DRUG:	BHV-3500
STUDY NUMBER(S):	BHV3500-201
PROTOCOL(S) TITLE:	BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine
IND NUMBER:	134,120
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	30 JANUARY 2019
VERSION NUMBER:	4.0
VERSION DATE:	08 AUGUST 2019

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine

Study No: BHV3500-201

Original Protocol Date: 30 JANUARY 2019

Protocol Version No: V 4.0

Protocol Version Date: 08 AUGUST 2019

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

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

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

Name and Title	**Signature Approval**	**Date**
Author/Protocol Writer: PPD I confirm, QC completed for required elements		
Clinical Operations: PPD		
Biostatistics: PPD		
Medical Lead: PPD		
Study Director: PPD		
Regulatory Affairs: PPD		

SUMMARY OF CHANGES

Change	**Page(s) Affected**	**Summary**
Corrected Table 1: Functional Disability Scale	28	Corrected Table 1 to add a "x" under Functional Disability Scale at the "Onset of moderate or severe migraine" timepoint. The "x" was inadvertently omitted previously. As described in Section 4.3.2.1, ratings of functional disability are recorded at the same time points as the headache severity ratings.

BHV-3500-201

BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-Ranging Trial of BHV-3500 for the Acute Treatment of Migraine

Confidentiality and Investigator Statement

The information contained in this protocol and all other information relevant to BHV-3500 are the confidential and proprietary information of Biohaven Pharmaceuticals, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Biohaven Pharmaceuticals, Inc.

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

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

_____ _____

Principal Investigator Name (printed) Signature

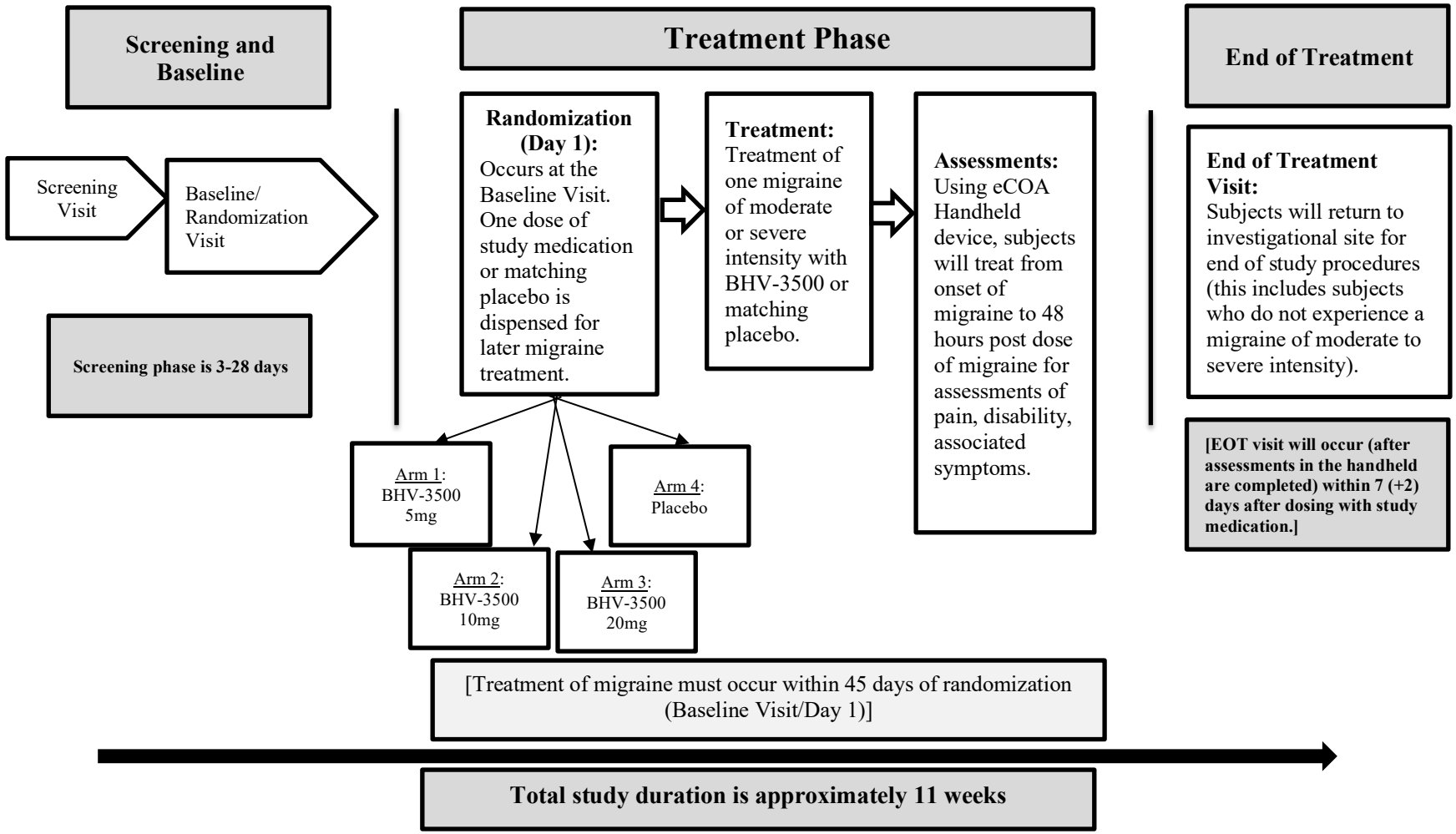
_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3500-201: Phase II/III: Double-Blind, Randomized, Placebo Controlled, Dose-ranging Trial of BHV-3500 for the Acute Treatment of Migraine
Rationale:	BHV-3500 is being developed for the treatment of migraine by the intranasal (IN) route. Nonclinical evidence suggests that BHV-3500, a CGRP receptor antagonist, possesses pharmacological properties suitable for the acute treatment of migraine. Intranasal administration of BHV-3500 in the single ascending dose study BHV3500-101 produced plasma levels predicted to be within the therapeutic range for compounds of this class. This study will evaluate the safety and efficacy of three different intranasal dose levels (5 mg, 10 mg, 20 mg) of BHV-3500, relative to placebo, in the acute treatment of moderate to severe migraine. This study was designed to identify at least one dose of BHV-3500 that is safe, well tolerated, and meets the registrational co-primary endpoints of pain freedom and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours post-dose. This information will be used in future trials to further define the safety and efficacy of the selected dose or doses.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a one-year history of migraines (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition,[1] including an age of onset prior to 50, migraine attacks that last 4 - 72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1900 subjects will be screened to randomize approximately 1600 subjects (approximately 400 per arm). The subjects will be randomized in a 3:1 ratio to the BHV-3500 or matching placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).
Objectives:	Primary: To evaluate the efficacy of BHV-3500 compared with placebo in the acute treatment of migraine as measured by co-primary endpoints of **pain freedom** and **freedom from the most bothersome symptom** (MBS), associated with migraine, at two hours post dose, while identifying an optimal dose for evaluation in the Phase 3 clinical trials.

STUDY SCHEMATIC



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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AT	Aminotransferase
AUC	Area Under the Curve
BHV	Biohaven Pharmaceuticals, Inc.
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Concentration
CGRP	Calcitonin gene-related peptide
CONMED	Concomitant Medication
CCI	[redacted]
CRO	Clinical Research Organizations
CV	Coefficient of Variation
DILI	Drug induced liver injury
DSMC	Data and Safety Monitoring Committee
DSM-V	Diagnostic and Statistical manual of mental Disorders Fifth edition
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report forms
EDC	Electronic Data Capture
eDiary	Electronic Diary
eGFR	Glomerular Filtration Rate
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice

GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHS	International Headache Society
IEC	Independent Ethics Committee
IN	Intranasal
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LDL	Low-density lipoprotein
kg	Kilogram
MBS	Most Bothersome Symptom
MDRD	Modification of Diet in Renal Disease
MedRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mg	Milligram
MI	Myocardial Infarction
Min	Minute
MQoL	Migraine Quality of Life Questionnaire
msecs	Milliseconds
MTD	Maximum tolerated dose
NOAEL	No-observable-adverse effect level
NSAIDs	Non-Steroidal Anti-Inflammatories
NRS	Numeric Rating Scale
OTC	Over the counter
PCI	Percutaneous Coronary Intervention
PCP	Phencyclidine

PK	Pharmacokinetic
PoM	Preference of Medication
PVG	Pharmacovigilance
QTc	Interval between Q-wave and T-wave in the cardiac cycle
SAD	Single Ascending Dose
SAE	Serious Adverse Event
S-STS	Sheehan Suicidality Tracking Scale
TBL	Total Bilirubin
TIA	Transient Ischemic Attack
T_{max}	Time of observed C_{max}
UDS	Unit Dose System
ULN	Upper Limit of Normal
USPI	US Prescribing Information
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Therapeutic Area Background

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. Migraine is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.[2] Triptans have been used to treat migraine attacks with varying results including incomplete and inconsistent relief at 2 hours, and the recurrence of migraine within 24-48 hours after treatment. In addition, triptans are contraindicated in patients with cardiovascular events (e.g., myocardial infarction), conditions (e.g., angina) and procedures (e.g., carotid endarterectomy) due to vasoconstrictive properties. Recent estimates indicate that there are 2.6 million Americans with migraine who have a cardiovascular event, condition or procedure, demonstrating the need for non-vasoactive migraine treatments.[3]

BHV-3500 is a selective, competitive CGRP receptor antagonist being developed for the treatment of migraine. BHV-3500 is being developed for IN administration. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells[4] and its activation is thought to play a causal role in migraine pathophysiology.[5] For example, research and clinical studies have shown that serum levels of CGRP are elevated during migraine attacks,[6] infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers,[7,8] and treatment with anti-migraine drugs normalizes CGRP levels.[9] Additionally, multiple clinical studies show that small molecule CGRP receptor antagonists, which inhibit the binding of endogenous CGRP to CGRP receptors, are effective in aborting migraine attacks.[10] Treatment with a CGRP receptor antagonist is believed to relieve migraine through the possible mechanisms of 1) blocking neurogenic inflammation, 2) decreasing artery dilation, and 3) inhibiting pain transmission. This new approach to the treatment of migraine avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists (e.g., sumatriptan [Imitrex™]).[11]

A summary of the nonclinical investigational programs can be found in the current Investigator's Brochure (IB).[12]

1.2 Product Development Background

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

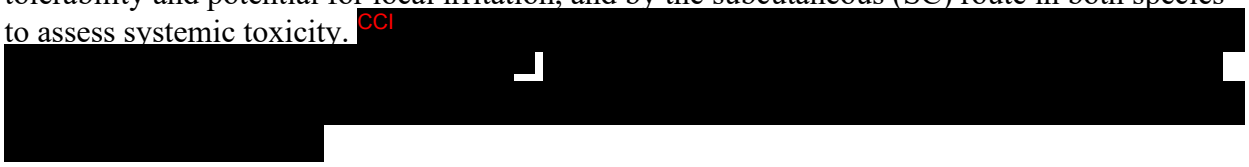
1.2.1 Non-clinical Pharmacology

1.2.1.1 Nonclinical Pharmacokinetics and Pharmacodynamics

A series of in vitro and in vivo pharmacokinetic (PK) and metabolism studies were conducted with BHV-3500 in rats, dogs, rabbits, mice and monkeys.

1.2.1.2 Nonclinical Toxicology

Safety studies in animals were performed by the IN route in rat and monkey to determine tolerability and potential for local irritation, and by the subcutaneous (SC) route in both species to assess systemic toxicity.



1.2.2 Clinical Experience

1.2.2.1 Single Ascending Dose (BHV3500-101)

Preliminary blinded data to date has shown BHV-3500 to be safe and well tolerated. No deaths or serious AEs have been reported in the study. No subjects have been discontinued due to AEs. Dose escalation to the highest planned dose of 40mg has been completed and no dose limiting toxicity has been observed. A Maximum Tolerated Dose (MTD) has not been identified.

All doses of BHV-3500 administered in the SAD study as of 07 March 2019 have been generally well tolerated, and all AEs graded as at least possibly related to study drug were mild in severity. CCI [redacted]

Thus far in the development of BHV-3500, clinical pharmacokinetic information is obtained from the SAD study.

1.2.3 Other Clinical/ Non-clinical Studies

1.2.3.1 CYP and Transporter Studies

BHV-3500 is not expected to cause any significant CYP-mediated drug interactions within the projected human dose range. CCI [redacted]

BHV-3500 was examined for effects in a transporter study.[15] CCI [redacted]

1.2.3.2 Phase 1 Studies

There is a planned series of clinical pharmacology studies with BHV-3500. Relevant information will be provided in the Investigator Brochure or protocol when available.

1.2.4 Clinical Adverse Event Profile

CCI [redacted]

Preliminary blinded data to date has shown BHV-3500 to be safe and well tolerated. No deaths or serious AEs have been reported in the study. No subjects have been discontinued due to AEs. The majority of AEs have been mild in severity. A Maximum Tolerated Dose has not been identified to date.

1.3 Study Rationale

BHV-3500 is being developed for the treatment of migraine by the intranasal route. Nonclinical evidence suggests that BHV-3500, a CGRP receptor antagonist, possesses pharmacological properties suitable for the acute treatment of migraine. Intranasal administration of BHV-3500 in the single ascending dose study produced plasma levels predicted to be within the therapeutic range for compounds of this class.

This study will characterize of the safety and efficacy of 3 different intranasal dose levels (5mg, 10mg, 20mg) of BHV-3500, relative to placebo, in the acute treatment of moderate to severe migraine.

This study is designed to identify at least one dose of BHV-3500 that is safe, well tolerated, and that meets the registrational co-primary endpoints of pain freedom and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours post-dose. This information will be used in future trials to further define the safety and efficacy of the selected dose or doses.

1.3.1 Study Design Rationale

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of BHV-3500 as compared to placebo in the treatment of moderate or severe migraine. The study drug will be intranasal BHV-3500 or a matching placebo. The subjects will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity.

The study will randomize approximately 1600 subjects in a 1:1:1:1 ratio across the 4 treatment groups [3:1 ratio of the BHV-3500 groups to the placebo group]. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

1.3.2 Dose Selection Rationale

Preclinical data predicts an effective human IN dose range of 2mg to 20mg. Clinical data to date from the BHV3500-101 study suggests the doses selected for this protocol will produce systemic exposures within the range predicted to have clinical efficacy.

The existing human safety data, and animal toxicity data, support these doses for inclusion in a single dose trial for the acute treatment of migraine. Given that acute migraine agents such as triptans and CGRP inhibitors often have step-function like dose-response curves, it is expected that the low dose, or doses, may have no effect, while a higher dose, or doses, will have full effect. This study is adequately powered to find a dose or doses of BHV-3500 that have strong effects in the treatment of acute migraine. If a dose is identified as safe and effective, the dose selected will be retested in a subsequent confirmatory trial.

Given the tolerability of BHV-3500 across a wide dose range, and in order to determine the optimal efficacious doses, this trial will study the efficacy and dose-response of BHV-3500 across a wide dose range in patients with a migraine attack.

1.3.3 Other Rationale related to the compound/study

Not Applicable

1.4 Research Hypothesis

The exploration of a range of BHV-3500 doses will reveal at least one dose that is safe and clinically superior to placebo in the acute treatment of migraine.

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the efficacy of BHV-3500 compared with placebo in the acute treatment of migraine as measured by the co-primary endpoints of **pain freedom** and **freedom from the most bothersome symptom** (MBS), associated with migraine, at two hours post dose, while identifying an optimal dose to support the Phase 3 clinical trials.

2.2 Secondary

1. To evaluate BHV-3500 compared to placebo on pain relief at 2 hours post-dose.

2. To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 2 hours post dose according to the Functional Disability scale.

3. To evaluate BHV-3500 compared to placebo on the probability of requiring rescue medication within 24 hours of initial treatment.

4. To evaluate BHV-3500 compared to placebo on freedom from photophobia at 2 hours post-dose.

5. To evaluate BHV-3500 compared to placebo on freedom from phonophobia at 2 hours post-dose.

6. To evaluate BHV-3500 compared to placebo on pain relief at 60 minutes post-dose.

7. To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 60 minutes post dose according to the Functional Disability scale.

8. To evaluate BHV-3500 compared to placebo on pain relief at 30 minutes post-dose.

9. To evaluate the effect of BHV-3500 relative to placebo on the patient's ability to function normally at 30 minutes post dose according to the Functional Disability scale.

10. To evaluate BHV-3500 compared to placebo on sustained pain relief from 2 to 24 hours post-dose.

11. To evaluate BHV-3500 compared to placebo on sustained pain freedom from 2 to 24 hours post-dose.

12. To evaluate BHV-3500 compared to placebo on sustained pain relief from 2 to 48 hours post-dose.

13. To evaluate BHV-3500 compared to placebo on sustained pain freedom from 2 to 48 hours post-dose.

14. To evaluate BHV-3500 compared to placebo on freedom from nausea at 2 hours post-dose.

15. To evaluate BHV-3500 compared to placebo for the incidence of pain relapse from 2 to 48 hours post-dose

2.3 Exploratory

1. To evaluate the effect of BHV-3500 relative to placebo on the patients ability to function normally at 24 hours post dose according to the Functional Disability scale.

2. To evaluate the effect of BHV-3500 relative to placebo on the Migraine Preference of Medication (PoM).

3. To evaluate BHV-3500 relative to placebo for pain freedom at all scheduled time points post dose.

4. To evaluate BHV-3500 relative to placebo for pain relief at all scheduled time points post dose.

5. To evaluate BHV-3500 relative to placebo for freedom from MBS at all scheduled time points post dose.

6. To evaluate BHV-3500 relative to placebo for freedom from functional disability at all scheduled time points post dose.

7. To evaluate the effect of BHV-3500 relative to placebo on the Migraine Quality of Life Questionnaire (MQoL).

8. To evaluate the tolerability and safety of BHV-3500 in the acute treatment of migraine as measured by the frequency of adverse events of at least moderate intensity, serious adverse events; and clinically relevant laboratory abnormalities.

9. To evaluate the effect of BHV-3500 relative to placebo on the Sheehan Suicidality Tracking Scale (S-STS).

3 STUDY ENDPOINTS

3.1 Primary

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

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

3.2 Secondary

1. Pain Relief (aka "headache response"), at 2 hours post-dose, will be assessed using the number of subjects that report a pain level of none or mild (response of 0 or 1) at two hours post-dose.

2. The proportion of subjects able to function normally, at 2 hours, will be assessed by tabulating the number of subjects that report as being able to function normally on the functional disability scale in the subset of subjects that reported any level of disability at the migraine baseline.

3. 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.

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

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

6. Pain Relief at 60 minutes post-dose, will be assessed using the number of subjects that report a pain level of none or mild (response of 0 or 1).

7. The proportion of subjects able to function normally, at 60 minutes, will be assessed by tabulating the number of subjects that report as being able to function normally on the functional disability scale at 60 minutes in the subset of subjects that reported any level of disability at the migraine baseline.

8. Pain Relief at 30 minutes post-dose, will be assessed using the number of subjects that report a pain level of none or mild (response of 0 or 1).

9. The proportion of subjects able to function normally, at 30 minutes, will be assessed by tabulating the number of subjects that report as being able to function normally on the functional disability scale at 30 minutes in the subset of subjects that reported any level of disability at the migraine baseline.

10. Sustained pain relief, from 2 to 24 hours will be assessed using the number of subjects that do not experience any moderate or severe migraine pain through the time period of interest.

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

12. Sustained pain relief from 2 to 48 hours, will be assessed using the number of subjects that do not experience any moderate or severe migraine pain through the time period of interest.

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

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

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

3.3 Measures of Interest

Safety and Other assessments:

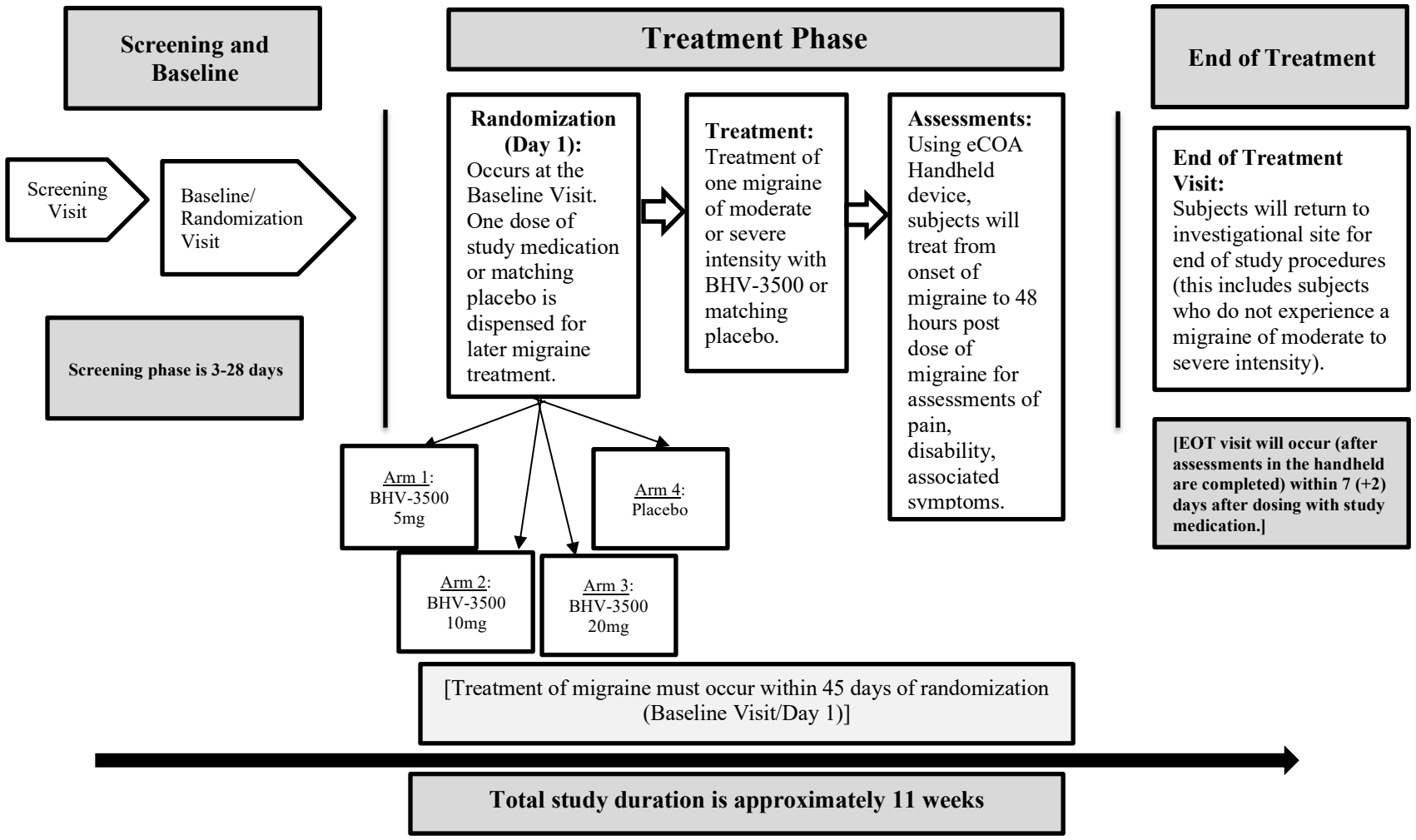
- Adverse Events
- ECG assessments
- Vital Sign and Physical Measurements
- Routine Laboratory Tests
- Sheehan Suicidality Tracking Scale (S-STS)
- Preference of Medication (PoM)
- Assessment of Migraine Pain and Symptoms
- Migraine Quality of Life Questionnaire (MQoL)
- Nasal Inspection

4 STUDY PLAN

4.1 Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of BHV-3500 as compared to placebo in the treatment of moderate or severe migraine. Subjects will be dispensed one Aptar Unit Dose System (UDS) liquid spray device containing a single dose of study medication BHV-3500 or a matching placebo. The total duration of the study will be approximately 11 weeks. This includes a 3-28 day Screening Period, a Treatment Phase that can last up to 45 days or until the subject has a migraine that reaches moderate or severe intensity, followed by an End of Treatment Visit 7 (+2) days after the administration of study medication.

4.2 Study Schematic



4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Onset of moderate or severe migraine[3]	Post Study Medication Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14]
Eligibility Assessments					
Informed Consent	X				
Inclusion/ Exclusion Criteria	X	X			
Medical History	X				
Migraine History Assessment (signs/ symptoms/ prior treatment/ frequency/ intensity)	X				
Rescue Medication paper diary, Concomitant Medication paper diary[4]	X	X	X	X	X
Randomize subject in IWRS[5]		X			
Safety Assessments					
Physical Examination	X				X
Nasal Inspection[6]	X	X			X
Vital Signs/ Physical Measurements[7]	X	X			X
Adverse Event and Serious Adverse Event Assessment[8]	X	X	X	X	X
Sheehan Suicidality Tracking Scale (S-STS)[9]	X	X			X
ECG	X				X
Clinical Safety Laboratory Testing	X				X

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Onset of moderate or severe migraine[3]	Post Study Medication Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14]
Liver Function Tests (LFTs)	X				X
Lipid Panel	X				
FSH, if applicable, to determine WOCBP status	X				
Pregnancy Test[10]	X (Serum)	X (Urine)	X (Urine)		X (Serum)
Urinalysis	X				X
Urine drug screen for drugs of abuse	X				X
Clinical Drug Supplies/Study Supplies					
eCOA Handheld device assigned		X			
Dispense study medication[11]		X			
Administer study medication			X		
Patient Education: Dose Administration		X			
Patient Education: eCOA Handheld		X			
Enter use of study medication in eCOA Handheld device			X		
Return used or unused study medication					X
eCOA Handheld returned/ reviewed for completeness[12]					X

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Onset of moderate or severe migraine[3]	Post Study Medication Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14]
Efficacy Assessments[12]					
Assessment of migraine pain[13]			X	X	
Assessment of Migraine Symptoms (photophobia, phonophobia, and nausea)[13]			X	X	
Functional Disability Scale[13]			X	X	
MQoL (Migraine Quality of Life Questionnaire)[13]				X (24-hour assessment)	
Preference of Medication (PoM)[13]				X (24-hour assessment)	

[1] **Screening Phase** will be 3 - 28 days. Subject should be entered in the IWRS once they sign the informed consent form to obtain their study subject identification code.

[2]The **Baseline/ Randomization Visit** may only occur ***after*** all screening procedures are completed and the subject meets all inclusion/exclusion criteria. If the subject does not meet all eligibility requirements, the subject should be screen failed in the IWRS.

[3] Subjects will use their assigned eCOA handheld device to answer questions about their migraine symptoms upon experiencing a moderate or severe migraine headache. The subject will administer study drug or matching placebo if the following criteria are met: 1) the headache remains moderate or severe; 2) the subject has completed all required migraine assessment questions in the handheld, including their current most bothersome migraine symptom, and 3) the subject has not already taken prohibited medications (see protocol section 5.4).

[4] Subjects should keep track of their concomitant and rescue medications on the appropriate study paper diary provided throughout the study. These diaries should be returned to the investigational site for review and electronic data capture (EDC) entry.

[5] The randomization visit is considered day 1 out of the 45 days subjects have to treat and report a migraine in their handheld device. Subjects will be randomized in the IWRS and will be stratified by answering “yes” or “no” to prophylactic migraine medication use in the IWRS.

[6]Nasal inspection – The nasal passages and turbinates will be visually inspected with a nasal speculum or otoscope at the screening, baseline and end of treatment visits to detect evidence of nasal inflammation or edema.

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

[8] SAEs are reported from the time of signed informed consent and non-serious AEs are reported from baseline. All ongoing non-serious AEs and SAEs will be followed to resolution or until the Investigator deems there will be no further status change. SAEs that occur during the treatment period should be reported to site in real time. Non-serious AEs that occur during the treatment period should be reported to the site at the EOT.

[9] The S-STS will be clinician administered on site with a paper form. The source document will be provided digitally by Biohaven. The assessment period for completing the scale will be 30 days prior to the Screening Visit, and since the last visit for the Baseline/Randomization and End of Treatment Visits.

[10] For WOCBP: A serum pregnancy test will be collected at the Screening and End of Treatment Visits as part of the standard laboratory tests. Confirmatory urine pregnancy test will be completed on site at Baseline Visit and any subsequent visits for confirmation at the Investigator's discretion. Home pregnancy test will be provided to WOCBP after completion of Baseline Visit. WOCBP subjects must complete the urine pregnancy test at home **prior** to taking study medication.

[11] Subjects should be instructed that the dose should be taken once the migraine attack reaches moderate or severe pain and after the subject has completed all required migraine assessments in the handheld. The handheld will prompt the subject to take study medication.

[12] Site staff to review and confirm all data points are transferred from the handheld and reset handheld for future subject use, PRIOR to the subject leaving the clinic.

[13] The Functional Disability, MQoL and Preference of Medication scales will be captured in the handheld device. Subjects will also be asked about their most bothersome symptom at the time of reporting and treating a qualifying migraine.

[14] Subjects will return to the site for their End of Treatment Visit (after assessments in the handheld are completed) within 7 (+2) days after dosing with study medication. The "+2" day window is included for scheduling purposes only.

4.3.1 Screening Phase (3-28 days)

Approximately 1900 subjects will be screened to randomize approximately 1600 subjects to study mediation (BHV-3500 or matching placebo).

Before any study procedures are performed, subjects must sign informed consent. After informed consent is signed, subjects will be enrolled in the IWRS system. The subject's migraine history and medical history will be collected at the Screening Visit. Subjects will also undergo all screening procedures as detailed in Table 1. Within 3-28 days from the Screening Visits, subjects will return to the site for the Baseline/ Randomization Visit; if the subject does not meet all eligibility criteria, the subject will be considered a Screen Failure.

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

4.3.2 Randomization Phase (45 days)

Subjects will return to the study site for the Baseline (Randomization) Visit.

Subjects who meet all eligibility criteria they may be randomized at the Baseline Visit. Randomization will occur in the IWRS. The subjects will be provided with an eCOA Handheld device. The study personnel will instruct the subject on the proper use of the handheld to ensure proper understanding and use of the tool, prior to the subject leaving the office.

After randomization is completed in the IWRS, study medication will be dispensed to subjects to take home for up to 45 days. The study personnel must train the subject on the proper use of Aptar UDS device using instructions to be provided to each study subject. This study medication is to be taken when a migraine attack reaches moderate or severe intensity on the numeric rating scale (NRS) as indicated in the handheld. The subject will be instructed to take their study medication, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe intensity **after they have answered questions about their current pain and symptoms and identified their currently most bothersome, migraine associated, symptom (phonophobia, photophobia or nausea) in the handheld**. The subject will complete assessments for forty-eight 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.

4.3.2.1 eCOA Handheld Device Data Collection

The eCOA handheld device may also be referred to as a handheld or an eDiary. Once a subject experiences a headache of moderate to severe intensity, they should record this in the handheld. The handheld will instruct the subject to take study medication after the initial assessments are completed in the device.

The following will be recorded in the eCOA handheld device:

- Onset time of headache, intensity of the headache prior to and at time of taking study medication
- Headache severity will be recorded using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours
- The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (four-point scale: normal, mildly impaired, severely impaired, requires bedrest) will be recorded at the same time points as the headache severity ratings.
- Subjects will also identify their currently most bothersome symptom before taking study medication
- Subjects will complete the migraine-specific quality-of-life questionnaire (MQoL), Functional Disability Scale and preference of medication (PoM) 24 hours after dosing.

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

Subjects should be encouraged to treat their first qualifying (moderate to severe) migraine that occurs during the treatment phase. If subjects are unable to treat their first qualifying migraine, refer to section 5.4.1 Rescue Medications for a list of medications that are allowed during the course of this study.

4.3.3 Extension Phase

Not Applicable

4.3.4 End of Treatment Visit

Subjects will return to the site for their End of Treatment Visit (after assessments in the handheld are completed) within 7 (+2) days after dosing with study medication. The “+2” day window is included for scheduling purposes only.

At the End of Treatment Visit, medication compliance, monitoring of tolerability and safety assessments (including vital signs, laboratory tests, nasal inspection and electrocardiography) will be performed. Refer to Table 1 for a full list of assessments completed at the EOT.

If a subject has NOT experienced a migraine headache of moderate or severe intensity within 45 days after randomization, they are still required to complete all EOT visit procedures. All subjects must return used and unused study medication and their handheld device to the investigational site.

4.4 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 migraines. The treatment setting for these subjects may include clinics, institutions or private office practices. Subjects may be recruited through a variety of sources, including referrals from physicians and other health care professionals.

5.1 Number of Subjects

It is anticipated that approximately 1900 subjects will need to be screened in order to randomize approximately 1600 subjects. The subjects will be randomized in a 3:1 ratio to the BHV-3500 or placebo treatment groups. It is anticipated that enrollment will occur at approximately 80 sites in the United States over a period of approximately 5 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. Subjects must be able to read English or Spanish.

2. Target Population

    Subjects with minimum 1 year history of migraines (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition,[1] including the following:

    a. Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age.

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

    c. Not more than 8 attacks of moderate or severe intensity per month within last 3 months.

    d. Subjects must be able to distinguish migraine attacks from tension/cluster headaches.

    e. At least 2 consistent migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and throughout the Screening Period (subject self-report).

f. Less than 15 days with headaches (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and throughout the Screening Period (subject self-report).

g. Subjects on prophylactic migraine medication are permitted to remain on therapy if they have been on a stable dose for at least 3 months prior to screening visit, and if the dose is not expected to change during the course of the study.

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

3. Age and Reproductive Status

   a. Male and Female subjects ≥18 years of age.

   b. Women of childbearing potential (WOCBP) with male partners and men with women partners of childbearing potential must use 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.

   c. Males with vasectomy are considered surgically sterile provided the procedure occurred greater than 6 months (24 weeks) prior to study participation.

   d. Women must not be lactating or breastfeeding.

   e. At the Baseline Visit prior to dispensing Investigational Study Medication, WOCBP must have a negative urine pregnancy test.

4. Other Inclusion Criteria

   a. 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 if in the opinion of the Investigator the finding is not clinically significant, will not introduce additional risk factors or interfere with the study procedures (not including exclusion criteria listed in Section 5 below).

5.3 Exclusion Criteria

1. Disease Target Exclusion

    a. Subjects with a history of basilar migraine or hemiplegic migraine.

2. Medical History and Concurrent Diseases

    a. Subjects history of HIV disease.

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

    c. Uncontrolled hypertension (high blood pressure), or uncontrolled diabetes (however, subjects can be included who have stable hypertension and/or stable diabetes for at least 3 months prior to being enrolled). A single blood pressure measurement of greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary.

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

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

    f. 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 (SAE) or interfere with assessments of safety or efficacy during the course of the trial.

    g. Acute or chronic treatment with OTC or prescription nasal sprays. Subjects must stop all OTC/Rx nasal sprays 14 days prior to the screening visit and refrain from use until study completion.

    h. History of nasal surgery in the 6 months preceding the screening visit.

i. Evidence at screening of significant nasal conditions that may affect the administration or absorption of the nasal product (e.g. severe septum deviation, nasal deformity or blockage, inflammation, perforation, mucosal erosion or ulceration, polyposis, nasal trauma) as evaluated by the Investigator or medically qualified delegate.

j. Presence of piercings in the nose that, in the opinion of the Investigator, would be likely to interfere with positioning of the Aptar UDS device and successful completion of the dosing procedure.

k. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria[16] for any significant substance use disorder within the past 12 months from the date of the screening visit.

l. 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:

   i. 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 baseline until the end of treatment visit occurs.

   ii. Detectable levels of marijuana in the drug screen are not exclusionary, if in the Investigator's documented opinion the subject does not meet DSM-V criteria[16] 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.

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

n. Body mass index $\geq$ 35 kg/m^2

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

3. Allergies and Adverse Drug Reactions

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

4. Sex and Reproductive Status

    a. Females of child-bearing potential who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for 90 days after the study.

    b. Women who are pregnant, lactating or breastfeeding.

    c. Women with a positive pregnancy test on enrollment or prior to study drug administration.

5. ECG and Laboratory Test Findings

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

    b. Corrected QT interval > 470 msec (QTc by method of Frederica), 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 or Direct) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for confirmation during the screening period).

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

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

    i. HbA1c ≥ 7%

6. Other Exclusion Criteria

    a. Prisoners or subjects who are involuntarily incarcerated.

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

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

d. Subjects who have previously participated in any BHV-3500 study within the last 2 years.

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

f. Score of > 0 on the Sheehan Suicidality Tracking Scale for the period of 30 days prior to Screening and during the study.

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

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

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

5.4 Prohibited Concomitant Medication

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

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

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

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

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

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

6. History of non-narcotic analgesic intake on greater than/equal 15 days per month for greater than/equal 3 month (e.g. acetaminophen, NSAIDs, gabapentin etc.) ***for other pain indications.*** (Please refer to Section 5.4.1 for rescue medication).

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

8. Use of all acetaminophen or acetaminophen containing products must be discontinued at least 2 days prior to randomization (acetaminophen up to1000mg/day is allowed as rescue

medication as directed in Section 5.4.1). During the screening phase (3-28 days) use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000mg/day is prohibited.

9. Use of marijuana is prohibited during the study.

10. Muscle relaxants (baclofen is allowed as rescue medication, see Section 5.4.1).

11. Concomitant use of strong CYP3A4 inhibitors with BHV-3500 is prohibited during the study. If use of a strong CYP3A4 inhibitor is required, such as use of HIV Protease Inhibitors, Hepatitis C protease inhibitors, certain azole antifungals, or clarithromycin, dosing with BHV-3500 should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inhibitor. Refer to Section 15.2, Appendix 2.

12. Concomitant use of strong CYP3A4 inducers with BHV-3500 is prohibited during the study. If use of a strong CYP3A4 inducer is required, such as use of carbamazepine, phenytoin, or rifampin, dosing with BHV-3500 should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inducer. Refer to Section 15.2, Appendix 2.

13. Use of OTC or prescription topical nasal steroids, oxymetazoline, topical nasal antihistamines, topical nasal anticholinergics, and topical nasal mast cell stabilizers should not be taken within 14 days prior to the screening visit and throughout the study.

14. Subjects on prophylactic migraine medication are permitted to remain on therapy provided they have been on a stable dose for at least 3 months prior to study entry.

15. The use of CGRP antagonists (biologic or small molecule) is prohibited during the study. CGRP antagonist biologics must be discontinued 6 months prior to screening.

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

5.4.1 Rescue Medications

After dosing with study medication, all other headache medication is prohibited during the first 2 hours post dose of study drug administration. A subject who does not experience relief of their migraine headache at the end of 2 hours after dosing with study medication (***and after the two hour assessments have been completed on the handheld device***), will be permitted to use ONLY the following rescue medication: ***aspirin, ibuprofen, acetaminophen up to 1000mg/day (this includes Excedrin Migraine) Naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours post dose of study medication.***

If the migraine is relieved by study medication at 2 hours after dosing but then returns to a moderate or severe intensity level between 2 and 48 hours, the subject will be permitted to take the same rescue therapy as outlined above.

If needed, 48-hours after dosing with the study medication (and before returning to the clinical site for the End of Treatment Visit), the subject may take their prescribed standard of care medications for treatment of migraine (including triptans if not contraindicated), provided all of the assessments have been completed on the handheld.

In all circumstances, the subject will always continue to complete the handheld entries through the 48-hour assessment after taking the study medication. Use of concomitant medication after randomization, including rescue medication, will be recorded by the subject on a paper diary and returned 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) in the EDC.

During the 45 days of the treatment phase, if the subject has a nonqualifying migraine (mild migraine) or a migraine that they do not treat with study medication, the subject is permitted to use only the following medications: ***aspirin, ibuprofen, Naprosyn (or any other type of non-steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen***.

After completing all assessments (through 48 hours and before End of Treatment Visit) in their handheld, if subjects experience a migraine they are allowed to take their prescribed (excluding prohibited medications) standard of care medication (including triptans if not contraindicated and acetaminophen up to 1000mg/day, this includes Excedrin Migraine).

5.5 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 tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Menopause is defined as:

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

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

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

4. Woman on hormone replacement therapy (HRT)

Women of childbearing potential (WOCBP) with male partners, and men with female partners of childbearing potential, must commit to use two acceptable methods of contraception to avoid pregnancy throughout the study and for up to 90 days after the last dose of investigational product in such a manner that risk of pregnancy is minimized. It is required to use two methods of contraception for the duration of the study (i.e. this study begins with signed consent form through 90 days after dosing with study medication). The two methods should include one barrier method (i.e. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include oral contraceptives or another barrier method (note, an Intra Uterine Device is considered one method).

Women who suspect that they have become or may have become pregnant despite using proper birth control methods, should use the home pregnancy test provided at Baseline Visit. All WOCBP must administer the home pregnancy test prior to taking Investigational Study Drug. If the pregnancy test is positive, subjects should not take study medication and should immediately contact the Investigator.

Male subjects must be willing not to donate sperm until 90 days following the last study drug administration.

5.6 Other Restrictions and Precautions (if applicable)

Not Applicable

5.7 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion criteria, exclusion criteria, study conduct, or study procedures will be documented as a protocol deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Clinically significant deviations will be reported to the IRB/EC at the frequency as required by local IRB/EC requirements. There will be no protocol exceptions granted by the Sponsor for Inclusion/Exclusion criteria.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

- Investigator File/Study Binder
- Drug Accountability Logs
- Sample source documents
- Concomitant and Rescue Medication Logs (take home for subject)
- Investigator Brochure
- Interactive Web-based Response System (IWRS) manual
- Electronic Case Report Forms (eCRF)
    - Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields
- eCOA Handheld devices
    - One device to be kept onsite for training purposes with training materials
    - Supply of devices for each randomized subject to receive one device to use during the treatment phase
- Drug administration instructions
- Laboratory kits and laboratory manual
- Home pregnancy test for each randomized subject of WOCBP
- ECG Machine and instructions
- Serious Adverse Event (SAE) forms and Serious Adverse Events (SAE) Reporting instructions
- Pregnancy surveillance forms
- S-STS source documents

- Single use, disposable nasal speculum provided upon request
- Study system access:
    - Electronic Data Capture (EDC) tool to submit study data to Sponsor/ CRO
    - IWRS
    - Central Laboratory

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

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

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

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at 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.

6.2.3 Physical Exam

Subjects will undergo a routine physical examination during the Screening Phase and at the scheduled visits as outlined in Table 1. Physical exam will include nasal inspection.

6.2.3.1 Nasal Inspection

The nasal passages and turbinates will be visually inspected by the Investigator or medically qualified delegate with a nasal speculum or otoscope at the screening, baseline and end of treatment visits to detect evidence of significant nasal conditions that may affect the administration or absorption of the nasal product (e.g. severe septum deviation, nasal deformity or blockage, inflammation, perforation, mucosal erosion or ulceration, polyposis, nasal trauma). Nasal findings will be recorded as appropriate and followed until resolution.

6.2.4 Laboratory Assessments

6.2.4.1 Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 for clinical laboratory evaluations. A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site. **If possible, 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.

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

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

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

Urine Drug Screen: For drugs of abuse.

6.2.4.2 Pregnancy Testing

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

6.2.5 Sheehan Suicidality Tracking Scale (S-STS)

The S-STS is a prospective clinician administered rating scale that contains questions that track both treatment-emergent suicidal ideation and behaviors [17,18]. The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is within the last 30 days prior to the screening visit; at all other visits, the recall period for completing the S-STS is since the last visit. Subjects who have a S-STS score of >0 should be evaluated by the Investigator. If the Investigator determines that a subject is at risk of suicide or self-harm,

appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. The subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the Investigator and reported within 24-hours to the Sponsor.

6.3 Efficacy Assessments

6.3.1 Pain

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

6.3.2 Nausea, Phonophobia and Photophobia

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

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

6.3.3 Rescue Medication

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

6.3.4 Functional Disability

Impact of treatment on functional disability will be assessed using a single-question scale. Subjects rate the level of disability they perceive as a result of their migraine in performing normal actions. This is done in the handheld, at the times indicated in Table 1, using a 4 point numeric rating scale (normal function, mild impairment, severe impairment, required bedrest).

6.3.5 Migraine Quality of Life Questionnaire

Impact of treatment on subject-reported quality of life will be assessed using The Migraine Quality of Life Questionnaire (MQoL) version 3.0. The MQoL is a 15-item instrument that has been validated in migraine subjects to assess the effect of migraine and its treatment on patients' health related quality of life in the following five migraine-specific domains: work functioning, social functioning, energy/vitality, feelings and concerns, and migraine headache symptoms. The handheld is used to evaluate the Migraine Quality of Life Questionnaire at 24 hours post-dose (see Table 1).

6.3.6 Migraine Preference of Medicine

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

6.4 Early Discontinuation from the Study

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the Investigator 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, Inc.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

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

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

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

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

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

The BHV-3500 or the matching placebo will be provided in single use Aptar UDS devices fully prepared and ready for administration. The BHV-3500 and placebo solution are identical in appearance.

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 as non-investigational products.

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

7.1.3 Packaging, Shipment and Storage

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

7.2 Dose and Administration

7.2.1 Method of Assigning Subject Identification

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

study through the 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 at the time of signing consent.

After completion of all screening evaluations all eligible subjects will be randomized in a 3:1 ratio to the BHV-3500 or placebo treatment groups. **The randomization will be stratified by the use of prophylactic migraine medications (yes or no). It is important to correctly enter subjects who are using prophylactic migraine medication in the IWRS system. Once a patient is stratified in the IWRS, this cannot be changed and will be considered a significant deviation.**

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

7.2.2 Selection and Timing of Dose and Administration

Study medication (Aptar UDS containing BHV-3500 or matching placebo) will be packaged in a carton. There are no dose adjustments in this study and subjects will receive study medication sufficient to treat one migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit). Subjects will be dispensed the study medication at randomization (Baseline Visit) and will take the Aptar UDS from the carton at the time of moderate or severe migraine headache onset ***ONLY after answering questions regarding their migraine symptoms in the handheld*** device. Subjects will administer a single spray of the medication from the device. Subjects must inform the study staff if they sneeze, if the device malfunctions or if the device does not dispense a complete spray.

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 for remaining site personnel 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 migraine occurs and reaches moderate or severe intensity. If the subject does not have a qualifying migraine or take their study medication within 45 days of the Baseline Visit, they should return to the clinic for their End of Treatment Visit and return their study medication.

7.5 Destruction and Return of Study Drug

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

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

8 ADVERSE EVENTS

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

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

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

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

8.1 SERIOUS ADVERSE EVENT

8.1.1 Definition of Serious Adverse Event (SAE)

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received BHV-3500
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization
    - Development of drug dependency or drug abuse
    - Potential drug-induced liver injury

Definition of Terms

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

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

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

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

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

2. Elective surgery, planned prior to signing consent;

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

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

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

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

8.1.2 Collection and Reporting Serious Adverse Events

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

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 8.1.3), potential drug induced liver injury (see Section 8.1.5) and pregnancies (see Section 8.1.4) must be reported within 24 hours of the Investigator becoming aware of the event. For this study we will be capturing SAEs through electronic data capture (EDC) and on the SAE form.

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

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

- PPD

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

- PPD

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)

8.1.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered excessive and medically important as determined by the Investigator. All occurrences of overdose (suspected or confirmed and irrespective of whether or not it involved BHV-3500 or placebo) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

8.1.3.1 Dose misadministration and Aptar UDS malfunction

All occurrences of dose misadministration or Aptar UDS malfunction should be communicated to Biohaven or a specified designee as soon as possible.

8.1.4 Pregnancy

If following the baseline visit, it is subsequently discovered that a study subject, or the female partner of a male 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's safety). Protocol-required procedures for the study discontinued and the 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 immediately if they become pregnant during the course of the study. The Investigator must immediately notify the Biohaven Medical Monitor (or designee) of the event and complete and forward the Pregnancy Report Form to CCI PVG immediately via telephone within 24 hours and in accordance with SAE reporting procedures as described in Section 8.1.2.

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

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

8.1.5 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

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

8.2 Non-serious Adverse Events

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

8.2.1 Collection and Reporting of Non-Serious Adverse Events

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

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

8.2.2 Laboratory Test Abnormalities

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

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

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

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

9 STATISTICS

9.1 General Procedures

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

For the calculation of descriptive statistics of observed data, subjects must have a baseline value to be evaluable for endpoints based on 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 95% of the 400 subjects randomized to each arm treat a migraine on study, there will be roughly 380 mITT subjects in each arm. If the true response rates for pain freedom at 2 hours are 22% and 12% in the BHV-35000 and placebo arms, then a chi-square test, at alpha=0.0167, will have 90% power. Similarly, if the true response rates for MBS freedom at 2 hours are 45% and 32% in the BHV-3500 and placebo arms, then a chi-square test, at alpha=0.0167, will have 90% power. Under the assumption that the endpoints are independent, the power for both endpoints jointly is roughly 80%.

9.3 Populations for Analysis

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

- Randomized subjects: Enrolled subjects who receive a randomization treatment assignment from the IWRS (BHV-3500 or placebo).

- Treated subjects: Enrolled subjects who take study therapy (BHV-3500 or placebo).

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

9.4 Statistical Methods

9.4.1 Primary Endpoint(s)

Each of the three doses of BHV-3500 is tested for superiority against placebo, at a Bonferroni corrected alpha=0.0167 level, on both pain freedom at 2 hours post-dose and freedom the most bothersome symptom at 2 hours post-dose. Both endpoints are evaluated using Cochran-Mantel Haenszel methodology to estimate the common risk difference, and are stratified by the use of prophylactic migraine medication (yes or no). These tests are conducted using the mITT subjects, with missing data at two hours imputed to be failure (i.e., Non-Completers = Failure; NC=F). Sensitivity analyses are described in the Statistical Analysis Plan (SAP).

9.4.2 Secondary Endpoint(s)

If the primary endpoint tests are both significant for a dose, then the secondary endpoints are evaluated for that dose using a hierarchical gate-keeping procedure, with each test in the hierarchy conducted at alpha=0.0167. These secondary endpoints will be tested in the order shown in the Study Objectives section of this protocol.

9.4.3 Analysis of Safety

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

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

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

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

9.4.4 Demographic and Baseline Characteristics

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

9.5 Interim Analysis

There is a final analysis after the database is locked. No interim analyses are anticipated.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IRB/IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, 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.

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

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

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

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data and Safety Monitoring Committee (DSMC). Safety will be closely monitored via the sites and procedures for unblinding in cases of emergency will be followed.

10.3 Institutional Review Board/Independent Ethics Committee

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

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

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

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

10.4 Informed Consent

Investigators must ensure that 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 and sign a written informed consent form. This signed informed consent form will be reviewed and approved by an IRB/IEC, revisions to the protocol and informed consent form will be reviewed and approved by the IRB/IEC, a copy retained in the Study Master File, and the date and time the subject signed the form will be entered in his or her CRF. The subject will be provided with a copy of his or her signed and dated informed consent form.

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

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

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

10.5 Case Report Forms

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

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

The confidentiality of records that could identify 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.

10.6 Records Management and Retention

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

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

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

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

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

1. amount of study drug received and placed in storage area
2. label ID number or batch number or Kit number as specified for the protocol
3. amount dispensed to and returned from each subject
4. amount transferred to another area or site for dispensing or storage if applicable
5. amount of drug lost or wasted
6. amount destroyed at the site if applicable
7. amount returned to sponsor, if applicable
8. retain sampled for bioavailability/bioequivalence, if applicable
9. record of dates and initials of personnel responsible for IM dispensing and accountability

10.7 Source Documentation

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

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

10.8 Study Files and Record Retention

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

11 AMENDMENTS

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

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

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

12 STUDY REPORT AND PUBLICATIONS

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

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

13 STUDY DISCONTINUATION

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

14 CONFIDENTIALITY

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

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

15 APPENDICES

15.1 APPENDIX I – Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals, Inc. Refer to study reference manual for contact information
Sponsor Medical Monitor:	PPD PPD
Clinical Research Organizations:	CCI Refer to contact list in Study Binder for contact information
Central Laboratory:	CCI Refer to study manual for contact information
Central ECG	CCI Refer to study manual for contact information
eCOA	CCI Refer to study manual for contact information
Pharmacovigilance Vendor	CCI Refer to SAE, Pregnancy Surveillance Forms and Study Binder for contact information.

15.2 APPENDIX II – Strong CYP3A4 Inhibitors and Inducers (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 CYP3A inhibitors is prohibited. Individual drug labels should be reviewed for specific information on propensity to inhibit CYP3A4 for a specific compound.

Strong CYP3A 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

The following medications and supplements are some of the strong inducers of CYP3A4. The list should not be considered all-inclusive. As described in the study protocol, concomitant use of strong CYP3A inducers is prohibited. Individual product labels should be reviewed for specific information on propensity to induce CYP3A4 for a specific compound.

Strong CYP3A inducers
Carbamazepine, phenytoin, rifampin, 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

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

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