontinuation from the study for poor compliance, after discussion with sponsor. Subjects in the Double-Blind Treatment Period who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be complete by the site with the subject.
[h] The paper diary will be dispensed at the Screening Visit, after all Screening Procedures are completed. The subject will be trained on the use of the paper diary. The subject will use the paper diary every day during the Screening and Double-Blind Phases to report Trigeminal Neuralgia pain, medication use and study drug/medication dosing (Double-BlindTreatment Phase only).

[i] Subjects who do not complete the Double-Blind Treatment Phase should completed the End of Treatment Visit and the 14 day Follow-up Safety Visits (they should not enter the Open-label Extension Phase).
[j] Due to COVID-19 Pandemic, very effort should be made to conduct the study visits within the specified windows. However, if necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation. See sections 3.5.1 - 3.5.3 for more information.
[k] For subjects who do not enter the Open-label Extension Phase, the follow-up visits should be scheduled based on date of their EOT Visit. The visit window for the 2 Week Follow-up Visit is 14 days (–2 / +7 days).
[l] If subject entering Open-label extension, dispense Open-label study drug/medication at day 35.
[m] If subject entering Open-label extension, dispense Open-label paper diaries.
[o] Re-screen procedures for the return of completed subjects will include all screening procedures except for the neuro exam/neuro imaging and the pain diaires

- **End of Treatment needs to be completed one (1) time, either during the double-blind treatment phase or open-label extension phase**
- All ***randomized*** subjects should complete the 2 Week Follow-up Safety Visit at any time they either complete or discontinue from the study with the exception of those subjects who discontinue early from the the study due to withdrawal of consent by subject, are lost to follow-up or death

Table 2: Schedule of Assessments- Open-Label Extension Phase

	Open-label Extension[n][p]			**Follow-up Phase[p][q]**
Procedure	**Day 63 (+/- 2 days)**	**Day 91 (+/- 2 days)**	**Day 119 (- 2 / +5 days)/ EOT Visit**	**2-Week Follow-up (day 133) post last dose (- 2/+7 days)[k]**
	Visit 6	**Visit 7**	**Visit 8**	
Concomitant Medications[r]	X	X	X	X
Physical Examination			X	X
Vitals Signs / Physical Measurements[d]	X	X	X	X (vital signs only)
Laboratory Assessments			X	X
Liver Function Test	X	X	X	X
Pregnancy Test (Serum)				
Pregnancy Test (Urine)	X	X	X	X
Urine Drug Screen			X	
12-Lead ECG	X	X	X	X
Serious Adverse Event Assessment	X	X	X	X
Sheehan Suicidality Tracking Scale (S-STS)	X	X	X	X
Daily Average Pain (NPRS)	X	X	X	
Patient Global Impression Change Scale (PGI-C)	X	X	X	
Pain Disability Index	X	X	X	
Penn Facial Pain Scale-Revised	X	X	X	
Record of Daily Rescue Medication	X	X	X	
Daily Worst Pain (NPRS)	X	X	X	
Dispense Study Drug/Medication[l][s]	X	X		
Study Drug/Medication Accountability	X	X	X	
Paper Diaries Dispensed[m]	X	X		

	Open-label Extension[n][p]			**Follow-up Phase[p][q]**
Procedure	**Day 63 (+/- 2 days)**	**Day 91 (+/- 2 days)**	**Day 119 (- 2 / +5 days)/ EOT Visit**	**2-Week Follow-up (day 133) post last dose (- 2/+7 days)[k]**
	Visit 6	**Visit 7**	**Visit 8**	
Pain Paper Diary returned/reviewed for completeness	X	X	X	

[l] If subject entering Open-label extension, dispense Open-label study drug/medication at day 35.
[n] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to their original visit schedule by calculating the visit window interval from the Baseline/Randomization Visit.
[p] All randomized subjects who discontinue early from the Open-label Extension Phase should complete the EOT Visit and return for the 14-day follow-up safety visit.
[q] For subjects who enter the Open-label Extension Phase, the follow-up visit should be scheduled based on date of their EOT Visit. The visit window for the Follow-up Week 2 Visit is 14 days (- 2/+7 days)
[r] Concomitant medications, including acute standard of care medications (both prescribed and OTC), taken during the Open-label Extension Phase and Follow-up Phase should be recorded in the subject's concomitant medication paper diary, reviewed by study personnel at each visit, and a copy made at each study visit to be maintained in source records. At end of study, the concomitant medication paper diary should be collected at the 2 Week Follow-up Visit.
[s] Subjects should finish a wallet of study drug/medication before starting a new wallet. Study drug/medication will be dispensed at monthly (every 4 weeks) study visits, as needed. Site staff must hand-write the first date for the tablet to be taken on the inside of the wallet. The subject will date each area on the inside of the wallet after the tablet is taken.
[t] Subjects must take study drug/medication daily regardless of whether they have TN pain. If a dose of study drug/medication for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the subject paper study log.

- All ***randomized*** subjects should complete the 2 Week Follow-up Safety Visit at any time they either complete or discontinue from the study with the exception of those subjects who discontinue early from the the study due to withdrawal of consent by subject, are lost to follow-up or death

3.5.1 Screening Phase (14 to 30 days)

Prior to randomization, patients will enter a 14 to 30 day screening period during which they will complete daily self-reported assessments of pain intensity over a 24 hour period using an 11 point Numeric Pain Rating Scale, ranging from 0 (for no pain) to 10 (for the worst imaginable pain.) Throughout the study, patients will be allowed to remain on their current medication regimens, provided they are on a stable dose for a minimum of 4 weeks prior to the randomization visit. The screening visit must be conducted in person.

3.5.2 Randomization Phase (35 Days)

Patients with a mean score of greater than or equal to 4 on the daily "average intensity" 11 point Numeric Pain Rating Scale, during the 14 to 30 day screening period, will be randomized to one of two treatment sequences to receive BHV-3000 (75 mg QD) administered orally vs placebo (QD) in a 1:1 ratio. Patients should be encouraged to take their dose of medication in the mornings. Patients with a diagnosis of typical and atypical TN will be stratified equally into the two sequences; and patients with atypical TN will not exceed 50% of the subjects. Each sequence will include a 2 week treatment phase, with daily dosing of study drug/medication or placebo. This will be followed by a 7 day placebo washout period. After the placebo washout period, another 2 week treatment phase will follow, again with once daily dosing of study drug/medication or placebo. In the first sequence, patients will receive placebo for the first treatment period and BHV-3000 75 mg during the second treatment period. The second sequence will have BHV-3000 75 mg during the first 2 week treatment period, followed by placebo in the second treatment phase.

During each 2 week treatment phase, patients will complete the 11 point Numeric Pain Rating Scale daily, as described above. In addition, patients will complete a paper diary daily to record efficacy data. The diary will include the daily recording of overall pain (average pain experienced over the 24 hour day) using the 11 point numeric pain rating scale, as well as a recording of daily use of rescue medications, and a daily rating of worst pain episode using the 11 point Numeric Pain Rating Scale. Other secondary endpoints will be assessed at the beginning and end of each treatment period, including the Penn Facial Pain Scale-Revised, a 12-item activities of daily living scale designed specifically to assess impact of Trigeminal Neuralgia symptoms on daily activities, Pain Disability Index, which measures the degree to which chronic pain interferes with 7 categories of daily activities, measured on a 11point scale ranging from 0 (no disability) to 10 (worst disability). The Patient Global Impression of Change (PGIC: a patient self-reported global index scale) will be assessed at the end of each treatment sequence. In addition, the Sheehan Suicidality Tracking Scale (S-STS) will be administered as a safety measure at screening, as well as at the beginning and end of each treatment phase.

Certain provisions may be implemented, in order to minimize potential hazards to study participants due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs and shipping of study drug/medication directly to study subject, if needed. Subjects must report to the site a negative pregnancy test for continued participation in the study (and must be documented) and completed before shipments of study drug/medication to any subject. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. The screening, baseline, Day 35, and Day 119 (end of treatment) visits must be conducted as an in-person visit. The Day 14, Day 21, Day 63, Day 91 and the Follow-Up Safety Visit may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.). However, local labs and a phone/telemedicine Sheehan Suicidality Tracking Scale must be completed at the Day 14, Day 21, Day 63, Day 91, and Follow-Up Safety Visit.

3.5.3 (Day 35)

All patients will return to the study site after the final dose of the second treatment phase, for review of the diary and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). All subjects must return any unused study drug/medication to the study center. If the subject does not enter OLE, complete the Day 119/EOT visit schedule. If subject is entering OLE, ensure Double-blind treatment bottle is returned and subject took their final dose of double-blind treatment at Day 35 BEFORE issuing OLE study drug/medication. OLE study drug/medication should first be taken the following day, Day 36.

3.5.4 Open-label Extension Phase (Days 36 to 119)

Subjects who complete the Double-Blind Phase, continue to meet all inclusion/exclusion criteria, and have been compliant with the paper diary and medication use may enter the OLE Phase. The study drug/medication will switch from an IR tablet to the ODT for the OLE. Subjects will be dispensed study drug/medication (rimgepant 75 mg orally disintegrating tablet) at the Day 35 visit. **Subjects will be instructed that they must take 1 tablet of rimegepant 75 mg orally disintegrating tablet (ODT) every day, beginning at Day 36**, regardless of whether they have TN pain on that day.

Study visits will be approximately every 4 weeks until Day 119. Study drug/medication compliance and concomitant medication use will be reviewed, and subjects will be dispensed additional study drug/medication as needed. Additional safety assessments (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

Please refer to the Open-label Schedule of Assessments Table 2 for details on procedures during the Extension Phase. There is a visit window of +/- 2 days during the Extension Phase of the study.

All patients will return to the study site after the final dose of the OLE phase, or at the end of treatment for early discontinuations for review of the diary and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). All subjects must return

any unused study drug/medication to the study center. The end of Treatment (Day 119) visit must be conducted as an in-person visit, but may be delayed (see protocol window) if necessary due to local COVID-19 safety requirements.

3.5.5 Follow-up Safety Visit (14 days post last dose)

All randomized subjects should complete the 2 Week Follow-up Safety Visit (regardless of completing the Double-blind Treatment Phase), except those who discontinue early from the Double-blind Treatment Phase due to withdrawal by subject, are lost to follow-up or death. Subjects will return to the study site 14 days after the Day 119 visit/EOT visit or early discontinuation visit (-2/+7 days) to collect laboratory tests, vital signs/physical measurements, physical exam, electrocardiography, assessment of AEs/SAEs, urine pregnancy test, pain rating scales, and Sheehan Suicidality Tracking Scale (S-STS). Subjects will return the concomitant medication paper diary which should be reviewed one final time by study staff. Investigators should assess subjects for AEs consistent with drug dependency or withdrawal effects and report as appropriate.

3.6 Post Study Access to Therapy

At the end of the study, the sponsor will not continue to supply study drug/medication to subjects/investigators. The investigator should ensure that the subject receives the appropriate standard of care to treat the condition under study.

4 POPULATION

Individuals entered in this trial will be patients with a clinical diagnosis of TN, purely paroxysmal (typical TN) or classical TN with concomitant continuous pain (atypical TN) based on the International Classification of Headache Disorders, 3rd edition, who have had an inadequate response to current treatments and symptoms for at least three months. This study will occur at multiple centers. Subjects may be recruited thorough a variety of sources, including referral from physicians and other health care professionals.

4.1 Number of Subjects

Approximately 120 patients will need to be screened in order to randomize 60 patients in a 1:1 ratio into 2 treatment sequences receiving 75 mg Rimegepant vs Placebo, using a 2-period, 2-sequence, crossover design.

In addition, subjects completing the double-blind phase of the study and who continue to meet eligibility criteria may be offered up to 12 weeks of Open-Label Extension treatment, provided the Principal Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Open-Label Extension Phase will not be required to have a wash-out period of drug, but instead should continue dosing as specified in the Open-Label Extension Phase.

Subjects who have completed the trial **prior to this amendment 08** will have an opportunity to return to the study to participate in the Open-Label Extension. Subjects will keep their original subject ID and will return to perform an unscheduled screening visit to confirm eligibility. If the subject is on a prohibited concominent medication, subject must washout per Section 4.4. This Open-Label Extension phase will not be open for those subjects who discontinued Double-Blind Phase or screen fail.

4.2 Inclusion Criteria

1. Informed Consent:

    a. Subjects (or legally acceptable representative as required by the IRB/IEC) must provide a written signed informed consent form/forms (IRB/EC specific) prior to the initiation of any protocol required procedures.

2. Target Population:

    a. Subjects with a clinical diagnosis of classical or idiopathic TN, purely paroxysmal (typical TN) or classical TN with concomitant continuous pain (atypical TN) based on the International Classification of Headache Disorders, 3rd edition, including the following:

        i. history of recurrent paroxysms of unilateral facial pain occurring in one or more divisions of the trigeminal nerve, most commonly in the second or third divisions, and with no radiation beyond the trigeminal distribution.

ii. Recurring as paroxysmal attacks lasting from a fraction of a second to 2 minutes

iii. Severe intensity of pain

iv. Sharp, shock-like lancinating in quality

v. Precipitated by innocuous stimuli within the affected trigeminal distribution

vi. Not better accounted for by another ICHD-3 diagnosis

b. Trigeminal neuralgia symptoms for a minimum of three months prior to screening visit.

c. Intolerance, contraindication, or inadequate response to current treatment.

d. A mean of ≥ 4 on the daily "average intensity" score on the Numeric Pain Rating Scale during the last 14 days in the screening period.

e. Neuroimaging to exclude another cause for the neuralgia, other than neurovascular compression.

f. Subjects must be on stable doses of their current trigeminal neuralgia medications for at least 4 weeks prior to their randomization visit.

3. Age and Reproductive Status

a. Male and female subjects ≥ 18 years of age and older

b. Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential 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 4.5 for the definition of WOCBP. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months prior to the screening visit

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 drug/medication, WOCBP must have a negative urine pregnancy test

e. Women must not be breastfeeding

4.3 Exclusion Criteria

1. Disease Target Exclusion

a. Subject has a structural lesion on neuroimaging, other than vascular compression of the trigeminal nerve or nerve root that would explain the neuralgia

b. Subject has a clinically evident neurologic deficit on neurologic examination of the cranial nerves (other than mild sensory changes in the distribution of the affected trigeminal nerve).

c. Subjects who have undergone rhizotomy of the trigeminal ganglion or nerve root (including radiofrequency ablation and glycerol injection) gamma knife surgery, or microvascular decompression surgery for the treatment of trigeminal neuralgia should be discussed with the Biohaven Medical Monitor on a case by case basis.

2. Medical History and Concurrent Diseases

a. Subjects history of HIV disease

b. Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with Myocardial Infarction (MI), Acute Coronary Syndrome (ACS), Percutaneous Coronary Intervention (PCI), cardiac surgery, stroke or transient focal neurological deficit during the 6 months prior to screening

c. Uncontrolled hypertension (high blood pressure) at screening (e.g., repeated diastolic measurement of ≥ 96mmHg)

d. Subject has a current diagnosis of major depression which is not related to current TN diagnosis, 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. Subject has a history of gastric, or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has a disease that causes malabsorption

f. Subject has a history or diagnosis of Gilbert's Syndrome or any other active hepatic or biliary disorder

g. The subject 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

h. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria[21] for any significant substance use disorder within the past 12 months from the date of the screening visit

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

(1) Detectable levels of cocaine, amphetamine, and phencyclidine (PCP) in the drug screen are exclusionary. Subjects who are positive for amphetamines, and who are on a prescribed amphetamine medication for an approved indication (e.g. ADHD) will be allowed into the study at the Investigator's discretion. This determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable 4 weeks from prior to randomization visit until the end of treatment visit occurs.

(2) Detectable levels of marijuana in the drug screen are not exclusionary, if in the investigator's documented opinion the subject does not meet DSM-V criteria [21] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results.

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

k. Body mass index ≥33.0 kg/m²

l. History of gallstones or cholecystectomy

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/medication 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 ≤ 40ml/min/1.73m^2

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

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. HbA1C ≥ 8.0% at screening

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)

i. GGT >1.5 x ULN (Abnormal values > 1.5x ULN may be repeated once for confirmation during the screening period)

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

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. Non-compliance with or inability to complete the Paper Diary during the Screening Period. Non-compliance is 2 or more missed evening reports during the Screening Phase. Subjects should be considered for discontinuation after discussion with the sponsor.

d. Participation in clinical trial with non-biological investigational agents or investigational interventional treatments within the 30 days prior to Baseline Visit

e. Subjects who have previously participated in any BHV-3000/ BMS-927711/ rimegepant study within the last 2 years

f. Participation in clinical trial with biological investigational agents within the 90 days prior to Baseline visit

g. Score of > 1 (“a little”) on Question 2 on the Sheehan Suicidality Tracking Scale for the period of 30 days prior to screening and during the study. All other questions must be scored a “0” (“Not at all”). Please see section 5.2.8 for additional guidance on study discontinuation based on results from the S-STS

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

i. Please see section 4.4 for Prohibited medications and section 5.3.5 for allowable rescue medications

j. Subjects who were considered screen failures from BHV3000-202 may be considered for re-screening provided the ineligibility was due to one of the eligibility items adjusted in Amendment 04, Protocol Version 5. BMI less than 33.0 kg/m^2 (previously BMI less than or equal to 30kg/m^2). Stable dose of 4 weeks prior to randomization visit (previously 3 month prior to screening and/or randomization visit). Subjects who were considered screen failures from BHV3000-202 for other reasons should be discussed with the Sponsor and approval must be granted prior to re-screening. Adequate documentation in source records must support the previously failed criteria.

4.4 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. Barbiturate-containing products (e.g. Fioricet, Fiorinal, butalbital, phenobarbital) should not be taken 14 days prior to randomization and throughout the study.

3. Modafinil (PROVIGIL®) should not be taken 14 days prior to randomization and throughout the study.

4. Butterbur root or extracts should not be taken 14 days prior to randomization and throughout the study.

5. History of use of ergotamine medications on greater than/equal 10 days per month on a regular basis for greater than/equal 3 months.

6. Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) for at least 2 days prior to randomization.

7. Use of all acetaminophen or acetaminophen containing products must be discontinued at least 2 days prior to randomization (acetaminophen < 1000 mg/day is allowed as rescue medication, see Section 5.3.5). During the screening phase (14 to 30 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000 mg/day is prohibited.

8. Use of marijuana is prohibited during the study.

9. Muscle relaxants are prohibited during the study. The use of baclofen is permitted, provided that patients are on stable dosing for at least 8 weeks prior to their randomization visit.

10. Concomitant use of strong CYP3A4 inhibitors with rimegepant is prohibited during the study. If use of a strong CYP3A4 inhibitor is required, such as use of HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, dosing with rimegepant should be stopped. Please see section 17, Appendix 2.

11. Concomitant use of strong CYP3A4 inducers with rimegepant is prohibited during the study. Therefore, the use of carbamazepine during this study will be prohibited. However, patients taking oxcarbazepine for the treatment of their trigeminal neuralgia may continue with their current therapy, provided they have been on stable dosing for at least 4 weeks prior to their randomization visit. Patients on carbamazepine may be transitioned to oxcarbazepine. Similarly, these patients must be on stable doses of oxcarbazepine for at least 4 weeks prior to the randomization visit. Please see section 17, Appendix 2.

12. Concomitant use of strong inhibitors of the P-gp transporter with rimegepant is prohibited during the study. Please see section 17, Appendix 2.

13. The use of CGRP antagonists (biologic [e.g. Aimovig™ and Ajovy™] or small molecule) other than rimegepant.

4.4.1 Trigeminal Neuralgia Medications

Throughout the study, patients will be permitted to use Standard of Care Trigeminal Neuralgia medications, with the exception of carbamazepine, including rescue medications, provided that these medications have been used at stable dosing for at least 4 weeks prior to randomization visit. Use of these concomitant medications will be recorded daily by the subject on a paper diary and reported to the site.

4.5 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:

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

- 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

- Woman on hormone replacement therapy (HRT)

Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential 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 drug/medication to 56 days after dosing). The two methods should include one barrier method (i.e. . 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). Subjects should not take

Investigational Study drug/medication if they are pregnant and subject should immediately contact Study Investigator.

4.6 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Clinically significant 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.

5 STUDY CONDUCT

5.1 Study Materials

The sponsor will provide investigational product which will include BHV-3000 (75 mg) IR tablets, ODT, and matching placebo.

The site will also be provided with a Regulatory binder, and IWRS Manual. Instructions on all specimens collected, as well as Laboratory Kits and Laboratory Manual will be provided by a central laboratory.

The following materials will also be provided at study start:

- Daily paper diaries for recording average daily pain, worst pain episode, record concomitant medication and procedures, rescue medications, and study drug/medications.
- Pharmacy Binder
- Drug Accountability Logs
- Rating Scales
- Investigator Brochure
- Serious Adverse Event (SAE) Forms
- Pregnancy Surveillance Forms
- Sheehan Suicidality Tracking Scale (S-STS)

The site will use a Paper Data Capture tool to submit study data. Case Report Forms (CRFs) will be prepared for all data collections including Serious Adverse Event (SAE) Reporting.

Sites will be provided with a Biohaven approved protocol and any amendments.

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

5.2 Safety Assessments

5.2.1 Vital Signs and Physical Measurements (Height and Weight)

Sitting vital sign measurements (temperature, blood pressure, respiration rate, and heart rate) will be recorded during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary.

Body weight and height will be recorded at scheduled visits, per the Schedule of Assessments.

5.2.2 Electrocardiogram (ECG)

A 12-Lead ECG will be recorded during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary.

5.2.3 Physical Exam

Subjects will undergo a complete physical exam during the screening phase and at the follow up visit at the end of the study. The Physical Exam should include at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, lymph nodes, lungs, cardiovascular, abdomen, skin, and musculoskeletal evaluation by the Principal Investigator or a medically qualified delegate. If a subject is discontinued for any reason, an attempt should be made to conduct a final physical exam.

5.2.4 Neurologic Exam

Subjects should undergo a routine neurologic exam at the screening visit. Any abnormal neurological deficit on cranial nerve examination, other than mild sensory changes in the affected trigeminal nerve, that is not consistent with a Trigeminal Neuralgia diagnosis should exclude the subject from participation.

5.2.5 Neuroimaging

Subjects should have neuroimaging prior to randomization to rule out structural lesions other than vascular compression of the trigeminal nerve or nerve root. This can include prior imaging that occurred during the patient's diagnostic work-up for trigeminal neuralgia. The patient must provide the results of this imaging to the site. If no neuroimaging is provided by the subject during the screening phase, an MRI should be done at the site prior to randomization.

5.2.6 Laboratory Assessments

Laboratory testing will include the following:

1. Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count

2. Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, BUN, uric acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase or Lipase, TSH, and T4;

3. Estimated glomerular filtration rate (eGFR) using the estimated MDRD formula will be calculated and reported at each visit that clinical laboratory tests are collected as outlined in the Schedule of Assessments;

4. Urinalysis: macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and occult blood will be performed during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary. If blood, protein, or leukocytes, are positive microscopic examination will be performed on abnormal findings;

5. Serum pregnancy test will be conducted at screening and baseline visits. Urine pregnancy tests will be performed prior to dosing at Baseline and at scheduled visits, at study visits where lab assessments are not performed, or at the discretion of the Investigator;

6. HBsAg, HCV, HIV antibody detection will be performed at screening.

7. Urine Drug Screen for drugs of abuse will be conducted as outlined in the Schedule of Assessments (Table 1).

Any lab value outside of the normal range must be brought to the attention of a physician (Investigator or Sub-Investigator) at the site. The Investigator will indicate whether or not a flagged value is of clinical significance. In addition, if warranted repeat labs can be drawn.

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5.2.8 Sheehan Suicidality Tracking Scale (Sheehan STS)

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. The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is 30 days prior; at all other visits, the recall period for completing the S-STS is since the last visit. Subjects who have a S-STS score > 0 should be immediately evaluated by the investigator. 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 event should be recorded as either an AE or SAE determined by the investigator and reported within 24 hours to the Sponsor**. Subjects with a response of 1 ("a little") to Question 2 may be allowed in the study at the Screening and/or Baseline visits and eligible to continue participation in treatment phase . Investigator's review and assessment should be documented in subject source. Subjects with a response greater than 1 on Question 2 should not be enrolled in the study.

5.3 Efficacy Assessments

According to the most recent recommendations of the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT), 6 core outcome domains (namely pain, physical functioning, emotional functioning, participant rating of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition) should be considered for

clinical research trials assessing chronic pain.[33] Outcome measures for the current study were chosen in accordance with these guidelines.

5.3.1 Numeric Pain Rating Scale (NPRS)

The Numeric Pain Rating Scale is a segmented, 11-item, numeric scale ranging from 0-10. The NPRS is anchored by items ranging from "0" which represents "no pain;" to "10" which reflects "worst pain imaginable."

Subjects will be given a paper diary to record daily pain intensity on the Numeric Pain Rating Scale. They will be asked to keep a daily record of their average pain intensity over a 24 hour period. A reduction of 2 points on the NPRS has been chosen to reflect a clinically important improvement in pain symptoms.

5.3.2 Penn Facial Pain Scale

The Penn Facial Pain Scale-Revised a 12-item scale used to assess the impact of trigeminal neuralgia pain on health-related quality of life and activities of daily living. Developers of the original Penn Facial Pain Scale applied standard validation metrics (e.g., concept elicitation, cognitive debrief, reliability, responsiveness) to the Penn Facial Pain Scale-Revised as a measure for use in assessing treatment impacts on TN symptoms.[34] The response categories for each of the 12 items range from 0 ('does not interfere') to 10 ('completely interferes'). The specified recall period is for the 'past week.' Anchors to scale 0 to 10 were added by Biohaven.

Subjects will be asked to complete the Penn Facial Pain Scale-Revised at the beginning and end of each treatment phase, as outlined in the Schedule of Assessments.

5.3.3 Pain Disability Index

The Pain Disability Index is designed to measure the degree to which a patient's daily life is disrupted by their pain. The seven items of the scale reflect different "life activities" and are scored on an 11-point Likert Scale, with "0" representing "no disability" and "10" representing "worst disability."

Subjects will be asked to complete the Pain Disability Index at the beginning and end of each treatment phase, as outlined in the Schedule of Assessments.

5.3.4 Patient Global Impression of Change Scale (PGIC)

The PGIC is a patient-rated scale which assesses how the subject's current illness state has improved or worsened relative to the baseline visit. The subject is asked to rate a change in their overall disease condition on a 7-point scale, from 1 ('no change') to 7 ('a great deal better'). The PGIC is a global index scale that may be used to rate the response of a condition to a therapy. The PGIC will be conducted at the beginning and end of each treatment phase as indicated in the Schedule of Assessments and Events.

5.3.5 Rescue Medication

The subject's use of rescue medication will be recorded daily in the paper diary. After dosing with study drug/medication, all other Trigeminal Neuralgia medication is prohibited during the 2 hours post daily dose. However, a subject who does not experience relief of the Trigeminal Neuralgia at the end of two hours after dosing, will be permitted to use the following rescue medications: aspirin, ibuprofen, acetaminophen up to 1000mg/day, 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 daily dose of study drug/medication.

5.3.6 Worst Pain Episode

Using the 11-point Numeric Pain Rating Scale (NPRS) described above, subjects will be asked to record an intensity rating of their worst pain episode over a 24-hour period daily in their paper diary.

5.4 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 or sponsor, 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
- Please see section 5.2.8 for guidance on study discontinuation based on results from the S-STS.
- Subjects who discontinue early from the Double-Blind Phase are not eligible to enter the Open-label Extension Phase.

All subjects who discontinue should comply with protocol specified Follow-Up Safety Visit procedures as outlined in Table 1 or Table 2. The only exception to this requirement is when a subject withdraws consent for all study procedures, lost to follow up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

6 STUDY DRUG/MEDICATION MANAGEMENT

6.1 Description of Study Drug/Medication

6.1.1 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 the local regulations. It is the responsibility of the investigator to ensure that the investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

- During the Double-Blind Treatment Phase, investigational product (study drug/medication) is rimegepant (BHV-3000) 75 mg Immediate Release (IR) Tablet or matching placebo dosed daily.

- During the Open-label Extension Phase, investigational product (study drug/medication) is rimegepant (BHV-3000) 75 mg orally disintegrating tablet (ODT) dosed daily.

- All subjects, regardless of the treatment phase, will take study drug/medication daily.

NOTE: During the Double-blind and Open-label Extension Phase, if a dose of study drug/medication for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the **subject paper study log**.

6.1.2 Packaging, Shipment, and Storage

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

6.2 Dose and Administration

6.2.1 Method of Assigning Subject Identification

The investigator or designee will need to access an Interactive Web-based Response System (IWRS) in order to register each subject in the Double-Blind Treatment Phase. Initially the investigator or designee will enter the subject into the study at the Screening Visit after informed

consent is obtained and a subject number is assigned. After completion of all screening evaluations, all eligible subjects will be randomized, in a 1:1 into one of two treatment sequences to receive 75 mg IR tablet of rimegepant or Placebo, using a 2-period, 2-sequence, crossover design. Patients with atypical TN and typical TN will be stratified equally into each of the two treatment sequences, with atypical TN patients not exceeding 50 percent of the subjects.

Study Staff will access the IWRS at each scheduled study visit throughout the Double-Blind Treatment Phase. The IWRS system will assign specific bottle numbers for all blinded study drug/medication to be dispensed to the subject. Once a bottle has been assigned it cannot be dispensed to another study subject.

During the Open-Label Extension Phase, study drug/medication (ODTs) will be supplied to the sites in bulk and specific drug wallets will be dispensed outside of the IWRS by the study staff to each subject. Once a wallet has been assigned it cannot be dispensed to another study subject.

Once a subject completes the Double-Blind Treatment Phase, or if a subject is discontinued early from the study, the investigator or designee must access the IWRS to discontinue the patient from participation in the study.

6.2.2 Selection and Timing of Dose Administration

During the Double-Blind Phase of the study, subjects will be randomized to a sequence of either rimegepant (75 mg QD) and then placebo or placebo then rimegepant (75 mg QD) in a 2-sequence, 2-period, crossover design. Study drug/medication will be dispensed at the baseline visit and at Days 14 and 21. Subjects should take the first dose the day of the baseline visit. Study drug/medication should be administered in the morning without regard to meals. Subjects who showed continued compliance during the Double-Blind Phase may choose to enter a 12 week Open-label Extension Phase with daily dosing of rimegepant (75 mg QD) ODT. Open-label study drug/medication will be dispensed at Day 35 visit for subjects who enter the Open-label Extension Phase. Subjects should take the first dose of OLE study drug/medication on Day 36.

During the Open-label Extension Phase, if a dose of study drug/medication for a given day is missed, lost, or otherwise unable to be taken, the subject should document that as a missed dose on the **subject paper study log.**

6.2.3 Dose Modifications

There will be no dose adjustments in this study.

6.3 Blinding and Unblinding

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

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

A pharmacokinetics, IWRS randomization manager, and pharmacovigilance role may be unblinded before data are more generally unblinded after the Randomized Phase of the study. Except as noted above, other members of the BHV research team will remain blinded.

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

6.4 Treatment Compliance

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

Subjects will be counseled on the importance of taking the study drug/medication as directed at all study visits. During the Double-Blind Phase, if poor compliance (i.e., multiple missed doses resulting in less than 80% overall compliance during the Double-Blind Phase), the subject will be re-counseled on proper drug adherence and should not be considered for participation in the Open-Label Extension Phase. Any subject having poor compliance during the Open-Label Extension Phase resulting in less than 80% should be re-counseled and discontinuation of the subject from the trial should be considered if adherence does not improve.

6.5 Destruction and Return of the Study drug/medication

All unused and/or partially used study drug/medication can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible BHV Study monitor or the sponsor's designee.

If it is site policy to destroy study drug/medication 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 drug/medications can only be destroyed after being inspected and reconciled by the responsible BHV Study monitor or the sponsor's designee.

7 ADVERSE EVENTS

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

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

Subjects should be instructed to notify the Investigator when a Serious Adverse Event occurs.

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

8 SERIOUS ADVERSE EVENT

8.1 Definition of Serious Adverse Event

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

- 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 BVH-3000 (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:
    - 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

8.1.1 Definition of Terms

Mild: A mild adverse event is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A moderate adverse event is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.

Severe: A severe adverse event interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Life threatening: An AE is life threatening if the subject was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without

evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

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

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.

8.2 Collection and Reporting Serious Adverse Events

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug/medication, 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/medication or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

If the investigator believes that an SAE is not related to the study drug/medication, 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/medication, overdose (see section 8.2.1), potential drug induced liver injury (see section 8.2.3) and pregnancies (see section 8.2.2) must be reported within 24 hours of the Investigator becoming aware of the event. For this study we will be capturing SAEs through electronic data capture (EDC) and on the SAE form.

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to PPD within 24 hours of learning of the event. PPD will then immediately notify the Biohaven Medical Monitor of the event. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for submitting the SAE information to PPD (i.e.: event term, start stop dates, causality, severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to PPD Pharmacovigilance (PVG). A written description of any serious adverse event, using the PPD SAE report form, must be sent to PPD PVG by facsimile (fax) within 24 hours after awareness of the event:

North America – 1-888-488-9697

If a form is unable to be submitted within 24 hours, the SAE may be reported by telephone via the Safety Hotline Number:

North America – 1-800-201-8725

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/medication or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

- Sender of report (Site number, Investigator name)
- Subject identification (subject number)
- Protocol number
- SAE term (if an SAE is being reported)

8.2.1 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered both excessive and medically important. Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved rimegepant (BHV-3000) 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.

8.2.2 Pregnancy

If following initiation of the investigational product, it is subsequently discovered that a 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 will be 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.

Sites should instruct patients to contact the investigator if they become pregnant during the course of the study. The investigator must immediately notify PPD of the event within 24 hours of the Investigator becoming aware of the information. The site must complete a Pregnancy Report Form. Follow up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must also be reported on a Pregnancy Report Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to PPD.

8.2.3 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 8.2.

Potential drug induced liver injury is defined as:

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

  AND

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

  AND

- 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 should immediately be contacted for further instruction on dosing adjustments and whether the patient must discontinue from the trial and appropriate follow up requirements.

8.3 Non-Serious Adverse Events

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

8.3.1 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 subject.

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/medication or those that are present at the end of study treatment.

8.3.2 Laboratory Test Abnormalities

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

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

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

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

9 STATISTICS

Detailed plans for analysis will be summarized in a separate Statistical Analysis Plan document, to be written and approved prior to database unblinding. A summary of statistical aspects of the design and intended analysis is provided here.

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 drug/medications; adverse events; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject within the period.

9.2 Sample Size

The sample size for this study will be approximately 60 randomized patients. Approximately 120 patients will be screened, assuming no more than 50 percent of patients will be ineligible for randomization.

The calculation for the sample size is based on a paired t-test crossover design, assuming a low correlation ($r = 0.2$) between the active and placebo response to treatment. Assuming a paired difference standard deviation of 3.8, 60 randomized patients will provide >90% power to detect a 2-point difference between rimegepant and placebo using a two-sided significance level of 0.05 and a 20% dropout rate with no imputation.

9.3 Populations for Analysis

The following analysis sets are defined for this protocol:

- Enrolled subjects: Patients who signed an informed consent form and were assigned a Patient Identification number (PID)

- Randomized subjects: Enrolled subjects who received a treatment assignment from the Interactive Web Response System (IWRS) (rimegepant or placebo).

- Treated subjects: Enrolled subjects who received at least 1 dose of blinded study therapy (rimegepant or placebo).

- Modified Intent to Treat (mITT) subjects: Randomized subjects that received at least one dose of study therapy and provided a baseline and at least one post-baseline efficacy assessment in each sequence

9.4 Statistical Methods

9.4.1 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be summarized for all treated subjects. A separate set of tabulations will be made for subjects enrolled but not randomized.

9.4.2 Primary Endpoint(s)

The primary endpoint will estimate the effect of rimegepant relative to placebo over 2 weeks of treatment when added to a standard of care therapy, and regardless of the effect of other concomitant medication. The pain score will be the average of the daily 11-point NPRS recorded within each period using the mITT population. This treatment effect will be summarized as the difference in the average daily score in total NPRS between rimegepant and placebo.

The treatment comparison of rimegepant versus placebo will use a two-sided alpha level of 0.05 and a Mixed Model for Repeated Measures (MMRM) that will include fixed effect factors for treatment group, randomization strata (typical/atypical) and sequence, with baseline NPRS as a covariate and subject as a random factor. MMRM-based estimates with corresponding SD, 95% CI, and p-value from MMRM will also be presented.

Observed values and changes from baseline in NPRS will also be summarized using descriptive statistics over time by treatment group.

9.4.3 Secondary Endpoint(s)

Continuous secondary, change-from-baseline efficacy endpoints (Penn Facial Pain Scale, Pain Disability Index , Worst pain episode using the NPRS) will be analyzed using the same methodology as the primary endpoint. As the PGI-C, does not have a baseline value, the summary will be computed using an analysis of variance, that will include fixed effect factors for treatment group, randomization strata (typical/atypical) and sequence. Achievement of at least a 2-point reduction in NPRS will be analyzed using logistic regression, that will include terms for treatment group, randomization strata (typical/atypical), sequence, and baseline NPRS.

9.4.4 Adjustment for Multiplicity

Type 1 error will be controlled for the primary and secondary efficacy endpoints by testing them with a gate-keeping procedure. The primary endpoint will be tested at a two-sided alpha level of 0.05. If this test is significant, then the secondary efficacy endpoints will be tested using Hochberg's procedure. If the test of the primary endpoint is not significant, then the unadjusted p-values for the secondary endpoints will be presented only for descriptive purposes, and no conclusions will be drawn from this result

CCI

CCI

9.4.6 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 and overall: SAEs; all AEs, nonserious AEs, AEs by intensity; AEs by relatedness and clinically relevant laboratory abnormalities.

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

9.5 Schedule of Analyses

The final analysis of the Double-blind Treatment Phase will occur after the last subject randomized has completed this phase of the study or discontinues from the Double-blind Treatment Phase. The study will be unblinded and analyses will summarize all efficacy, safety, laboratory and other data collected throughout the double-blind phase of study.

A final analysis of the study will be completed after the last subject has completed their last study visit of the Open-Label Extension Phase of the study. These analyses will summarize all efficacy, safety, laboratory and other data collected throughout the Open-Label Extension Phase of the study. In addition throughout the study, data may be locked, analyses conducted, and reports produced as required to support safety monitoring or regulatory requirements.

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 study 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., loss 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 drug/medication BHV-3000 has been tested and found to be well tolerated. 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 IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IRB/IEC favorable written approvals for the above-mentioned study documents. 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 IRB/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 IRB/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.

Paper CRFs will be prepared for all data collections fields.

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.

11 RECORDS AND MANAGEMENT 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/medication is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

1. Amount of study drug/medication 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. Retained samples for bioavailability/bioequivalence, if applicable;
9. Record of dates and initials of personnel responsible for IM dispensing and accountability.

11.1 Source Documentation

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

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

11.2 Study Files and Record Retention

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

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by 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.

13 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.

14 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 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.

15 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 and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials, screening and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

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17 APPENDICES

Appendix 1: Names of Study Personnel

Sponsor:	Biohaven Pharmaceutical Holding Company c/o Biohaven Pharmaceuticals, Inc. 234 Church Street New Haven, CT 06510
Medical Monitor:	PPD
Clinical Research Organizations:	PPD
Central Laboratory:	LabConnect, LLC
Pharmacovigilance Vendor:	PPD

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

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

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

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

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

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

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

As described in the study protocol, concomitant use of strong P-gp inhibitors is prohibited.

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

Resources:

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

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

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