DRUG:	BHV-3000 (rimegepant)
STUDY NUMBER(S):	BHV3000-317
PROTOCOL TITLE:	A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD)
IND NUMBER:	158955
SPONSOR:	Biohaven Pharmaceuticals Holding Company Limited
ORIGINAL PROTOCOL DATE:	09 December 2021
VERSION NUMBER:	Amended Protocol Version 3
VERSION DATE:	31 March 2022

SUMMARY OF CHANGES

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	09 December 2021
Version 2.0 – Amendment 1	To further clarify how a subject should choose which rescue medication to take, the following sentence has been added to the Study Design section in the synopsis and to Sections 4.1.2.1 and 5.5: Subjects may administer whichever protocol permitted standard of care rescue medication they choose to reduce symptoms and that they have available. The following sentence was added to the same sections to clarify how a subject should choose which medication to take when they have non-qualifying TMD pain: Subjects may administer whichever protocol permitted standard of care medication they choose to reduce symptoms and that they have available. To provide guidance to women of childbearing potential who will administer a home pregnancy test, Table 1 Schedule of Activities and Section 6.3.4.2 have been updated to include the following statement: Subjects will be provided with the accompanying package insert that contains instructions for use and interpretation of results. To ensure safety to subjects and ensure that subjects do not experience opioid withdrawal, Section 5.4, Number 10 was updated from "Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone and hydrocodone) is prohibited for at least 2 days prior to randomization" to "Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone and hydrocodone) is prohibited for at least 30 days prior to the Screening Visit and throughout the study". To clarify that the eDiary will be recording the date and time subjects take study therapy and the eDiary is set up to follow study-specific specifications developed by the eDiary Vendor and the Sponsor, Section 4.1.2.1 was updated from "Subjects will record the date and time study therapy was taken in their eDiary" to "Subjects will record the date and time study therapy was taken in their eDiary according to the eDiary vendor's specifications." In Section 5.5, Cyclobenzaprine was removed from the list of allowable daily medication because cyclobenzaprine is allowed as a rescue medication and as a permitted medication to treat a non-qualifying TMD-associated pain (i.e., pain < 6 on a NRS[0-10] in the jaw and/or temple area on either side).	09 February 2022

Version 3.0 – Amendment 2	Synopsis and Section 2.1 Primary Objective(s): The primary objective was changed from To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of Temporomandibular Disorders ***on change from baseline of pain on NRS (0-10) score at 2 hours post-dose***. To To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of Temporomandibular Disorders ***on the time-weighted sum of pain intensity difference from baseline scores for the first 2 hours post-dose (SPID-2)***. Synopsis and Section 2.2 Secondary Objective(s): The secondary objectives were changed from: ***1. To evaluate rimegepant compared to placebo on ≥ 30% reduction from baseline of pain NRS (0-10) score at 2 hours post-dose. (this objective was deleted)*** ***2. To evaluate rimegepant compared to placebo on ≥ 50% reduction from baseline of pain NRS (0-10) score at 2 hours post-dose. (this objective was deleted)*** 3. To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose. 4. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment. To ***1. To evaluate rimegepant compared with placebo on the time-weighted sum of pain intensity difference from baseline scores for the first 24 hours post-dose (SPID-24). (this objective was added*** ***2. To evaluate rimegepant compared to placebo on change from baseline of pain on NRS (0-10) score at 2 hours post-dose.(this was the old primary objective. It was moved and is now a secondary objective)*** 3. To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose. ***4. To evaluate rimegepant compared to placebo on time to onset of meaningful pain relief post-dose. (this is a new secondary objective)*** ***5. To evaluate rimegepant compared to placebo on time to onset of initial pain relief post-dose. (this is a new secondary objective)***	31 March 2022

	6. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment. Synopsis and Section 2.3 CCI : Two secondary objectives were moved to CCI The two are: CCI The remainder of the CCI remained unchanged. Section 3.1 Primary Endpoint(s) was changed from: ***Change from baseline of pain will be assessed using the number of evaluable*** subjects that report TMD-associated pain level of ≥ 6 on NRS (0-10) at baseline and report pain level at 2 hours post-dose recorded in the eDiary. To: ***Difference in SPID-2 scores between treatment groups will be assessed across the first 2 hours post-dose using the number of randomized and treated*** subjects. Section 3.2 Secondary Endpoints was changed from: ***1. Greater than 30% reduction from baseline of pain will be assessed using the number of subjects that experience at least a 30% reduction from baseline of pain on NRS (0-10) at 2 hours post-dose recorded in the eDiary (this was removed).*** ***2. Greater than 50% reduction from baseline of pain will be assessed using the number of subjects that experience at least a 50% reduction from baseline of pain on NRS (0-10) at 2 hours post-dose recorded in the eDiary. (this was removed)*** 3. **Pain freedom** will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on NRS (0-10). 4. The **probability of requiring rescue medication** will be assessed using the number of subjects that take rescue medication within 24 after administration of study medication (rimegepant or placebo).	

	To: ***1. Difference in SPID-24 scores between treatment groups will be assessed across the first 24 hours post-dose using the number of randomized and treated subjects on NRS (0-10). (this was added)*** ***2. Change from baseline will be assessed at 2 hours post-dose using the number of randomized and treated subjects. (this was added)*** 3. **Pain freedom** will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on NRS (0-10). ***4. Onset of meaningful pain relief will be assessed by the first nominal timepoint at which the pain on NRS (0-10) decreases by 30% from baseline. (this was added)*** ***5. Onset of initial pain relief will be assessed by the first nominal timepoint at which the pain on NRS (0-10) decreases by 1 point from baseline. (this was added)*** 6. The **probability of requiring rescue medication** will be assessed using the number of subjects that take rescue medication within 24 hours after administration of study medication (rimegepant or placebo). 5.2 Inclusion Criteria #2.e: The following text was removed The following is not exclusionary but does not qualify as primary diagnosis for inclusion: ! Disc disorders (I.2.A.1-4), when not associated with mechanically induced arthralgia ! Degenerative joint diseases (I.3.A.1-2) ! Tendonitis (II.1.B) ! Contracture (II.2) ! Hypertrophy (II.3) ! Headache attributed to TMD (III.1) Section 5.3 Exclusion Criteria Number 1.c.ii. Joint Disorders was clarified. Previous text: i. Joint Disorders: (1) Disc disorders (I.2.A.1-4), when	

	associated with mechanically induced arthralgia (2) Hypomobility disorders ***other than disc disorders (I.2.B)*** (3) Hypermobility disorders (I.2.C.) New text: i. Joint Disorders: (1) Disc disorders (I.2.A.1-4) **only** when associated with mechanically induced arthralgia (2) ***Other*** hypomobility disorders (I.2.B***), such as adhesions/adherence, ankylosis*** (3) Hypermobility disorders (I.2.C.), ***such as subluxation, luxation*** In addition, Contracture (II.2) was added as vii, which also caused the remainder of the list under section 2.C to be renumbered viii through xi. Section 5.3, 1.d was clarified as follows: From: d. Subject has a history of neuropathic/idiopathic pain disorder. To: d. Subject has a history of neuropathic ***(e.g., trigeminal neuralgia, postherpetic neuralgia) or*** idiopathic pain disorder. Section 5.3 Exclusion Criteria, 5.g.: Severe hepatic impairment (Child-Pugh C) is exclusionary in all cases was added. Section 9.2 Sample Size was updated from If 80% of the 200 randomized (100 per treatment arm) ***have a TMD associated pain reaching intensity of ≥ 6 on the NRS prior to treatment, and provide at least one post baseline efficacy data point***, we expect roughly 160 total or 80 per treatment group in the ***Modified Intent to Treat (mITT)*** population for analysis. To If 80% of the 200 randomized (100 per treatment arm) ***treat with study drug,*** we expect roughly 160 total or 80 per treatment group in the ***randomized and treated*** population for analysis.	

	The third paragraph in Section 9.3 Population for Analysis was updated from The set of treated subjects consists of all subjects who take study therapy (rimegepant or placebo) to The set of treated subjects consists of all ***randomized*** subjects who take study therapy (rimegepant or placebo). In addition the following paragraph was deleted from Section 9.3: ***The mITT set consists of randomized subjects that take study therapy, have a TMD associated pain in the jaw and/or temple area which reaches pain intensity of ≥ 6 on the NRS (0-10) prior to treatment, and provide at least one post baseline efficacy data point***, Section 9.4.2 Primary Endpoint(s) was updated from The ***change from baseline efficacy endpoint*** is analyzed on the ***mITT*** population using ***a generalized linear mixed effect*** model that includes ***subject as a random effect***, the baseline NRS (0-10) value as a covariate, and ***fixed*** effects for treatment group, stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms), ***scheduled time point, and time point by treatment group interaction. Time points included in the model are nominally at 15, 30, 45, 60, 90 and 120 minutes post-dose. Repeated measurements within-subject will be modeled using an unstructured covariance structure for within-subject error. In the case that the model fails to converge, a Huynh-Feldt error structure will be attempted, followed by an AR(1) structure. Error degrees of freedom will be calculated using a Kenward-Roger approximation.*** ***The difference*** estimate (rimegepant - placebo), ***standard error***, 95% ***confidence interval***, and p-value ***will be reported for 2 hours post-dose.*** In the event a subject uses a non-study rescue medication on or before 2 hours post-dose, all data points after rescue medication was administered will be set to ***missing*** (RM = M: Rescue medication use = ***Missing***). Likewise, if a subject fails to log their pain score after study drug is administered, through 2 hours post-dose, this data will be ***considered missing*** (NC = M: Non-completers = ***Missing***). Sensitivity analyses will be described in the SAP. To The ***SPID-2 will be calculated by multiplying the PID score (difference between NRS at each time point and baseline NRS) at each post-dose timepoint by the duration (in hours) since the preceding timepoint, then summing the values over the 2 hours. This is*** analyzed on the ***treated*** population using ***an analysis of covariance (ANCOVA)*** model that includes the baseline NRS (0-10) value as a covariate, and ***main*** effects for treatment group ***and*** stratification factor (use of daily medications / oral devices	

	to reduce the intensity of TMD symptoms). The ***least squares mean (LS mean), standard error (SE), and 95% confidence interval (CI) for each treatment group will be reported, as well as the*** difference estimate (rimegepant - placebo), ***SE***, 95% ***CI***, and p-value. ***Intercurrent events will be treated as failures, with the assumption that the subject does not improve once the intercurrent event occurs.*** In the event a subject uses a non-study rescue medication on or before 2 hours post-dose, all data points after rescue medication was administered will be set to **the last available observation prior to rescue medication usage** (RM = Rescue medication use, F = Failure). Likewise, if a subject fails to log their pain score **at any time** after study drug is administered, through 2 hours post-dose, this data will be ***imputed to the last available observation*** (NC = Non-completers, F= Failure). Sensitivity analyses will be described in the SAP. The first paragraph in Section 9.4.3 Secondary Endpoint(s) was updated from If the primary endpoint test is significant, then the secondary endpoints ***are evaluated using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at p=0.05. These secondary endpoints will be tested in the order shown in the Study Objectives section of this protocol***. Secondary endpoints will be analyzed on the ***mITT*** population. to If the primary endpoint test is significant ***at alpha ∀ 0.05, then the secondary endpoints will be analyzed at an alpha level of ∀ 0.05 using Hochberg's procedure.*** Secondary endpoints will be analyzed on the ***treated*** population. Section 9.4.3.1 SPID-24; Section 9.4.3.2 Change from Baseline of Pain on NRS; Section 9.4.3.4 Time to Onset of Meaningful Pain Relief; section 9.4.3.5 Time to Onset of Initial Pain Relief were all added. Sections 9.4.3.3 Pain Freedom at 2 Hours, and 9.4.3.6 Rescue Medication Use through 24 Hours are new sections that were edited from previous Section 9.4.3 text. Section 9.4.4 Adjustment for Multiplicity was updated from Type 1 error is ***controlled through the use of hierarchical testing***. The significance of the primary endpoint is evaluated at the two-sided alpha level of 0.05. If the primary endpoint is significant, then the ***following*** secondary endpoints ***will be tested hierarchically in the following order, each at the 0.05 level***: ***1. Proportion of subjects with a ≥ 30% reduction from baseline of pain NRS (0-10) score at 2 hours post-dose.***	

	2. Proportion of subjects with a ≥ 50% reduction from baseline of pain NRS (0-10) score at 2 hours post-dose. ***3. Proportion of subjects that are pain free at 2 hours post-dose.*** ***4. Proportion of subjects requiring rescue medication within 24 hours of initial treatment.*** ***Thus, a secondary endpoint will be tested only if the preceding secondary endpoint in the hierarchy is determined to be significant. Descriptive p-values will be provided for any non-significant secondary endpoints and comparative*** CCI [redacted] [redacted] The significance of the primary endpoint is evaluated at the two-sided alpha level of 0.05. If the primary endpoint is significant, then ***the*** secondary endpoints are tested using Hochberg's procedure. No attempt will be made to adjust for multiplicity when testing the CCI [redacted] Section 9.4.5 Missing Data was updated from For the primary ***endpoint of change in NRS from baseline, subjects who fail to record their pain at 2 hours post-dose will be considered missing (NC = M); the MMRM analysis model will be used, which assumes missing data are missing at random (MAR).*** For the secondary endpoints of proportion of subjects ***with 30% reduction from baseline of pain at 2 hours post-dose, 50% reduction from baseline of pain at 2 hours post-dose, and*** pain free***dom*** at 2 hours post-dose, missing data at 2 hours post-dose will be imputed as a failure (NC = F). For the secondary endpoint of proportion of subjects who use rescue medication through 24 hours-post dose, there will be no imputation for missing data, the analysis will be based on non-missing, observed data. Additional methods for handling of missing data, including sensitivity analyses, will be described in detail in the SAP. to For the primary ***and secondary endpoints of SPID-2, SPID-24, change in NRS from baseline, time to onset of***	

	meaningful pain relief, and time to onset of initial pain relief, subjects who fail to record their pain during the timeframe of interest for each endpoint will be considered failures (NC = F) and this data will be imputed to the last available observation prior to the missing data occurrence. For the secondary endpoint of proportion of subjects ***that are pain free at 2 hours post-dose***, missing data at 2 hours post-dose will be imputed as a failure (NC = F), ***and these subjects will not be considered as having achieved pain freedom.*** For the secondary endpoint of proportion of subjects who use rescue medication through 24 hours-post dose, there will be no imputation for missing data, the analysis will be based on non-missing, observed data. Additional methods for handling of missing data, including sensitivity analyses, will be described in detail in the SAP. Section 9.4.6 Rescue Medication was updated from For the primary ***endpoint of change from baseline in NRS, the intercurrent event of use of*** non-study rescue medications on or before the time point of interest ***(2 hours post-dose)*** will be handled ***with a hypothetical strategy***. Specifically, the assumption will be that ***had the subject not used a rescue medication, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did not use rescue medication. These data points after rescue medication was administered will be set to missing (RM = M).*** For the secondary endpoints ***of proportion of subjects with 30% reduction from baseline of pain at 2 hours post-dose, 50% reduction from baseline of pain at 2 hours post-dose, and*** pain freedom at 2 hours post-dose, subjects that take rescue medication on or before the time point of interest (2 hours post-dose) will be considered as failures (RM = F). Rescue medications are described in more detail in Section 5.5 to For the primary ***and secondary endpoints of SPID-2, SPID-24, change in NRS from baseline, time to onset of meaningful pain relief, and time to onset of initial pain relief,*** use of non-study rescue medications on or before the time point of interest ***(2 hours post-dose or 24 hours post-dose) will be handled as failures (RM = F). Specifically, the assumption will be that once the subject has used a rescue medication, their pain will not improve any further and these data points will be set to the last value recorded prior to the use of the rescue medication.***	

	For the ***secondary endpoint of pain freedom at 2 hours post-dose***, subjects that take rescue medication on or before the time point of interest (2 hours post-dose) will be considered as failures (RM = F). Rescue medications are described in more detail in Section 5.5	

BHV3000-317

A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD)

Protocol v3.0 Amendment 2: 31Mar2022

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to BHV-3000 (rimegepant) are the confidential and proprietary information of Biohaven Pharmaceutical Holding Company Limited.

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

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Biohaven Pharmaceutical Holding Company Limited or specified designees. I will discuss the material with them to ensure that they are fully informed about BHV-3000 (rimegepant) and the study.

Principal Investigator Name (printed)	Signature	Date

STUDY SUMMARY (SYNOPSIS)

Title:	A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Acute Treatment of Temporomandibular Disorders (TMD)
Rationale:	Temporomandibular Disorders (TMD) is a heterogenous group of 30+ conditions involving the temporomandibular joint and surrounding muscles and tissues. It is characterized by pain, functional limitations of the mandible, and/or clicking in the TMJ during motion. TMD is considered the most common cause of non-dental facial pain, with reported prevalence ranging from 4.6-25% of the US population.[1] Despite high prevalence and disability associated with TMD, there are no clear guidelines for treatment or evidence to support a single agent. Treatment can be invasive or non-invasive and first-line approach is usually a combination of self-care techniques and NSAIDs.[2] The proposed study is based on the evolving preclinical and clinical evidence suggesting a role for calcitonin gene related peptide (CGRP) in the development of TMD. BHV-3000 (rimegepant) is a small molecule CGRP receptor antagonist that is being developed for the potential treatment of TMD. The data from this study will allow characterization of the safety and efficacy of orally disintegrating tablet (ODT) of rimegepant versus placebo in the treatment of Temporomandibular Disorders.
Target Population:	The study will recruit male and female subjects 18 years of age and older with a history of TMD diagnosed by healthcare provider that meets the criteria consistent with a diagnosis according to the DC/TMD (Diagnostic Criteria for Temporomandibular Disorders) and includes at least one of the following: Myalgia (II.1.A.1-3) and/or Arthralgia (I.1.A.).[3] Subjects will have had a minimum 3-month to a maximum 5-year history of TMD prior to the Screening Visit. Subjects must have had at least one instance of TMD-associated pain in the jaw and/or temple area on either side that reached intensity of # 6 on a 11-point Numerical Rating Scale (NRS, 0-10) in the past 30 days prior to the Screening Visit.
Number of Subjects:	Approximately 200 subjects will be randomized to result in 160 (80 per arm) evaluable subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of daily medications and/or oral devices to reduce the

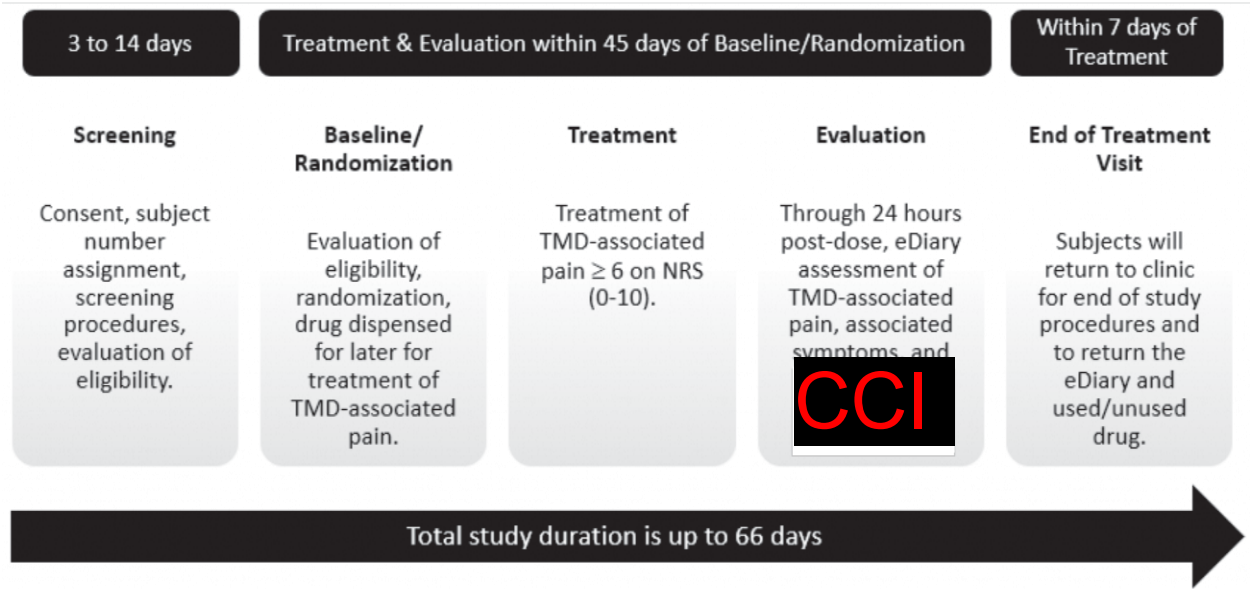
	intensity of TMD symptoms (yes or no).
Objectives (Primary):	To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of Temporomandibular Disorders on the time-weighted sum of pain intensity difference from baseline scores for the first 2 hours post-dose (SPID-2).
Objectives (Secondary):	1. To evaluate rimegepant compared with placebo on the time-weighted sum of pain intensity difference from baseline scores for the first 24 hours post-dose (SPID-24). 2. To evaluate rimegepant compared to placebo on change from baseline of pain on NRS (0-10) score at 2 hours post-dose. 3. To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose. 4. To evaluate rimegepant compared to placebo on time to onset of meaningful pain relief post-dose. 5. To evaluate rimegepant compared to placebo on time to onset of initial pain relief post-dose. 6. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment. CCI [redacted]

	CCI [redacted]
Study Design:	This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo for the acute treatment of Temporomandibular Disorders (TMD). The study drug will be rimegepant presented in a 75 mg ODT or matching placebo. A subject whose TMD-associated pain of # 6 on a NRS (0-10) and who is otherwise found acceptable for entry into this trial based on inclusion and exclusion criteria will first participate in the screening phase (3 to 14 day period). Subjects must remain on the same dose of daily medications used to reduce the intensity of TMD symptoms from screening through the duration of the study and may not start new daily medication. Subjects must remain on the consistent use of oral devices used to reduce the intensity of TMD symptoms from screening through the duration of the study and may not start use of new oral devices. After randomization, the subject will be dispensed a single dose of the double-blind study medication. The subject will be instructed to take their study medication, as an outpatient, when (if) they have an TMD-associated pain in the jaw and/or temple area on either side which reaches pain intensity of # 6 on the NRS (0-10). The subject will record efficacy data in an eDiary for 24 hours after taking study medication. CCI [redacted] Pain severity will be recorded using a NRS (0-10) at time of taking study medication and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 4, 8 and 24 hours. CCI [redacted] The subject will be instructed to

	telephone the study center immediately if a severe or serious adverse event occurs. At the end of 2 hours after dosing with study medication (and after the 2-hour assessments have been completed on the eDiary), subjects will be permitted to use the following rescue medication: acetaminophen (up to 1000 mg/day); or aspirin, ibuprofen, naproxen (or any other type of non-steroidal anti-inflammatory [NSAID]), or cyclobenzaprine (all up to the daily recommended dose indicated on the drug packaging). Subjects may administer whichever protocol permitted standard of care rescue medication they choose to reduce symptoms and that they have available. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. If at the end of 24 hours after dosing with study medication (but before the End of Treatment Visit) subjects are in need of pain relief, they may take their prescribed standard of care medications, including muscle relaxants if not contraindicated, provided all of the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids and butalbital compounds are not allowed on this study. Similarly, if the TMD-associated pain is relieved by study medication at 2 hours after dosing but then recurs to a pain intensity of # 6 on the NRS (0-10) between 2 and 24 hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete his or her eDiary for up to 24-four hours after consuming the study medication. During the [up to] 66 days the subject is participating in the study, if the subject has a non-qualifying TMD-associated pain (i.e., pain < 6 on a NRS[(0-10]) in the jaw and/or temple area on either side), the subject is permitted to use only the following medications: acetaminophen (up to 1000 mg/day); or aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-inflammatory [NSAID]), or cyclobenzaprine (all up to the daily recommended dose indicated on the drug packaging). Subjects may administer whichever protocol permitted standard of care medication they choose to reduce symptoms and that they have available. Subjects will return to the study site within 7 days (+2) of study treatment for review of the eDiary, assessment of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a subject has NOT experienced a TMD-associated pain of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures. All subjects must return used/unused study medication and eDiary to the study center.

STUDY SCHEMATIC

BHV3000-317 Acute Treatment of Temporomandibular Disorders Study



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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGRP	Calcitonin Gene Related Peptide
CRF	Case Report Form
C-SSRS	Columbia Suicidality Severity Rating Scale
ECG	Electrocardiogram
EOD	Every other day
ePRO	Electronic Patient Reported Outcome
GCP	Good Clinical Practice
HRT	Hormone Replacement Therapy
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
CCI	[redacted]
mg	Milligram
mm	Millimeter
min	Minute
NRS	Numerical Rating Scale
ODT	Oral disintegrating tablet
PK	Pharmacokinetic
PRN	As needed pro re nata
SAE	Serious Adverse Event
TMD	Temporomandibular Disorder
TMJ	Temporomandibular Joint
ULN	Upper Limit of Normal

1 INTRODUCTION AND RATIONALE

1.1 Background

Temporomandibular disorders are a large group of conditions associated with the temporomandibular joint, masticatory muscles, and surrounding musculoskeletal tissues.

Most common symptoms are pain in the jaw and/or temple area, masticatory muscle soreness, functional limitations of the jaw and "clicking" sounds in the temporomandibular joint (TMJ).[4,5] Other associated symptoms may include ear pain, headache, neck pain, and teeth grinding (bruxism).[2,6] Symptoms can range from mild and intermittent to severe and continuous causing significant disability, and a reduction in quality of life and work productivity.[4,6] In the epidemiological studies, the prevalence ranged between 4.6 - 25% of the US population.[1,6]

The etiology of TMD is multifactorial, encompassing biologic, environmental, social, behavioral, and multiple co-morbid factors in the development. In addition, multiple medical conditions co-occur with TMD, such as headaches, fibromyalgia, back pain, and irritable bowel syndrome.[7]

Diagnosis is primarily based on patient history and physical exam, while imaging modalities are typically reserved for those with severe and persistent symptoms.

Noninvasive therapies, such as self-care and pharmacological agents, should be attempted first and those typically include NSAIDs and acetaminophen as first line agents.[5] In addition, muscle relaxants and benzodiazepines may be useful for muscle spasm and chronic bruxism while antidepressants are used for management of chronic pain. However, none of these agents have consistent efficacy demonstrated in clinical trials.[1]

BHV-3000 (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of TMD. The CGRP receptor is located within pain-signaling pathways, intracranial arteries, and the trigeminal ganglion. Its activation is thought to play a causal role in TMD pathophysiology.

Treatment with a CGRP receptor antagonist is believed to exert multiple downstream effects that may provide benefits in treatment of TMD through the following possible mechanisms:

- **Blocking Neurogenic Inflammation**: Binding of CGRP receptor antagonists to CGRP receptors located on satellite glial cells would inhibit inflammation caused by trigeminal nerve release of CGRP onto satellite glial cells and cell bodies of a-delta fibers in the trigeminal ganglion.

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

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

1.2 Product Development Background

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

1.2.1 Clinical Adverse Event Profile

Nurtec® ODT (rimegepant) is approved in the United States for the treatment of acute migraine and the preventive treatment of episodic migraine in adults. Nurtec® ODT (rimegepant) is generally safe and well tolerated in humans when given as single oral dose of 75 mg for the acute treatment of migraine as well as when given every other day for the preventive treatment of migraine. The BHV3000-201 study is a Phase 2/3, 52-week, open-label, safety study with rimegepant 75 mg, in which 1800 subjects received rimegepant up to once daily for up to one year. In the BHV3000-305 preventive treatment of migraine study, long-term safety was assessed in an open-label extension that included 603 patients who received rimegepant 75 mg at least every other day for up to one year. 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

Temporomandibular Disorders (TMD) is a large group of 30+ conditions involving the temporomandibular joint and surrounding muscles and tissues. It typically manifests as intermittent or continuous pain in the jaw area, functional limitations of the jaw, and clicking sounds in the TMJ during motion.[1]

The joint and surrounding tissues receive sensory and nociceptive innervation from distal branches of mandibular nerve, the largest of the three divisions of the trigeminal nerve. Although the underlying mechanisms of TMD have not been fully elucidated, numerous studies have implicated trigeminal nerve and CGRP in the pathophysiology of the disease and suggested therapeutic benefits of CGRP antagonism. For example, a preclinical study showed that injection of CGRP into the TMJ capsule in rodents upregulated expression of proteins implicated in the development and maintenance of peripheral and central sensitization and nociception.[8] Furthermore, in the acute TMD model in mice, pretreatment with CGRP antagonist led to significant reduction in spontaneous orofacial pain behaviors.[9] Moreover, induction of myogenic-TMD in mice triggered migraine-like hypersensitivity that could be attenuated by pretreatment with a CGRP antagonist and sumatriptan.[10] Clinical studies have also shown that synovial CGRP levels are elevated in TMD patients and correlate with pain, impairment of mandibular mobility, and occlusal alterations.[11,12]

BHV-3000 (rimegepant) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute treatment of TMD. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and the trigeminal ganglion, and its activation is thought to play a causal role in TMD pathophysiology.

Currently, there are no TMD-specific therapies or clear guidelines on the treatment and most often TMD is treated with self-care techniques and NSAIDs. However, most patients have an inadequate relief of pain and recurrence of symptoms, prompting the need for novel pharmacologic interventions.[1,2]

This study is being conducted to evaluate the efficacy, safety, and tolerability of rimegepant for the acute treatment of TMD. It will also further define the safety profile of rimegepant administration in this patient population, separately from the approved indication of acute and preventive treatment of migraine.

1.3.1 Study Design Rationale

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the acute treatment of TMD-associated pain. The study drug will be rimegepant formulated in a 75 mg ODT (administered sublingually) or a matching placebo. The subjects will be instructed to take their study medication, as an outpatient, when (if) they have a TMD-associated pain which reaches pain intensity of # 6 on the NRS (0-10).

The study will randomize approximately 200 subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization will be stratified by the use of daily medications / oral devices to reduce the intensity of TMD symptoms (yes or no).

This study design is being utilized to assess the safety and efficacy in the acute treatment of Temporomandibular Disorders.

1.3.2 Dose Selection Rationale

The Phase 2b dose-ranging study CN170003 established that rimegepant 75 mg is the minimum effective dose for the acute treatment of migraine. The three Phase 3 studies BHV3000-301, BHV3000-302, and BHV3000-303 confirmed this efficacy using the current registrational endpoints for acute treatment of migraine. This observation and the flat dose-response with rimegepant and other CGRP receptor antagonists suggest that rimegepant 75 mg may be an effective dose for the acute treatment of Temporomandibular Disorders. The pharmacokinetic profile of rimegepant supports the dosing schedule of this protocol with up to daily dosing. Please refer to the current version of Investigators Brochure for a summary of the clinical safety profile.

1.3.3 Research Hypothesis

Rimegepant will have efficacy superior to placebo in the acute treatment of Temporomandibular Disorders with a favorable safety profile.

1.3.4 Benefit/Risk

1.3.4.1 Benefit/Risk Assessment

As of the approval in February 2020 of Nurtec® ODT, more than 6,000 subjects have participated in Phase 1 studies in healthy subjects or Phase 2 and 3 studies in subjects with migraine. Among these subjects, more than 3,569 unique subjects have received the rimegepant clinical dose of 75 mg in Phase 2b/3 studies. Additionally, at the time of the Nurtec® ODT sNDA submission for the treatment of prevention in migraine, the pivotal prevention study had a total of 526 subjects received rimegepant (EOD or EOD plus as needed [EOD + PRN] up to once daily) for at least 6 months, and 138 subjects received rimegepant for at least 1 year. Collectively, the current data demonstrate a favorable benefit-risk profile for rimegepant in adults for the acute and preventative treatment of migraine and suggests a favorable benefit/risk assessment for the acute treatment of Temporomandibular Disorders.

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

To evaluate the efficacy of rimegepant compared with placebo in the acute treatment of Temporomandibular Disorders on the time-weighted sum of pain intensity difference from baseline scores for the first 2 hours post-dose (SPID-2).

2.2 Secondary Objective(s)

1. To evaluate rimegepant compared with placebo on the time-weighted sum of pain intensity difference (SPID) from baseline scores for the first 24 hours post-dose (SPID-24).

2. To evaluate rimegepant compared to placebo on change from baseline of pain on NRS (0-10) score at 2 hours post-dose.

3. To evaluate rimegepant compared to placebo on the proportion of subjects that are pain free at 2 hours post-dose.

4. To evaluate rimegepant compared to placebo on time to onset of meaningful pain relief post-dose.

5. To evaluate rimegepant compared to placebo on time to onset of initial pain relief post-dose.

6. To evaluate rimegepant compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.

CCI [redacted]


CCI

3 STUDY ENDPOINTS

3.1 Primary Endpoint(s)

Difference in SPID-2 scores between treatment groups will be assessed across the first 2 hours post-dose using the number of randomized and treated subjects.

3.2 Secondary Endpoint(s)

1. **Difference in SPID-24 scores** between treatment groups will be assessed across the first 24 hours post-dose using the number of randomized and treated subjects on NRS (0-10).

2. **Change from baseline** will be assessed at 2 hours post-dose using the number of randomized and treated subjects.

3. **Pain freedom** will be assessed using the number of evaluable subjects that report no pain at 2 hours post-dose. Pain will be measured on NRS (0-10).

4. **Onset of meaningful pain relief** will be assessed by the first nominal timepoint at which the pain on NRS (0-10) decreases by 30% from baseline.

5. **Onset of initial pain relief will be assessed** by the first nominal timepoint at which the pain on NRS (0-10) decreases by 1 point from baseline.

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

3.3 Measures of interest

Safety and Other assessments:

- Adverse Events
- ECG assessments
- Vital Sign and Physical Measurements
- Routine Laboratory Tests
- Columbia Suicidality Rating Scale
- Assessment of TMD-associated Pain and Symptoms
- [redacted]
- [redacted]

4 STUDY PLAN

4.1 Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared to placebo in the acute treatment of Temporomandibular Disorders. Subjects will be dispensed one dose of study medication consisting of a rimegepant 75 mg ODT (administered sublingually) or a matching placebo. The total duration of the study will be up to approximately 66 days. This includes a 3 to 14 day (+2 days for scheduling purposes, if needed) Screening Period, an Acute Treatment Phase that can last up to 45 days or until the subject has a TMD-associated pain that reaches intensity of # 6 on the NRS (0-10), followed by an End of Treatment Visit 7 days after the administration of the study medication.

Table 1 BHV3000-317 Schedule of Assessments

Procedure	Screening Visit (3-14 days)	Baseline Visit (Randomization)	TMD-associated pain # 6 on NRS (0-10)	During Treatment 15, 30, 45, 60 and 90 mins Post-Dose	During Treatment 2, 4, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	End of Treatment Visit (within 7 (+2) days of treating TMD-associated pain)	Comments
Eligibility Assessments								
Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Collect Daily Use of Medications / Oral Devices to Reduce Intensity of TMD Symptoms / Concomitant Medications	X	X					X	Subjects will be given a paper diary to track of concomitant medications, including rescue medications, and use of oral devices. All medications taken for any reason should be documented. Site staff should instruct subjects on proper use of the paper diary(ies) and instruct subjects that the diary(ies) will be collected, reviewed, and discussed with the subject at each visit.
Assessment of TMD History (Signs and Symptoms)	X							**Paper source document** will be used to capture TMD History and entered in eCRF

Procedure	Screening Visit (3-14 days)	Baseline Visit (Randomization)	TMD-associated pain # 6 on NRS (0-10)	During Treatment 15, 30, 45, 60 and 90 mins Post-Dose	During Treatment 2, 4, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	End of Treatment Visit (within 7 (+2) days of treating TMD-associated pain)	Comments
Safety Assessments								
Physical Examination	X						X	
Vital Signs/Physical Measurements	X	X					X	Vital Signs consist of sitting arterial systolic and diastolic blood pressure, heart rate, oral body temperature, body weight and height. Height and weight will only be measured at Screening.
Clinical Safety Laboratory Testing	X						X	All **Screening visit** laboratory test results must be received prior to Baseline Visit (randomization)
Urine drug screen for drugs of abuse	X						X	
HbA1c, Lipid Panel, FSH	X							
ECG	X						X	
Pregnancy Test	X	X	X				X	A serum pregnancy test will be completed at Screening and End of Treatment Visits as part of the standard laboratory tests (if appropriate). Confirmatory urine pregnancy test for WOCBP should be completed on site at the Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion. Home pregnancy test will be

Procedure	Screening Visit (3-14 days)	Baseline Visit (Randomization)	TMD-associated pain # 6 on NRS (0-10)	During Treatment 15, 30, 45, 60 and 90 mins Post-Dose	During Treatment 2, 4, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	End of Treatment Visit (within 7 (+2) days of treating TMD-associated pain)	Comments
								provided to WOCBP after completion of baseline visit. Subjects will be provided with the accompanying package insert that contains instructions for use and interpretation of results. WOCBP subjects must complete the urine pregnancy test at home. WOCBP must have a negative serum or urine pregnancy test at the Screening Visit, Baseline Visit, and prior to taking study medication.
Adverse Event and Serious Adverse Event Assessment	X	X	X	X	X	X	X	SAEs are reported from the time of informed consent and non-serious AEs are reported from baseline. See Section 8 of the protocol for further information.
Columbia Suicidality Rating Scale	X	X					X	This scale will be clinician administered, completed on site, and will be in paper. The source document will be provided by Biohaven. At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit.

Procedure	Screening Visit (3-14 days)	Baseline Visit (Randomization)	TMD-associated pain # 6 on NRS (0-10)	During Treatment 15, 30, 45, 60 and 90 mins Post-Dose	During Treatment 2, 4, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	End of Treatment Visit (within 7 (+2) days of treating TMD-associated pain)	Comments
Clinical Drug Supplies/Study Supplies								
Randomize		X						Subjects will be randomized in the IWRS system at the Baseline Visit (Randomization)
Dispense Study Medication		X						
Administer 1 dose of study medication			X					Instruct subjects: STUDY DRUG only to be taken to treat a **TMD-associated pain # 6 on NRS (0-10)** AND **after the subject has completed all required assessments in the eDiary. The eDiary will prompt the subject to take study medication.**
Return used study medication packaging or unused study medication							X	
eDiary returned/ reviewed for completeness							X	Staff to review eDiary entries with subjects, confirm all data points are transferred to the system, and reset eDiary for future subject use, PRIOR to the subject leaving the clinic

Procedure	Screening Visit (3-14 days)	Baseline Visit (Randomization)	TMD-associated pain # 6 on NRS (0-10)	During Treatment 15, 30, 45, 60 and 90 mins Post-Dose	During Treatment 2, 4, 8 hours Post-Dose	During Treatment 24 hours Post-Dose	End of Treatment Visit (within 7 (+2) days of treating TMD-associated pain)	Comments
Efficacy Assessments (±windows for timeframe around efficacy assessments (15, 30, 45, 60, 90 min, 2, 4, 8, and 24 hours) will be automated and captured in the eDiary.)								
Assessment of TMD-associated pain			X	X	X	X		This scale is captured in the eDiary,
CCI [redacted]						[redacted]		[redacted]
[redacted]		[redacted]				[redacted]		[redacted]

4.1.1 Screening Phase (3-14 days)

All subjects who are screened will be entered into the IWRS system and assigned a patient identifier. After obtaining informed consent, subjects will undergo all screening procedures as detailed in Table 1. After all screening procedures are complete, subjects may return 3 to 14 days (+2 days if needed for scheduling purposes) from signing informed consent to be randomized at the Baseline visit if they meet all eligibility criteria.

Subjects in this study may be screened only once. Rescreening is not permitted.

4.1.2 Acute Treatment (Randomization) Phase

If the subject meets all eligibility criteria, they will be randomized at the Baseline Visit via the IWRS. The subjects will be provided with an eDiary. Study personnel will educate the subject on the proper use of the eDiary, accurate reporting, and placebo response prior to the subject leaving the office.

After randomization via the IWRS, the subject will be dispensed a single dose of the double-blind study medication to take home for up to 45 days. This study medication is to be taken when an TMD-associated pain in the jaw and/or temple area on either side which reaches pain intensity of # 6 on the NRS (0-10) in the eDiary. The subject will be instructed to take their study medication, as an outpatient, when (if) they have an TMD-associated pain in the jaw and/or temple area on either side which reaches pain intensity of # 6 on the NRS (0-10) after they answer eDiary questions about their current pain and symptoms. The subject will complete an eDiary for 24 hours after taking study medication to record efficacy and other quality of life measures.

Subjects in this study may be randomized only once. Under no circumstances may a subject be re-randomized.

4.1.2.1 eDiary Data Collection

Subjects will record efficacy and other quality of life measures in their eDiary. This includes the following: onset time of TMD-associated pain, intensity of the TMD-associated pain prior to and at time of taking study medication. The subjects should not dose with study medication until the TMD-associated pain in the jaw and/or temple area on either side which reaches pain intensity of # 6 on the NRS (0-10). TMD-associated pain severity will be recorded using a NRS (0-10) at the onset of the pain and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 4, 8, and 24 hours. Subjects will record the date and time study therapy was taken in their eDiary according to the eDiary vendor's specifications. CCI [redacted]

After dosing with study medication, all other medication to relieve TMD-associated symptoms is prohibited during the 2 hours post dose. At the end of 2 hours after dosing with study medication (and after the 2-hour assessments have been completed on the eDiary) subjects will be permitted to use the following rescue medication: acetaminophen (up to 1000 mg/day); or aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-

inflammatory [NSAID]), or cyclobenzaprine (all up to the daily recommended dose indicated on the drug packaging). Subjects may administer whichever protocol permitted standard of care rescue medication they choose to reduce symptoms and that they have available. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication. However, if needed, after 24 hours of administering the one dose of study medication (and before returning for the End of Treatment Visit) subject may take their prescribed standard of care medications for treatment of TMD-associated pain provided all the assessments have been completed on the eDiary. Exclusionary rescue medication such as, opioids, butalbital compounds, and muscle relaxants (except cyclobenzaprine used as rescue medication, see above) are not allowed on this study. Similarly, if the TMD-associated pain is relieved by study medication at 2 hours after dosing but then recurs to intensity level of # 6 on the NRS (0-10) between 2 and 24 hours, the subject will be permitted to take the same rescue therapy as outlined above.

Subjects should be encouraged to treat the first qualifying TMD-associated pain (intensity level of # 6 on the NRS (0-10)) that occurs during the treatment phase. If subjects are unable to treat their first qualifying TMD-associated pain due to scheduling, etc. the same medication restrictions would still apply (i.e., acetaminophen [up to 1000 mg/day]; or aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-inflammatory [NSAID]), or cyclobenzaprine [all up to the daily recommended dose indicated on the drug packaging]). Subjects may administer whichever protocol permitted standard of care medication they choose to reduce symptoms and that they have available.

Similarly, for treatment of non-qualifying TMD-associated pain (i.e., pain of < 6 on the NRS (0-10), or other non-TMD related pain in the jaw and/or temple area on either side) that occur during the randomization period before a qualifying TMD-associated pain is reported, subject will only be permitted to use the medications listed above. Acetaminophen (over 1000 mg/day) is prohibited after randomization except as rescue medication as described in Section 5.5. In all circumstances, the subject will continue to complete his or her eDiary for up to 24 hours after consuming the study medication.

4.1.3 Extension Phase

Not applicable.

4.1.4 Washout Phase

Not applicable.

4.1.5 End of Treatment

Subjects will return to the study site within 7 days of study treatment (+2 days) for review of the eDiary assessment, of medication compliance, and monitoring of tolerability and safety (including vital signs, laboratory tests, and electrocardiography). If a subject has NOT experienced a TMD-associated pain of sufficient severity within 45 days after randomization, they still are required to complete all EOT visit procedures. All subjects must return unused study medication and eDiary to the study center.

4.2 Post Study Access to Therapy

At the end of the study, the Sponsor will not continue to supply study drug to subjects/Investigators. The Investigator should ensure that the subject receives the appropriate standard of care to treat the condition under study.

5 POPULATION

Individuals entered in this trial will be subjects who suffer from temporomandibular disorders as specified under Section 5.2. The treatment setting for these subjects may include clinics, institutions, or private office practices. Subjects may be recruited through a variety of sources, including referral from physicians and other health care professionals.

5.1 Number of Subjects

It is anticipated that approximately 200 subjects will be randomized to result in approximately 160 evaluable subjects. The subjects will be randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. It is anticipated that enrollment will occur at approximately 25 sites in the United States over a period of approximately 10 months during this trial.

5.2 Inclusion Criteria

1. Signed Written Informed Consent

    a. Written informed consent must be obtained from the subject in accordance with requirements of the study center's Institutional Review Board (IRB) or Ethics Committee prior to the initiation of any protocol-required procedures.

    b. Subject must agree to provide all requested demographic information (i.e. gender, race).

    c. Subject must be able to read and understand English or Spanish.

2. Target population

    a. Subject has a minimum 3-month to a maximum 5-year history of temporomandibular disorder diagnosed by a healthcare provider, including the following:

        i. Meets criteria consistent with a diagnosis according to the DC / TMD (Diagnostic Criteria for Temporomandibular Disorders)[3] that include at least one of the following:

            (1) Arthralgia (I.1.A.)

            (2) Myalgia (II.1.A.1-3)

    b. At least one instance of pain # 6 on a Numeric Rating Scale (0-10) in the jaw and/or temple area on either side in the past 30 days prior to the Screening Visit.

c. Subject with daily use of medications to reduce intensity of TMD symptoms is permitted to remain on therapy if they have been on a stable dose for at least 3 months prior to the Screening Visit, and the dose is not expected to change during the course of the study.

d. Subject with daily use of oral devices to reduce intensity of TMD symptoms is permitted to remain on therapy if they have been using them consistent for at least 3 months prior to the Screening Visit, and the regimen is not expected to change during the course of the study.

e. Subject agrees to not commence new pain medication, injection therapy, occlusal splint therapy or any other pain management techniques during the course of the study.

3. Age and Reproductive Status

a. Male and Female subjects ≥ 18 years 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 5.5 for the definition of WOCBP. WOCBP must agree to use an acceptable contraceptive method or abstinence to avoid pregnancy from the Screening Visit through 60 days after dosing with study drug. 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. WOCBP must have a negative serum or urine pregnancy test at the Screening Visit, Baseline Visit, and prior to taking study medication.

e. Women must not be breastfeeding.

5.3 Exclusion Criteria

1. Disease Target Exclusion

a. Subject has a history of primary headache disorder consistent with diagnostic criteria according to the International Classification of Headache Disorders, 3rd Edition. If the majority of pain associated with tension-type headache diagnosis is attributable to TMD by the site PI, then it is not exclusionary.

b. Subject has a history of headache disorder attributed to trauma or injury to the head and/or neck consistent with diagnostic criteria according to the International Classification of Headache Disorders, 3rd Edition.

c. Meets criteria consistent with a diagnosis according to the DC / TMD (Diagnostic Criteria for Temporomandibular Disorders)[3] that include at least one of the following:

   i. Joint Pain:

      (1) Arthritis (I.1.B)

   ii. Joint Disorders:

      (1) Disc disorders (I.2.A.1-4) only when associated with mechanically induced arthralgia

      (2) Other hypomobility disorders (I.2.B), such as adhesions/adherence, ankylosis

      (3) Hypermobility disorders (I.2.C.), such as subluxation, luxation

   iii. Joint Diseases:

      (1) Systemic arthritides (I.3.B)

      (2) Condylysis/idiopathic condylar resorption (I.3.C)

      (3) Osteochondritis dissecans (I.3.D)

      (4) Ostonecrosis (I.3.E)

      (5) Neoplasm (I.3.F)

      (6) Synovial chondromatosis (I.3.G)

   iv. Fractures:

      (1) Fractures (I.4)

   v. Congenital/Developmental Disorders:

      (1) Aplasia (I.5.A)

      (2) Hypoplasia (I.5.B)

      (3) Hyperplasia (I.5.C)

   vi. Muscle Pain:

      (1) Myositis (II.1.C)

      (2) Spasm (II.1.D)

   vii. Contracture (II.2)

   viii. Neoplasm:

(1) Neoplasm (II.4)

ix. Movement Disorders:

(1) Orofacial dyskinesia (II.5.A)

(2) Oromandibular dystonia (II.5.B)

x. Masticatory Muscle Pain Attributed to Systemic/Central Pain Disorders:

(1) Fibromyalgia/widespread pain (II.6.A)

xi. Associated Structures:

(1) Coronoid hyperplasia (IV.1)

d. Subject has a history of neuropathic (e.g., trigeminal neuralgia, postherpetic neuralgia) or idiopathic pain disorder.

e. Subject has a history of pain of dental origin within the 3 months prior to the Screening Visit.

f. Subject has a history of trauma in the craniocervical area, including joint sprain/strain, within the 3 months prior to the Screening Visit.

g. Subject has a history of or is planning TMJ surgery (e.g., arthrocentesis, arthroscopy, TMJ implants) or ear surgery.

h. Subject has a history of radiation treatment to head and neck.

i. Subject has a history of connective tissue disorders.

2. Medical History and Concurrent Diseases

a. Body Mass Index # 33kg/m^2

b. Subject history of HIV disease.

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

d. Uncontrolled hypertension (high blood pressure) or uncontrolled diabetes (however subjects can be included who have stable hypertension and/or diabetes for at least 3 months prior to the Screening Visit).

e. Subject has a current diagnosis of major depression, other pain syndromes, psychiatric conditions (e.g., schizophrenia), dementia, or significant neurological disorders that, in the Investigator's opinion, might interfere with study assessments.

f. Subject has a history of gastric or small intestinal surgery (including Gastric Bypass, Gastric Banding, Gastric Sleeve, Gastric Balloon, etc.), or has a disease that causes malabsorption.

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. Severe hepatic impairment (Child-Pugh C) is exclusionary in all cases.

h. Subjects with a history of, treatment for, or evidence of, alcohol or drug abuse or who have met DSM-V criteria[13] 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:

   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 from 3 months prior to the Screening Visit until the end of treatment visit occurs.

   Detectable levels of cannabinoids (e.g., marijuana, CBD) in the drug screen at the Screening Visit are not exclusionary, if in the Investigator's documented opinion the subject does not meet DSM-V criteria[13] 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 the Screening Visit.

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. ECG and Laboratory Test Findings

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

   b. Corrected QT interval > 470 msec (QTc by method of Frederica), 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. Neutrophil count ≤ 1000/μL (or equivalent).

h. HbA1c ≥ 6.5%.

i. 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***).

5. Excluded Current or Recent Treatments

a. Subject has a history of new or recently modified use of night guards, splints, dental orthotics, or dental appliances within the 3 months prior to the Screening Visit.

b. Subject has a history of dental orthodontic use within the 3 months prior to the Screening Visit.

c. Subject has a history of dental restorative care (e.g., crowns, bridges) within the 3 months prior to the Screening Visit.

d. Subject has a history of new or recently modified physical therapy treatment in the head and/or neck area within the 3 months prior to the Screening Visit.

e. Subject has a history of new or recently modified botulinum therapy (e.g., onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A) within the 3 months prior to the Screening Visit.

f. Subject has a history of injection therapy other than botulinum therapy (e.g., lidocaine, corticosteroids, hyaluronic acid) within the 30 days prior to the Screening Visit.

g. Subject has a history of Transcutaneous Electrical Nerve Stimulation (TENS) use within the 3 months prior to the Screening Visit.

6. Other Exclusion Criteria

a. Prisoners or subjects who are involuntary incarcerated.

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

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

d. Subjects who have previously participated in any BHV-3000/ BMS-927711/ rimegepant study.

e. Participation in clinical trial with biological investigational agents within the 3 months prior to Screening Visit.

f. Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to the Screening Visit, OR subjects who endorse any of the five C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within the last 10 years prior to the Screening Visit, OR subjects who, in the opinion of the Investigator, present a serious risk of suicide (See Section 6.3.5).

g. Planned participation in any other investigational clinical trial while participating in this clinical trial.

h. Subjects engaged in, or with plans to engage in, litigation or Worker's Compensation in which monetary gain or loss (or other compensation) may affect their objective participation in the trial.

See Section 5.4 for prohibited medications and Section 5.5 for allowable medications to consider when evaluating subject eligibility.

Subjects must be willing to comply with all concomitant medication requirements and study procedures.

5.4 Prohibited and Restricted Concomitant Medications

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

1. History of non-narcotic analgesic intake on greater than/equal to 15 days per month for greater than/equal to 3 months (e.g., acetaminophen, NSAIDs, gabapentin etc.) for other pain indications. (Please refer to Section 5.5 for rescue medication).

2. 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 5.5). During the screening phase (3-14 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000 mg/day is prohibited.

3. Muscle relaxants should not be taken 14 days prior to randomization and throughout the study (cyclobenzaprine is allowed as rescue medication, see Section 5.5).

4. Systemic corticosteroids should not be taken 30 days prior to randomization and throughout the study.

5. Benzodiazepines should not be taken 14 days prior to randomization and throughout the study.

6. St. John's Wort should not be taken 14 days prior to randomization and throughout the study.

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

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

9. The use of CGRP antagonists (biologic or small molecule) is prohibited during the study. CGRP antagonist biologics must be discontinued 3 months prior to screening. CGRP small molecule antagonists must be discontinued 2 weeks prior to screening and throughout the course of the study.

10. Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone and hydrocodone) is prohibited for at least 30 days prior to the Screening Visit and throughout the study.

11. Use of cannabinoids (e.g., marijuana, CBD) is prohibited during the study.

12. Concomitant use of strong CYP3A4 inhibitors, such as HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, is prohibited during the study. Strong CYP3A4 inhibitors must be discontinued 14 days prior to screening and throughout the course of the study. Please see Section 17.1, Appendix I, for additional resources.

13. Concomitant use of moderate to strong CYP3A4 inducers, such as carbamazepine, phenytoin, or rifampin, is prohibited during the study. Moderate or strong CYP3A4 inducers must be discontinued 14 days prior to screening and throughout the course of the study. Please see Section 17.1, Appendix I, for additional resources.

14. Atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or Depakote/Depakene (valproic acid/valproate) should not be taken 3 months prior to randomization and throughout the study.

15. LAMICTAL (lamotrigine) should not be taken 3 months prior to randomization and throughout the study.

16. Subjects with daily use of medications to reduce intensity of TMD symptoms are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry (see Section 5.5. Daily and Rescue Medications and Oral Devices)

Low dose aspirin (e.g., 81 mg or less) for documented cardiovascular prophylaxis is allowed.

5.5 Daily and Rescue Medications and Oral Devices

Subjects may not use more than 1 of the following medications and not more than 1 of the oral devices if not otherwise prohibited by the protocol. Medication doses must be **stable**

within 3 months prior to the Screening Visit and throughout the study. Use of oral devices must be **consistent (i.e., non-active) within 3 months prior to the Screening Visit** and throughout the study.

Daily medications and therapy that are permitted during the study include:

- Tricyclic antidepressants (such as: amitriptyline, nortriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Gabapentin, pregabalin
- Feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- Botulinum therapy (e.g., onabotulinum toxin A, abobotulinum toxin A, and incobotulinum toxin A)

Oral devices that are permitted during the study include:

- Night guards, splints, dental orthotics, dental appliances
- Dental orthodontics

The use of CGRP antagonists (biologic [e.g., Aimovig®, Ajovi®, Emgality®, Vyepti®] or small molecule) other than rimegepant is prohibited during the study.

After dosing with study medication, all other pain medication is prohibited during the 2 hours post dose. However, a subject who does not experience relief of their pain at the end of 2 hours after dosing with study medication (and after the 2-hour assessments have been completed on the eDiary), will be permitted to use the following rescue medication: acetaminophen (up to 1000 mg/day); or aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-inflammatory [NSAID]), or cyclobenzaprine (all up to the daily recommended dose indicated on the drug packaging). Subjects may administer whichever protocol permitted standard of care rescue medication they choose to reduce symptoms and that they have available. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication.

However, if needed, after 24 hours of administering the one dose of study medication (and before coming in for the End of Treatment Visit) subject may take their prescribed standard of care medications for treatment of TMD provided all the assessments have been completed on the eDiary. Exclusionary rescue medication such as opioids, butalbital compounds, and muscle relaxants (except cyclobenzaprine as a rescue medication, see above) are not allowed on this study. Similarly, if the pain is relieved by study medication at 2 hours after dosing but then recurs to intensity level of # 6 on NRS (0-10) between 2 and 24 hours, the subject will be permitted to take the same rescue therapy as outlined above. In all circumstances, the subject will always continue to complete his or her eDiary entries through the 24-hour assessment after consuming the study medication. Use of concomitant medication after randomization, including rescue medication, will be recorded by the subject on a paper diary and reported to the site. The site will record medications that were taken within 14 days of dosing with study medication (or until the End of Treatment Visit).

During the [up to] 66 days the subject is participating in the study, if the subject has a non-qualifying TMD-associated pain (i.e., pain < 6 on a NRS (0-10) in the jaw and/or temple area on either side), the subject is permitted to use only the following medications: acetaminophen (up to 1000 mg/day); or aspirin, ibuprofen, naproxen (or any other type of non- steroidal anti-inflammatory [NSAID]), or cyclobenzaprine (all up to the daily recommended dose indicated on the drug packaging). Subjects may administer whichever protocol permitted standard of care medication they choose to reduce symptoms and that they have available.

After completing all assessments (through 24 hours and before End of Treatment Visit) in their eDiary, if subjects experience pain they are allowed to take their prescribed standard of care medication.

5.6 Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Tubal ligation is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill contraception requirements for the study. Essure, tubal occlusion and endometrial ablation are not acceptable methods of contraception. 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 > 35 mIU/mL.
>
> **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 1 year.
>
> ***OR***
>
> Woman on hormone replacement therapy (HRT) who no longer menstruate.

Women of childbearing potential (WOCBP) and all men must understand the following requirements and use an acceptable method of contraception to avoid pregnancy throughout the study and for up to 60 days for WOCBP and 90 days for male subjects after the last dose of investigational product in such a manner that risk of pregnancy is minimized.

It is required that all WOCBP use 2 methods of contraception to prevent pregnancy, for the duration of the study (i.e., this study begins with signed consent form through 60 days after dosing with study drug). The 2 methods should include 1 barrier method (ex. condom with spermicidal gel, non-hormonal intrauterine devices, cervical cap etc.) and 1 other method. The other method could include another barrier method or hormonal contraceptives (e.g., oral contraceptives, injectable contraceptives, patch, or contraceptive implant [e.g., hormonal intrauterine device]) used since at least 4 weeks prior to sexual intercourse.

WOCBP and all male subjects must be counseled on the requirements to avoid pregnancy throughout the study and for 60 days for WOCBP and 90 days for male subjects after the last dose of study drug, as well as acceptable methods of contraception to use during the study. Subjects who report abstinence, or who report exclusively being in same-sex relationships are still required to understand the contraception requirements in this study to prevent pregnancy.

If subjects who report abstinence or who report exclusively being in a same-sex relationship engage in heterosexual activity, then the contraception requirements must be followed.

Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months (24) weeks prior to the screening visit. Vasectomy is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill the contraception requirements for the study. Male subjects must not donate sperm until 90 days following the last study drug administration.

All WOCBP must complete the pregnancy test schedule in Table 1.

5.7 Other Restrictions and Precautions

Not applicable.

5.8 Protocol Deviations

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 throughout the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by the IRB/EC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. See Section 10.1 for further information on serious breaches of the protocol.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

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

All sites will use an Electronic Data Capture (EDC) tool to submit study data to the Sponsor's CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields. SAE data (including responses to queries) will be submitted to the CRO using a paper SAE report form. Electronic Patient Reported Outcomes (ePRO) will be used for all patient-rated scales and will be captured on an eDiary. Any assessment completed by the subject in the eDiary will be transferred from the site/subject to the vendor and from the vendor to the CRO

and/or Sponsor. No additional source documents are required for scales and assessments completed by the subject in eDiary.

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

6.2 Eligibility Assessments

6.2.1 Symptom Questionnaire – DC/TMD

Subjects will undergo an assessment using the DC/TMD Symptom Questionnaire during the Screening Phase as outlined in Table 1.

6.2.2 Clinical Exam Form (NA) – DC/TMD

Subjects will undergo an assessment during the Screening Phase using the DC/TMD Symptom Questionnaire at the scheduled visits as outlined in Table 1.

6.3 Safety Assessments

6.3.1 Vital Signs and Physical Measurements (Height and Weight)

Sitting arterial systolic and diastolic blood pressure and pulse rate, height, weight and body temperature will be measured at Screening and End of Treatment. Height and weight will be done at Screening only see Table 1.

6.3.2 Electrocardiogram (ECG)

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

6.3.3 Physical Exam

Subjects will undergo a routine physical examination during the Screening Phase and at the scheduled visits as outlined in Table 1. Physical examinations include examination of the heart, abdomen, lungs, and any other body system to be guided by symptoms.

6.3.4 Laboratory Assessments

6.3.4.1 Safety Laboratory Testing

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

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

Blood chemistry/electrolyte: Sodium, potassium, chloride, bicarbonate, calcium; glucose, BUN (urea), serum creatinine, uric acid, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, CK. End of Treatment Visit – elevations in CK (>5x ULN) may have further CK fractionation tests performed through the central lab.

Lipid Panel: Total cholesterol, LDL, HDL and triglycerides will be performed through the central lab at screening.

HbA1c: measured at screening only.

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

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

Urine Drug Screen: For drugs of abuse.

Reflex tests: If ALT or AST ≥ 3 x ULN OR total bilirubin ≥ 2 x ULN at any visit after the baseline visit, the central laboratory will perform reflex tests that may include: CK, GGT, and anti-viral serologies. Subjects may have to return to the study site to provide additional blood samples for these laboratory tests.

FSH: A confirmatory FSH level will be measured at screening on post-menopausal women (as defined in Section 5.6) to confirm post-menopausal status. FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to 1 year.

Additional laboratory tests may be required.

6.3.4.2 Pregnancy Testing

Pregnancy tests will be conducted on women of childbearing potential as outlined in Table 1. Women of childbearing potential must have a negative serum or urine pregnancy test at the Screening Visit, Baseline Visit, and prior to taking study medication. Subjects will be provided with the accompanying package insert that contains instructions for use and interpretation of results.

6.3.5 Columbia Suicidality Severity Rating Scale (CSSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment.[14] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[15] will be used at subsequent visits in this study.

The C-SSRS Assessment is intended to help establish a person's immediate risk of suicide. The C-SSRS is a clinician administered scale that should be administered by a certified rater.

This scale will be collected on site with a paper form. The C-SSRS should be reviewed by the Investigator or designee before the subject is allowed to leave clinic.

At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit (Table 1).

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

6.4 Efficacy Assessments

6.4.1 Pain

Subjects are given an eDiary to record their current TMD-associated pain score, on a NRS (0-10) at the time points indicated in Table 1.

6.4.2 Rescue Medication

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

CCI [redacted]

6.5 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.

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

6.5.1 Lost to Follow Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

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

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

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

In this protocol, investigational product is/are:

! Rimegepant ODT and matching placebo. The rimegepant ODT and the matching placebo appear identical visually, via touch, smell, and taste.

7.1.2 Non-Investigational Product

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

In this protocol, non-investigational product(s) is/are:

! Standard of care / rescue medications and/or oral devices for the treatment of TMD-associated symptoms.

7.1.3 Packaging, Shipment and Storage

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

7.2 Dose and Administration

One dose of rimegepant ODT (75 mg) or matching placebo will be dispensed to the subject and will be taken at the time the subject has a TMD-associated pain that reaches intensity of # 6 on a NRS (0-10) ***and after*** completing the eDiary questions.

7.2.1 Method of Assigning Subject Identification

Immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential subject number for identification throughout the study through an IWRS. This subject number must not be reused for any other subject in the study. The physician/coordinator must contact the IWRS to enroll each subject into a centralized database after signing consent.

After completion of all screening evaluations, all eligible subjects will be randomized in a 1:1 ratio to the rimegepant or matching placebo treatment groups. The randomization will be stratified by the daily use of medications / oral devices to reduce intensity of TMD symptoms (yes or no). It is important to correctly enter subjects who are using daily medications / oral devices in the IWRS system. Once a subject is stratified in the IWRS, this cannot be changed.

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

The randomization will trigger dispensation for the subject and assign a bottle number for the appropriate randomized treatment type. The drug is dispensed at the time of randomization.

7.2.2 Selection and Timing of Dose and Administration

Study medication (one 75 mg orally disintegrating tablet or matching placebo) will be packaged in a single blister in a subject-specific bottle. There are no dose adjustments in this study and subjects will receive one dose to treat TMD-associated pain of # 6 on a NRS (0-10) within 45 days of randomization (Baseline Visit). Subjects will be dispensed the study medication at randomization (Baseline Visit) and will take the ODT from the blister/bottle at the time of TMD-associated pain of # 6 on a NRS (0-10) onset **ONLY** after answering questions regarding their TMD-associated symptoms in the eDiary device. The ODT should be placed on or under the tongue until fully dissolved then swallowed. Subjects should be instructed to use dry hands when handling the study medication.

7.2.3 Dose Modifications

There will be no dose adjustments in this study.

7.3 Blinding and Unblinding

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

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

7.4 Treatment Compliance

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

Subjects have to be counseled on the importance of taking the study drug as directed when a TMD-associated pain occurs and reaches intensity of # 6 on a NRS (0-10). If the subject does not have a TMD-associated pain of # 6 on a NRS (0-10) or take their study medication within 45 days of the Baseline Visit, they should return to the clinic for their End of Study Visit and return their unused study medication.

7.5 Destruction and Return of Study Drug

Subjects will be instructed to return all unused study drug or packaging from used study drug to the study site for drug accountability. All unused study drug can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible Study monitor or the Sponsor's designee. If it is site policy to destroy study drug on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The used study drug packaging can only be destroyed after being inspected and reconciled by the responsible Study Monitor or the Sponsor's designee.

8 ADVERSE EVENTS

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

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

Definition of terms related to all Adverse Events (serious and non-serious):

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

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

Severe: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

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

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

Assessment for Determining Relationship of AE to Study Drug:

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

Related: This category applies to AEs that are considered, with a high degree of certainty, to be related to the study drug. An AE may be considered related when it follows a temporal sequence from the administration of study drug, it cannot reasonably be explained by the known characteristics of the subject's clinical state, environment, or toxic factors, or other modes of therapy administered to the subject. An AE may be considered related when it follows a known pattern of response to the study drug, or if the AE reappears upon re-challenge. This category also applies to AEs that are considered to have an unlikely connection to study drug, but a relationship cannot be ruled out with certainty.

Unrelated: This category applies to AEs that are considered with a high degree of certainty to be due only to extraneous causes (e.g., subject's clinical state, environment, toxic factors, disease under study, etc.) and does not meet the criteria of other categories above.

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

8.1 Serious Adverse Events

8.1.1 Definition of Serious Adverse Event (SAE)

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

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

- Potential drug induced liver injury (see Section 8.5)
- Abuse or Overdose of medication
  - Potential study medication abuse (including cases of excessive non-compliance with study medication dosing instructions or subjects who discontinue treatment without returning study medication) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor subjects for possible cases of abuse of study medication (subjects taking study drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies.
  - Potential study medication overdose is defined in Section 8.3.

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

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

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

! Elective surgery planned prior to signing consent.

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

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

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

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

8.1.2 Collection and Reporting Serious Adverse Events

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the screening period and throughout the course of the study up to and including the End of Treatment Visit / 30 days after last dose. The Investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study drug, overdose (see Section 8.3), potential drug induced liver injury (see Section 8.5) and pregnancies (see Section 8.4) must be reported within 24 hours of the Investigator becoming aware 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 entering the SAE information into the Case Report Form (CRF) and/or system (i.e., event term, start/stop dates, causality, and severity).

Any serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to 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), which is the preferred method of submission, 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 or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

! Sender of report (Site number, Investigator name)

! Subject identification (subject number)

! Protocol number

! SAE term (if an SAE is being reported)

8.2 Non-serious Adverse Events

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

8.2.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the initiation of study drug through the Follow up Safety Visit (End of Treatment Visit).

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

8.2.2 Laboratory Test Abnormalities

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

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

! Any laboratory abnormality that required the subject to have the study drug discontinued or interrupted.

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

8.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both **excessive** and **medically important**.

All occurrences of medically significant overdose (suspected or confirmed and irrespective of whether it involved 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 treatments administered.

Asymptomatic dosing errors (e.g., accidentally taking two tablets instead of prescribed dose of one tablet in one calendar day) should be reported as deviations.

8.4 Pregnancy

If, following the Baseline Visit, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of the investigational 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 subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Sites should instruct subjects to contact the Investigator if they become pregnant during the course of the study. The Investigator must immediately notify the Biohaven (or designee) Medical Monitor and PPD of the event and complete the Pregnancy Form in accordance with SAE reporting procedures as described in Section 8.1.2. The pregnancy should be reported

using paper forms, which should be faxed to PPD PVG by facsimile (fax), which is the preferred method of submission, within 24 hours after Investigator/site awareness of the event:

! North America - 1-888-488-9697

Or if the form cannot be faxed or emailed (wilsafety@ppdi.com; subject line must include "Biohaven Protocol BHV3000-314"), reported via phone to the PPD Safety Hotline at North America: 1-800-201-8725.

Once the paper form is available, the data must be reported per standard procedures.

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 the Sponsor/PPD. Information on this pregnancy will be collected on the Pregnancy Report Form, as appropriate.

8.5 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

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

8.6 Adverse Events of Special Interest

None

9 STATISTICS

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

9.1 General Procedures

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

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

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

9.2 Sample Size

If 80% of the 200 randomized (100 per treatment arm) treat with study drug, we expect roughly 160 total or 80 per treatment group in the randomized and treated population for analysis.

Assuming rimegepant provides a 2-point reduction in NRS pain, and a 1.5-point advantage over placebo on the primary endpoint, and a common standard deviation of 3.0, then the study will have roughly 88% power on the primary endpoint.

9.3 Populations for Analysis

The set of enrolled subjects consists of all subjects who signed the informed consent form and were assigned a subject identification number.

The set of randomized subjects consists of enrolled subjects who were assigned a randomized treatment group.

The set of treated subjects consists of all randomized subjects who take study therapy (rimegepant or placebo).

9.4 Statistical Methods

9.4.1 Demographic and Baseline Characteristics

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

9.4.2 Primary Endpoint(s)

The SPID-2 will be calculated by multiplying the PID score (difference between NRS at each time point and baseline NRS) at each post-dose timepoint by the duration (in hours) since the preceding timepoint, then summing the values over the 2 hours. This is analyzed on the treated population using an analysis of covariance (ANCOVA) model that includes the baseline NRS (0-10) value as a covariate, and main effects for treatment group and stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms).

The least squares mean (LS mean), standard error (SE), and 95% confidence interval (CI) for each treatment group will be reported, as well as the difference estimate (rimegepant - placebo), SE, 95% CI, and p-value.

Intercurrent events will be treated as failures, with the assumption that the subject does not improve once the intercurrent event occurs. In the event a subject uses a non-study rescue medication on or before 2 hours post-dose, all data points after rescue medication was administered will be set to the last available observation prior to rescue medication usage (RM = Rescue medication use: F = Failure). Likewise, if a subject fails to log their pain score at any time after study drug is administered, through 2 hours post-dose, this data will be imputed to the last available observation (NC = Non-completers; F = Failure).

Sensitivity analyses will be described in the SAP.

9.4.3 Secondary Endpoint(s)

If the primary endpoint test is significant at alpha ∀ 0.05, then the secondary endpoints will be analyzed at an alpha level of ∀ 0.05 using Hochberg's procedure. Secondary endpoints will be analyzed on the treated population.

9.4.3.1 SPID-24

The SPID-24 will be analyzed in the same manner as the primary endpoint, with the SPID calculated by multiplying the PID score at each post-dose timepoint by the duration (in hours) since the preceding timepoint, then summing the values over the 24 hour period.

9.4.3.2 Change from Baseline of Pain on NRS

The change from baseline of pain on NRS score at 2 hours post-dose will be analyzed with a generalized linear mixed effect model that includes subject as a random effect, the baseline NRS (0-10) value as a covariate, and fixed effects for treatment group, stratification factor (use of daily medications / oral devices to reduce the intensity of TMD symptoms), scheduled time point, and time point by treatment group interaction. Time points included in the model are nominally at 15, 30, 45, 60, 90 and 120 minutes post-dose. Repeated measurements within-subject will be modeled using an unstructured covariance structure for within-subject error. In the case that the model fails to converge, a Huynh-Feldt error structure will be attempted, followed by an AR(1) structure. Error degrees of freedom will be calculated using a Kenward-Roger approximation. The difference estimate (rimegepant - placebo), SE, 95% CI, and p-value will be reported for 2 hours post-dose.

Interurrent events of use of a non-study rescue medication at or before 2 hours post-dose, or if a subject fails to log their pain score at any time after study drug is administered through 2 hours post-dose, will be handled in the same manner as they are for the primary endpoint.

9.4.3.3 Pain Freedom at 2 Hours

The number of subjects that are pain free at 2 hours post-dose will be analyzed after first imputing missing data at 2 hours to be failure (NC = F). Additionally, subjects who use rescue medication on or before assessment of pain at 2 hours will also be assigned as failures (RM = F). The analysis will be done using a stratified Cochran-Mantel-Haenszel (CMH) test after imputation is done, with the stratification factor as use of daily medications / oral devices to reduce the intensity of TMD symptoms.

9.4.3.4 Time to Onset of Meaningful Pain Relief

Time to onset of meaningful pain relief post-dose will be defined as the first nominal timepoint at which a 30% reduction of pain from baseline on NRS is achieved. This will be analyzed using Kaplan-Meier methods for a "time to event" analysis. Rimegepant will be compared to placebo using a log-rank test which will compare the survival distributions. Intercurrent events will be handled in the same manner as they are for the primary endpoint.

9.4.3.5 Time to Onset of Initial Pain Relief

Time to onset of initial pain relief post-dose will be defined as the first nominal timepoint at which a 1-point reduction of pain from baseline on NRS is achieved. This will be analyzed using Kaplan-Meier methods for a "time to event" analysis. Rimegepant will be compared to placebo using a log-rank test which will compare the survival distributions. Intercurrent events will be handled in the same manner as they are for the primary endpoint.

9.4.3.6 Rescue Medication Use through 24 Hours

The number of subjects that use rescue medication through 24 hours post-dose will be analyzed using a stratified CMH test, with the stratification factor as use of daily medications/oral devices to reduce the intensity of TMD symptoms.

9.4.4 Adjustment for Multiplicity

Type 1 error is addressed in this study using a gatekeeping procedure. The significance of the primary endpoint is evaluated at the two-sided alpha level of 0.05. If the primary endpoint is significant, then the secondary endpoints are tested using Hochberg's procedure.

CCI [redacted]

9.4.5 Missing Data

For the primary and secondary endpoints of SPID-2, SPID-24, change in NRS from baseline, time to onset of meaningful pain relief, and time to onset of initial pain relief, subjects who fail to record their pain during the timeframe of interest for each endpoint will be considered

failures (NC = F) and this data will be imputed to the last available observation prior to the missing data occurrence.

For the secondary endpoint of proportion of subjects that are pain free at 2 hours post-dose, missing data at 2 hours post-dose will be imputed as a failure (NC = F), and these subjects will not be considered as having achieved pain freedom.

For the secondary endpoint of proportion of subjects who use rescue medication through 24 hours-post dose, there will be no imputation for missing data, the analysis will be based on non-missing, observed data.

Additional methods for handling of missing data, including sensitivity analyses, will be described in detail in the SAP.

9.4.6 Rescue Medication

For the primary and secondary endpoints of SPID-2, SPID-24, change in NRS from baseline, time to onset of meaningful pain relief, and time to onset of initial pain relief, use of non-study rescue medications on or before the time point of interest (2 hours post-dose or 24 hours post-dose) will be handled as failures (RM = F). Specifically, the assumption will be that once the subject has used a rescue medication, their pain will not improve any further and these data points will be set to the last value recorded prior to the use of the rescue medication.

For the secondary endpoint of pain freedom at 2 hours post-dose, subjects that take rescue medication on or before the time point of interest (2 hours post-dose) will be considered as failures (RM = F).

Rescue medications are described in more detail in Section 5.5.

9.4.7 Analysis of Safety

The Investigators determine the intensity of AEs and the relationship of AEs to study therapy. The Investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs are presented by system organ class and preferred term, ordered by the overall frequency of events. If a subject had an adverse event with different intensities over time, then only the greatest intensity is reported.

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

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

Clinically significant laboratory test abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017), if available. Otherwise, if CTCAE grades are not available, then results will be graded according to numeric laboratory test criteria in Division of AIDS (DAIDS) Table for Grading the Severity

of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017). If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported.

Further safety analyses will be described in the statistical analysis plan.

9.5 Schedule of Analyses

The data from this study may be locked and analyzed at any point after the last subject completes their end of treatment visit and adequate time has been allowed for follow-up.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), International Conference on Harmonization guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any Independent Ethics Committee (IEC) requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, 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 subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

As per Section 5.8, any significant event that does not comply with the inclusion / exclusion criteria, study conduct, or study procedures will be documented as a deviation. A serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study. All serious breaches must be reported to Biohaven (or designee) immediately. Examples include (but are not limited to):

- Missing, inadequate, or delinquent informed consent.
- Randomization of a subject that does not meet key eligibility criteria.
- Failure to withdraw a subject meeting discontinuation criteria.
- Unreported serious adverse events.
- Improper breaking of the blind.
- Conducting the study without IRB approval.
- Working under an expired medical license, or a debarred or disqualified status.
- Falsifying research or medical records.

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).

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.

10.2 Institutional Review Board/Independent Ethics Committee

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

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

10.3 Informed Consent

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

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, sign and date an IRB/IEC approved written informed consent form for study. The signed and dated ICF will be retained at the Investigator's site, with a copy provided to the study subject and date will be entered in his or her CRF or appropriate system. The IRB/IEC must review and approve all protocol versions and informed consent form versions and a copy of each version of the IRB/IEC approved protocol and informed consent form is to be retained in the Study Master file. Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and subjects will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

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

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

10.4 Case Report Forms

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

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

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

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

11 RECORDS MANAGEMENT

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

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 (may be supplied by the Sponsor) is maintained at each study site where the study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

! amount of study drug received and placed in storage area

! label ID number or batch number or Kit number as specified for the protocol

! amount dispensed to and returned from each subject

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

! amount of drug lost or wasted

! amount destroyed at the site if applicable

! amount returned to sponsor, if applicable

! retain samples for bioavailability/bioequivalence, if applicable

! record of dates and initials of personnel responsible for IM dispensing and accountability

11.1 Source Documentation

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

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical records for each subject for verification of data

points, unless otherwise instructed by the Sponsor or designee to enter data directly on the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

11.2 Study Files and Record Retention

The Sponsor does not require original documents that have already been scanned and entered into the eTMF system to be forwarded to the Sponsor. Any original documents (i.e., 1572, signed financial disclosure, signed ICF, etc.) will be retained in the regulatory binder at the study site. The CRO will conduct a final TMF reconciliation to ensure all study files and regulatory documents have been correctly uploaded to the TMF prior to the close or termination of the study. Any materials or documents to support the clinical 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 the CRO or at another facility for a longer period of time at the Sponsor's expense.

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

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Biohaven (or specified designee). 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 or specified designee will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or 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 (or specified designee) is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of 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. However, authorized regulatory officials, IRB/IEC personnel, Biohaven and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs shall be by initials (when allowed), 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.

The Sponsor may approve the sharing of de-identified data from this study to be made available to researchers for the purpose of advancing the understanding of neurologic or psychiatric illness, rating scales, or trial methodology for the affected population. In any publication of this data, confidentiality of individual subjects will be protected.

16 CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Trial of BHV-3000 (rimegepant) Orally Disintegrating Tablet (ODT) for the Treatment of Temporomandibular Disorders (TMD)

Study No: BHV3000-317

Original Protocol Date: 09 Dec 2021

Protocol Version No: V3.0

Protocol Version Date: 31 Mar 2022

! The current risk-benefit evaluation of the investigational product.

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

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

Name and Title	Signature Approval	Date
Author: PPD MBA PPD Clinical Operations	PPD	
Clinical Operations: PPD PPD Clinical Operations	PPD	
Biometrics: PPD Ph.D PPD Biostatistics	PPD Ph.D. PPD	
Medical Lead: PPD MD PPD	PPD	
Regulatory Affairs: PPD MA PPD Regulatory Affairs	PPD	

17 APPENDICES

17.1 APPENDIX I – Strong Inhibitors and inducers of CYP3A4 protein (Not all-inclusive)

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

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

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

Resources:

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

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

Hachad H, Ragueneau-Majlessi I, Levy RH. A useful tool for drug interaction evaluation: the University of Washington Metabolism and Transport Drug Interaction Database. Hum Genomics. 2010 Oct;5(1):61-72.

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

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