PROTOCOL TITLE:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
NCT Number:	NCT04571060
PROTOCOL DATE:	02-June-2021

DRUG:	Zavegepant (BHV-3500)
STUDY NUMBER(S):	BHV3500-301
PROTOCOL TITLE:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
IND NUMBER:	134,120
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	03-Feb-2020
VERSION NUMBER:	v 4.0
VERSION DATE:	02-Jun-2021

SUMMARY OF CHANGES

Version	Summary of changes	Date
Version 1.0	Not applicable	03-Feb-2020
Version 2.0	Updated study name from vazegepant to zavegepant throughout the protocol. Updated safety information from the release of Investigator Brochure version 3.0. Clarified the contraception guidance for subjects in same sex relationships, subjects who report abstinence, and male subjects with vasectomy. Added missing "x" for eCOA subject training in Table 1. Provided COVID-19 study visit requirements. Corrected inconsistencies, typographical errors throughout the protocol.	22-Sep-2020
Version 3.0	Update to Exclusion criteria 2f, 6e and added Exclusion criteria 6j	26-Apr-2021
Version 4.0	Addition of inclusion 2b, subjects can be rescreened if the ineligibility was due to one of the eligibility items adjusted in protocol version 4 or who are reasonably expected to be eligible. Removal of exclusion criteria of "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" Removal of HbA1c exclusion criteria. Updated BMI exclusion to $\geq$ 40kg/m^2 Updated requirements exclusion criteria for serum bilirubin, AST and ALT to >1.5xULN.	02-Jun-2021

	Updated exclusion criteria 6g to allow subjects who are participating in the observation phase of a COVID-19 mRNA vaccine trial if the potential subjects are at least 30 days post last dose of the vaccine.	

BHV3500-301

PHASE 3: DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, SAFETY AND EFFICACY TRIAL OF BHV-3500 (ZAVEGEPANT) INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to zavegepant (BHV-3500) are the confidential and proprietary information 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 zavegepant (BHV-3500) and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
Rationale:	Zavegepant is being developed for the acute treatment of migraine. Effectiveness against migraine was demonstrated in BHV3500-201, a fully powered, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant 5 mg, 10 mg, and 20 mg via intranasal (IN) administration. The data from this study will allow characterization of the relative safety and efficacy of IN zavegepant versus placebo in the acute treatment of moderate or severe migraine measuring freedom from pain and freedom from most bothersome system (nausea, photophobia or phonophobia) as reported just prior to treatment of the migraine. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom in subjects with migraine will also be obtained.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a 1-year history of migraine (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 about 4-72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects (approximately 700 per treatment group). Subjects will be randomized in a 1:1 ratio to the zavegepant or placebo treatment groups. Randomization will be stratified by prophylactic migraine medication use (yes or no).
Primary Objective:	To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.
Secondary Objectives:	1. To compare zavegepant with placebo for pain relief at 2 hours postdose. 2. To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.

	3. To compare zavegepant with placebo for sustained pain relief from 2 to 24 hours postdose. 4. To compare zavegepant with placebo for sustained pain relief from 2 to 48 hours postdose. 5. To compare zavegepant with placebo for sustained pain freedom from 2 to 24 hours postdose. 6. To compare zavegepant with placebo for sustained pain freedom from 2 to 48 hours postdose. 7. To compare zavegepant with placebo for phonophobia freedom at 2 hours postdose. 8. To compare zavegepant with placebo for photophobia freedom at 2 hours postdose. 9. To compare zavegepant with placebo for pain relief at 60 minutes postdose. 10. To compare zavegepant with placebo for return to normal function at 60 minutes postdose according to the Functional Disability scale. 11. To compare zavegepant with placebo for pain relief at 30 minutes postdose. 12. To compare the zavegepant with placebo for return to normal function at 30 minutes postdose according to the Functional Disability scale. 13. To compare zavegepant with placebo for pain relief at 15 minutes postdose. 14. To compare zavegepant with placebo for return to normal function at 15 minutes postdose according to the Functional Disability scale. 15. To compare zavegepant with placebo for rescue medication use within 24 hours postdose. 16. To compare zavegepant with placebo for nausea freedom at 2 hours postdose. 17. To compare zavegepant with placebo for pain relapse from 2 to 48 hours postdose.

Exploratory Objectives:	1. To evaluate zavegepant relative to placebo for pain freedom at all scheduled time points postdose. 2. To evaluate zavegepant relative to placebo for pain relief at all scheduled time points postdose. 3. To evaluate zavegepant relative to placebo for freedom from MBS at all scheduled time points postdose. 4. To evaluate zavegepant relative to placebo for return to normal function at all scheduled time points postdose. 5. To evaluate zavegepant relative to placebo for phonophobia freedom at all scheduled time points postdose. 6. To evaluate zavegepant relative to placebo for photophobia freedom at all scheduled time points postdose. 7. To evaluate zavegepant relative to placebo for nausea freedom at all scheduled time points postdose. 8. To evaluate zavegepant relative to placebo for the Migraine Quality of Life Questionnaire (MQoL). 9. To evaluate zavegepant relative to placebo for the Preference of Medication (PoM). 10. To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine, as measured by the frequency of adverse events of moderate or severe intensity, serious adverse events, clinically relevant laboratory test abnormalities, and nasal inspection abnormalities. 11. To evaluate zavegepant relative to placebo for the Sheehan Suicidality Tracking Scale (S-STS).
Study Design:	This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of zavegepant versus placebo in the treatment of moderate or severe migraine. The study drug will be IN zavegepant or matching placebo. The study will randomize approximately 1,400 subjects in a 1:1 ratio between the 2 treatment groups (zavegepant or placebo). Randomization will be stratified by prophylactic migraine medication use (yes or no).

	After randomization, subjects will be dispensed a single dose of double-blind study drug. Subjects will be instructed to take study drug as an outpatient, when (if) they have a migraine headache of moderate or severe pain intensity, and only after they have reported their pre-dosing migraine characteristics in the electronic clinical outcome assessment (eCOA) handheld device. After subjects confirm taking study drug in the eCOA handheld device, they will report the following efficacy data in the eCOA handheld device at 15, 30, 60 and 90 minutes postdose, and 2, 3, 4, 6, 8, 24 and 48 hours postdose: headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe); presence or absence of migraine symptoms (nausea, photophobia, phonophobia); functional disability level using a 4-point numeric rating scale (normal, mildly impaired, severely impaired, requires bedrest). Subjects will also complete the Migraine Quality of Life Questionnaire (MQoL) and Preference of Medication (PoM) rating scale at 24 hours postdose in the eCOA handheld device. Subjects will be instructed to contact the study center immediately if a severe or serious adverse event (SAE) occurs. Subjects will return to the study site within 7 (+2) days of taking study drug for review of the eCOA handheld device, assessment of study drug compliance, and monitoring of safety and tolerability (including vital signs, laboratory tests, and electrocardiograms [ECGs]). If a subject has NOT experienced a migraine headache of moderate or severe pain intensity within 45 days after randomization, they still are required to complete all End of Treatment (EOT) Visit procedures. All subjects must return unused study drug and eCOA handheld device to the study center.

STUDY SCHEMATIC

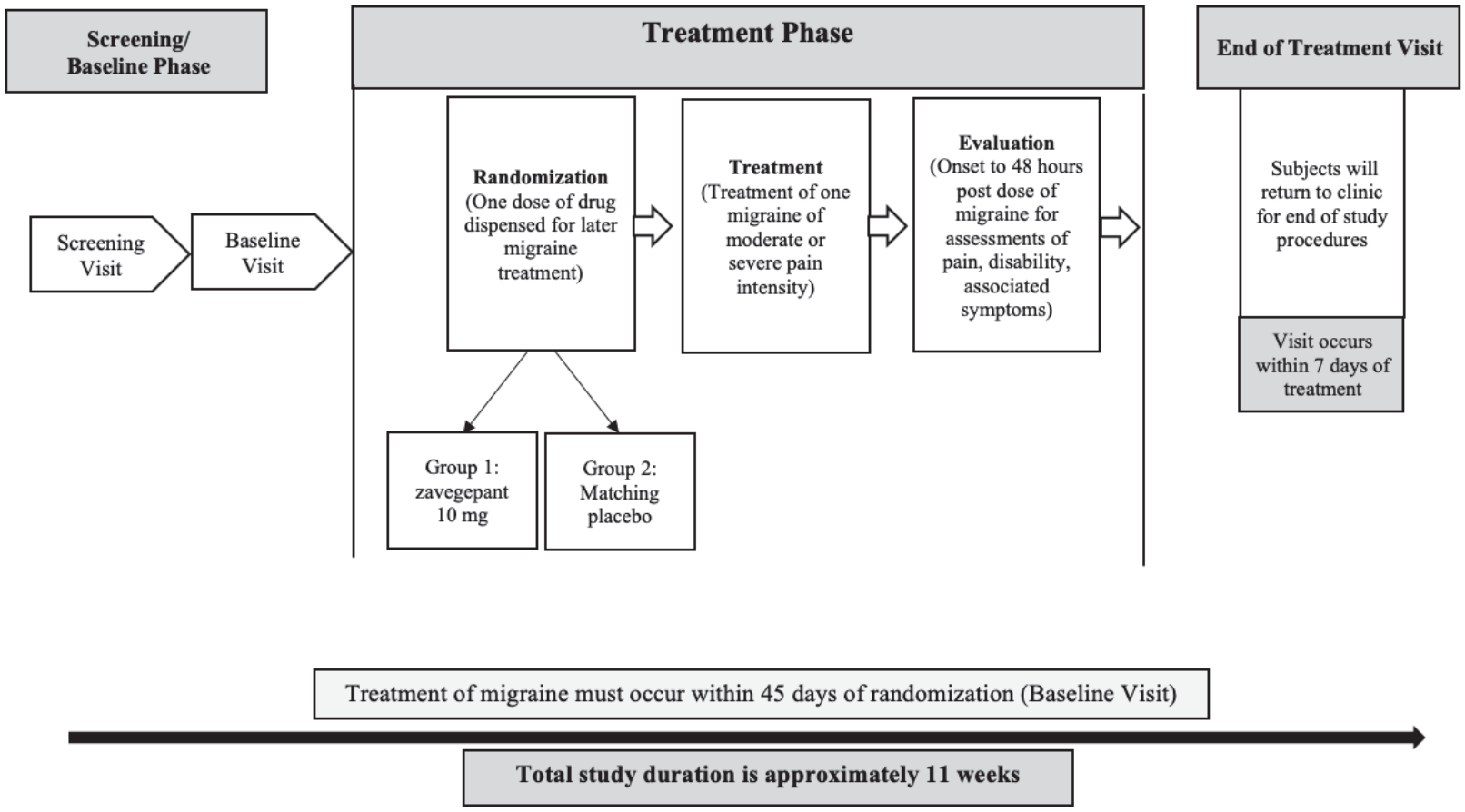


TABLE OF CONTENTS

LIST OF TABLES

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
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Concentration
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CONMED	Concomitant Medication
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTSdatabase	Clinical Trial Subject Database
DAIDS	Division of AIDS
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
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
ICF	Informed Consent Form
IB	Investigator's Brochure
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
kg	Kilogram
L	Liters
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MBS	Most bothersome symptom
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary regulatory activities
mITT	Modified intent to treat
mg	Milligram
MI	Myocardial Infarction
min	Minute
mmHg	Millimeters Mercury
MQoL	Migraine quality of life questionnaire
Msecs	Milliseconds
MTD	Maximum tolerated dose
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs

NRS	Numeric rating scale
OTC	Over the counter
PCI	Percutaneous coronary intervention
PCP	Phencyclidine
PK	Pharmacokinetic
po	By Mouth, Orally
PoM	Preference of medication
PVG	Pharmacovigilance
qd	Once Daily
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
Tmax	Time of observed Cmax
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.[1] 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.[2]

Zavegepant (BHV-3500) is a selective, competitive CGRP receptor antagonist being developed for the treatment of migraine. Zavegepant is being developed for intranasal (IN) administration. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and the trigeminal ganglion[3] and its activation is thought to play a causal role in migraine pathophysiology.[4] For example, research and clinical studies have shown that serum levels of CGRP are elevated during migraine attacks,[5] infusion of intravenous CGRP produces persistent pain in migraine sufferers and non-migraine sufferers,[6,7] and treatment with anti-migraine drugs normalizes CGRP levels.[8] 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.[9] 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™]).[10,11]

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 is presented below.

1.2.1 Non-Clinical Pharmacology

1.2.1.1 Non-Clinical Pharmacokinetics, Pharmacodynamics and Toxicology

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. Safety studies were also performed in rat and monkey to determine tolerability, potential for local irritation, and to assess systemic toxicity. The details of these studies can be found in the Zavegepant (BHV-3500) Investigator Brochure (IB).

1.2.2 Summary of Clinical Experience

1.2.2.1 Single Ascending Dose (SAD) BHV3500-101

Administration of intranasal zavegepant in the Phase 1, double-blind, placebo-controlled single ascending dose (SAD) study ranging from 0.1 mg to 40 mg was safe and well tolerated in healthy adult subjects. A total of 72 subjects were randomized and received a single dose of BHV-3500 or matched placebo as a single intranasal dose of 0.1 mg to 40 mg and completed the study. Dose escalation to the highest planned dose of 40 mg was completed and no dose limiting toxicity was observed. A Maximum Tolerated Dose (MTD) was not identified. IN administration of zavegepant in this study produced plasma levels predicted to be within the therapeutic range based on preclinical models predictive for compounds of this class.

There were no serious adverse events (SAEs), deaths or AEs leading to discontinuation reported in this study. The majority of adverse events (AEs) were mild intensity and resolved spontaneously by the end of treatment. The most frequently reported treatment-emergent adverse events were headache, dysgeusia, dizziness, nasal congestion and back pain. No nasal mucosal injury was observed at all doses tested. There was no apparent dose relationship in either the incidence or intensity of the AEs reported across the dose range of 0.1 mg to 40 mg.

1.2.2.2 Multiple Ascending Dose Study (MAD) BHV3500-102

The Phase 1, multiple ascending dose (MAD) study evaluating the safety, tolerability, and PK of zavegepant following IN administration of MAD (placebo, 5 mg, 10 mg, or 20 mg) in normal healthy subjects has concluded. In this study, a total of 36 healthy subjects (3 cohorts) were administered multiple ascending doses of IN zavegepant (planned doses of 5 mg, 10 mg or 20mg; N = 12 per treatment group [3:1 zavegepant:PBO]) with the first 3 Cohorts receiving a once daily dose for 14 days. Cohort 4 received two sequential 20 mg zavegepantdoses (n=9) or placebo (n=3) separated by two hours (40 mg total daily) for 8 consecutive days. Two additional alternate dosing cohorts received 2 repeated IN administrations of zavegepant 20 mg or placebo on a single day. Preliminary safety data from BHV3500-102 indicated that zavegepantwas well tolerated at all dose levels and a maximum tolerated dose was not identified. No deaths or SAE’s were reported in this study. Additional details can be found in the Investigator’s brochure.

1.2.2.3 Phase 2/3 Dose Ranging Study (BHV3500-201)

The pivotal Phase 2/3 dose-ranging study evaluating the safety and efficacy of 3 different IN dose levels (5 mg, 10 mg, 20 mg) of zavegepant, relative to placebo, in the acute treatment of migraine with moderate to severe pain intensity has concluded. Preliminary data from BHV3500-201 indicate that zavegepantas a single IN spray containing 5mg, 10mg, or 20 mg was well tolerated in adult subjects with moderate to severe migraine attacks and demonstrated a favourable safety profile comparable with placebo. The study met the primary endpoint and the 10 mg dose was identified as the lowest efficacious dose demonstrating statistically significant efficacy.

No deaths were reported in the study. SAEs were reported in two on treatment subjects including: thrombosis reported in 1 subject from the 10 mg group; and vestibular migraine reported in 1 subject in the placebo group. Both events were moderate in intensity, and judged by the investigator as not related to study therapy. The SAE of thrombosis was reported 13 days after the single dose of zavegepantas post trauma from an automobile accident. Additional details can be found in the Investigator's Brochure.

1.3 Study Rationale

Zavegepant is being developed for the acute treatment of migraine via the intranasal route.

This study will characterize the safety and efficacy of zavegepant relative to placebo, in the acute treatment of moderate to severe migraine, with or without aura, in adults.

1.3.1 Study Design Rationale

This is a Phase 3, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of zavegepant as compared to matching placebo in the acute treatment of moderate or severe migraine. The investigational product is formulated as zavegepant 10 mg intranasal (IN) or matching placebo. The study drug will be administered using an Aptar Unit Dose System (UDS) liquid spray device containing a single dose of zavegepant or matching placebo. The subjects will be instructed to take their study drug, as an outpatient, when (if) they have a migraine headache which reaches moderate or severe pain intensity.

The study will screen approximately 1,750 subjects to randomize approximately 1,400 subjects. The subjects will be randomized in a 1:1 ratio to the zavegepant or matching placebo treatment groups. The randomization will be stratified by the use of prophylactic migraine medications (yes or no).

1.3.2 Dose Selection Rationale

As of 10-Dec-2019, over 1,300 subjects have administered at least 1 dose of zavegepant (0.1 mg, 0.3 mg, 1 mg, 3 mg, 5 mg, 10 mg, 20 mg, or 40 mg) in Phase 1 studies in healthy subjects or Phase 2/3 studies in subjects with migraine. Among these subjects, more than 1,100 have received IN zavegepant at 5 mg, 10 mg, 20 mg or 40 mg doses.

Safety data are now available from the pivotal Phase 2/3 dose ranging study (BHV3500-201). BHV3500-201 is a concluded, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging (5 mg, 10 mg, or 20 mg) study of zavegepant IN for the acute treatment of migraine. The primary objective was to evaluate the efficacy of zavegepant compared with placebo in the acute treatment of migraine as measured by the coprimary endpoints of pain freedom, and freedom from most bothersome symptom (MBS) associated with migraine at 2 hours postdose, while identifying an optimal dose for evaluation in the Phase 3 clinical development program.

In this study, a total of 1,673 subjects were randomized to receive zavegepant (5 mg, 10 mg, or 20 mg) or matching placebo. The randomization was stratified by the use of prophylactic migraine medication (yes or no). A total of 1,588 subjects were treated with zavegepant IN 5 mg (388 subjects), 10 mg (394 subjects), 20 mg (403 subjects), or matching placebo (403 subjects). Overall, 1,578 subjects completed the study. The 10 mg and 20 mg doses achieved statistical superiority to placebo on both coprimary endpoints of pain freedom and freedom from the most bothersome symptom (MBS) at 2 hours. Rapid onset of pain relief was seen as early as 15min with return to normal function at 30 minutes. The benefits of zavegepant were durable and sustained without rescue medication through 48 hours.

Based on topline data from this pivotal study, a durable efficacy profile for zavegepant was established. This efficacy profile, together with a favorable safety profile led to the selection of the IN zavegepant 10 mg dose as the lowest fully efficacious dose to support Phase 3 clinical studies.

1.3.3 Other Rationale Related to the Compound / Study

Not Applicable.

1.3.4 Research Hypothesis

Zavegepant will have efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile suitable for use by a broad subject population.

2 STUDY OBJECTIVES

2.1 Primary Objectives

To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.

2.2 Secondary Objectives

1. To compare zavegepant with placebo for pain relief at 2 hours postdose.
2. To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.
3. To compare zavegepant with placebo for sustained pain relief from 2 to 24 hours postdose.
4. To compare zavegepant with placebo for sustained pain relief from 2 to 48 hours postdose.
5. To compare zavegepant with placebo for sustained pain freedom from 2 to 24 hours postdose.
6. To compare zavegepant with placebo for sustained pain freedom from 2 to 48 hours postdose.
7. To compare zavegepant with placebo for phonophobia freedom at 2 hours postdose.
8. To compare zavegepant with placebo for photophobia freedom at 2 hours postdose.
9. To compare zavegepant with placebo for pain relief at 60 minutes postdose.
10. To compare zavegepant with placebo for return to normal function at 60 minutes postdose according to the Functional Disability scale.
11. To compare zavegepant with placebo for pain relief at 30 minutes postdose.
12. To compare the zavegepant with placebo for return to normal function at 30 minutes postdose according to the Functional Disability scale.
13. To compare zavegepant with placebo for pain relief at 15 minutes postdose.
14. To compare zavegepant with placebo for return to normal function at 15 minutes postdose according to the Functional Disability scale.
15. To compare zavegepant with placebo for rescue medication use within 24 hours postdose.

16. To compare zavegepant with placebo for nausea freedom at 2 hours postdose.

17. To compare zavegepant with placebo for pain relapse from 2 to 48 hours postdose.

2.3 Exploratory Objectives

1. To evaluate zavegepant relative to placebo for pain freedom at all scheduled time points postdose.

2. To evaluate zavegepant relative to placebo for pain relief at all scheduled time points postdose.

3. To evaluate zavegepant relative to placebo for freedom from MBS at all scheduled time points postdose.

4. To evaluate zavegepant relative to placebo for return to normal function at all scheduled time points postdose.

5. To evaluate zavegepant relative to placebo for phonophobia freedom at all scheduled time points postdose.

6. To evaluate zavegepant relative to placebo for photophobia freedom at all scheduled time points postdose.

7. To evaluate zavegepant relative to placebo for nausea freedom at all scheduled time points postdose.

8. To evaluate zavegepant relative to placebo for the Migraine Quality of Life Questionnaire (MQoL).

9. To evaluate zavegepant relative to placebo for the Preference of Medication (PoM).

10. To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine, as measured by the frequency of adverse events of moderate or severe intensity, serious adverse events, clinically relevant laboratory test abnormalities, and nasal inspection abnormalities.

11. To evaluate zavegepant relative to placebo for the Sheehan Suicidality Tracking Scale (S-STS).

3 STUDY ENDPOINTS

The intercurrent event of rescue medication use will be handled using Rescue Medication = Failure (RM=F), i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all endpoints listed below, except the secondary endpoint of rescue medication use within 24 hours postdose.

3.1 Primary Endpoints

Pain freedom at 2 hours postdose will be assessed using the percentage of subjects with a pain intensity of none at 2 hours postdose. Pain intensity will be measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).

MBS freedom at 2 hours postdose will be assessed using the percentage of subjects with an MBS that is reported on study before dosing and is absent at 2 hours postdose. The MBS on study before dosing will be reported as nausea, phonophobia, or photophobia. Symptom status will be reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).

3.2 Secondary Endpoints

1. Pain relief at 2 hours postdose will be assessed using the percentage of subjects with a pain intensity of none or mild at 2 hours postdose.

2. Return to normal function at 2 hours postdose will be assessed using the percentage of subjects with a functional disability level of normal at 2 hours postdose in the subset of subjects with functional disability at the time of dosing. Functional disability level will be measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest), and functional disability will be defined as mildly impaired, severely impaired, or requires bedrest.

3. Sustained pain relief at all time points from 2 to 24 hours postdose will be assessed using the percentage of subjects with pain intensities of none or mild at all time points from 2 to 24 hours postdose.

4. Sustained pain relief at all time points from 2 to 48 hours postdose will be assessed using the percentage of subjects with pain intensities of none or mild at all time points from 2 to 48 hours postdose.

5. Sustained pain freedom at all time points from 2 to 24 hours postdose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 24 hours postdose.

6. Sustained pain freedom at all time points from 2 to 48 hours postdose will be assessed using the percentage of subjects with pain intensities of none at all time points from 2 to 48 hours postdose.

7. Phonophobia freedom at 2 hours postdose will be assessed using the percentage of subjects with phonophobia absent at 2 hours postdose in the subset of subjects with phonophobia present at the time of dosing.

8. Photophobia freedom at 2 hours postdose will be assessed using the percentage of subjects with photophobia absent at 2 hours postdose in the subset of subjects with photophobia present at the time of dosing.

9. Pain relief at 60 minutes postdose will be assessed using the percentage of subjects with a pain intensity of none or mild at 60 minutes postdose.

10. Return to normal function at 60 minutes postdose will be assessed using the percentage of subjects with a functional disability level of normal at 60 minutes postdose in the subset of subjects with functional disability at the time of dosing.

11. Pain relief at 30 minutes postdose will be assessed using the percentage of subjects with a pain intensity of none or mild at 30 minutes postdose.

12. Return to normal function at 30 minutes postdose will be assessed using the percentage of subjects with a functional disability level of normal at 30 minutes postdose in the subset of subjects with functional disability at the time of dosing.

13. Pain relief at 15 minutes postdose will be assessed using the percentage of subjects with a pain intensity of none or mild at 15 minutes postdose.

14. Return to normal function at 15 minutes postdose will be assessed using the percentage of subjects with a functional disability level of normal at 15 minutes postdose in the subset of subjects with any level of functional disability at the time of dosing.

15. Rescue medication use within 24 hours postdose will be assessed using the percentage of subjects who take rescue medication within 24 hours after taking study drug.

16. Nausea freedom at 2 hours postdose will be assessed using the percentage of subjects with nausea absent at 2 hours postdose in the subset of subjects with nausea present at the time of dosing.

17. Pain relapse from 2 to 48 hours postdose will be assessed using the percentage of subjects with a pain intensity of mild, moderate, or severe at any time point after 2 hours through 48 hours postdose in the subset of subjects with pain freedom at 2 hours postdose.

3.3 Exploratory Endpoint(s) (if applicable)

Not applicable.

3.4 Measures of Interest

Efficacy measures: Assessments of migraine pain intensity, migraine symptoms (phonophobia, photophobia, nausea), and functional disability

Safety measures:

- AEs
- ECGs
- Vital signs and physical measurements
- Clinical laboratory tests
- Sheehan Suicidality Tracking Scale (S-STS)
- Nasal inspection

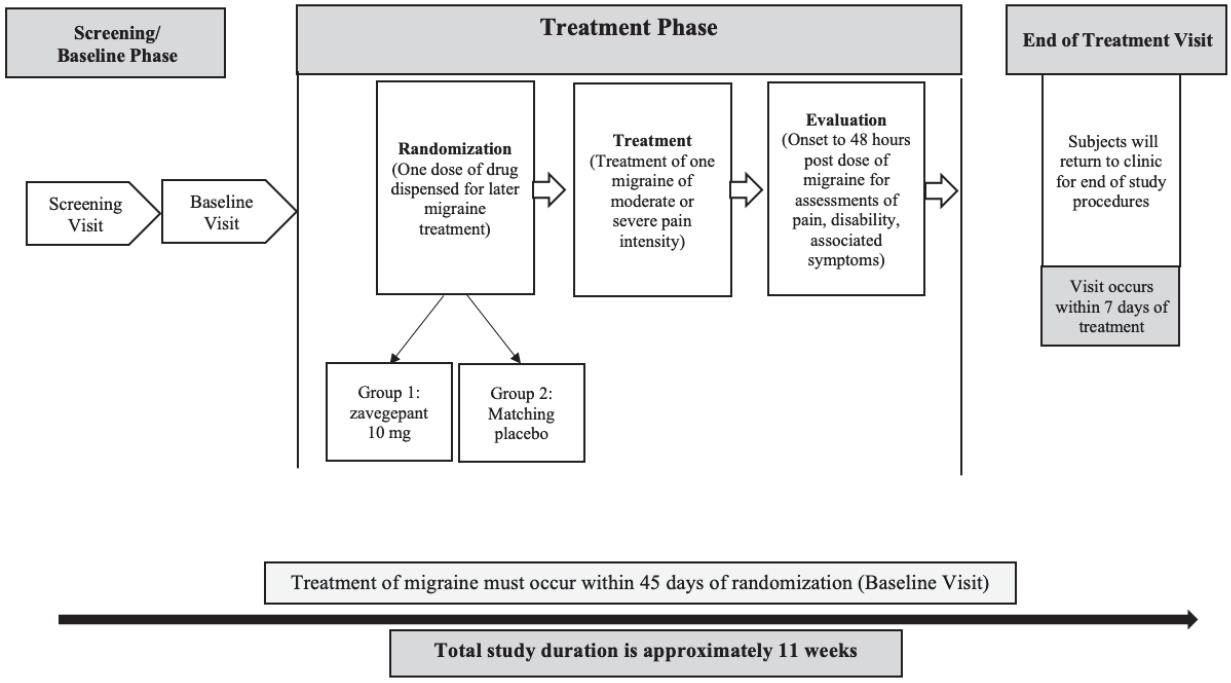
Outcomes research measures: Migraine Quality of Life Questionnaire (MQoL) and Preference of Medication (PoM)

4 STUDY PLAN

4.1 Study Design and Duration

This is a double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of zavegepant as compared to matching placebo in the acute treatment of moderate or severe migraine. Subjects will be dispensed 1 Aptar UDS liquid spray device containing a single dose of zavegepant 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 (EOT) Visit 7 (+2) days after the administration of study drug.

4.2 Study Schematic



4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Moderate or Severe Migraine Before Study Drug Administration[3]	Post Study Drug Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14, 16]
Eligibility Assessments					
Informed consent	X				
Duplicate subject check (in CTSdatabase)	X				
Inclusion/ Exclusion criteria	X	X			
Medical history	X				
Migraine History Assessment (signs/ symptoms/ prior treatment/ frequency/ intensity)	X				
Concomitant Medication paper diary[4]	X	X	X	X	X
Rescue Medication paper diary[5]		X	X	X	X
Randomize subject in IWRS[6]		X			

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Moderate or Severe Migraine Before Study Drug Administration[3]	Post Study Drug Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14, 16]
Safety Assessments					
Physical Examination	X				X
Nasal Inspection[7]	X	X			X
Vital Signs/ Physical Measurements[8]	X	X			X
Adverse Event and Serious Adverse Event Assessment[9]	X	X	X	X	X
Sheehan Suicidality Tracking Scale (S-STS)[10]	X	X			X
ECG	X				X
Clinical Safety Laboratory Testing	X				X
Liver Function Tests (LFTs)	X				X
Lipid Panel	X				X
FSH, if applicable, to determine WOCBP status	X				
Pregnancy Test[11]	X (Serum)	X (Urine)	X (Urine)		X (Serum)
Urinalysis	X				X
Urine drug screen for drugs of abuse	X				X

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Moderate or Severe Migraine Before Study Drug Administration[3]	Post Study Drug Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14, 16]
Clinical Drug Supplies/ Study Supplies					
eCOA handheld device assigned to subject		X			
Patient education: study medication administration with instruction for use document		X			
Patient education: eCOA handheld device subject online training/ training device		X			
Dispense study medication[12]		X[2]			
Administer study medication			X[12]		
Enter use of study medication in eCOA handheld device			X[12]		
eCOA handheld device returned/ reviewed for completeness[13]					X
Return unused or used study medication to site for reconciliation					X

Procedure	Screening Visit[1]	Baseline/ Randomization Visit (Day 1)[2]	Moderate or Severe Migraine Before Study Drug Administration[3]	Post Study Drug Administration: 15, 30, 45, 60 and 90 minutes 2, 3, 4, 6, 8, 24 and 48 hours	End of Treatment Visit[14, 16]
Efficacy and Outcomes Research Assessments[12]					
Assessments of migraine pain, migraine symptoms (phonophobia, photophobia, and nausea) and functional disability[14]			X	X	
MQoL (Migraine Quality of Life Questionnaire)[14]				X (24-hour assessment)	
Preference of Medication (PoM)[14]				X (24-hour assessment)	

[1] **Screening Phase** will be 3 - 28 days. Subject should be entered in the IWRS after 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. Subjects may be re-screened with a new subject ID.

[3] Subjects will use their assigned eCOA handheld device before study drug administration to answer questions about their migraine symptoms upon experiencing a moderate or severe migraine headache. The subject will administer zavegepant 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.

[4] Subjects should keep track of their concomitant medications on the IRB approved study paper diary provided throughout the study. A concomitant medication paper diary will be provided to subjects at the Screening visit. These paper diaries should be returned to the investigational site at each visit for review and electronic data capture (EDC) entry. The paper diaries should be kept as source documents.

[5] Subjects should keep track of their rescue medications on the IRB approved study paper diary provided throughout the study. A rescue medication paper diary will be provided to subjects at the Baseline visit. Reference the rescue medication section 5.5 for additional information. These paper diaries should be returned to the investigational site for review and electronic data capture (EDC) entry. The paper diaries should be kept as source documents.

[6] 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.

[7]Nasal inspection – The nasal passages and turbinates will be visually inspected with a nasal speculum or otoscope at the Screening, Baseline and end of EOT Visits to detect evidence of nasal inflammation or edema.

[8]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.

[9]SAEs are reported from the time of signed informed consent and non-serious AEs are reported from the Baseline Visit. 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 Visit.

[10]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 EOT Visits.

[11]For WOCBP: A serum pregnancy test will be collected at the Screening and EOT Visits as part of the standard laboratory tests. Confirmatory urine pregnancy test for WOCBP will be completed on site at the 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 drug.

[12]Subjects should be instructed that the dose should be administered 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 when they should administer study drug.

[13]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.

[14]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 before study drug administration.

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

[16]Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after dosing with study drug. However, if necessary due to local COVID-19 safety requirements, the EOT Visit may be performed outside of the window by an additional 5 days in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance. See Section 4.3.5 for more information.

4.3.1 Screening Phase (3-28 days)

Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects to study medication (zavegepant 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.

Screening visit must be completed in person.

4.3.2 Randomization Phase / Treatment 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 drug 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 drug 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 drug, 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 intensity 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 drug to record efficacy and other quality of life measures.

Randomization/ Baseline visit must be completed in person.

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 migraine headache of moderate to severe intensity, they should record this in the handheld. The handheld will instruct the subject to take study drug after the initial assessments are completed in the device.

The following will be recorded in the eCOA handheld device:

- Headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe) before taking study drug and after taking study drug at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours postdose.

- The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and functional disability level (4-point numeric rating scale: normal, mildly impaired, severely impaired, requires bedrest) recorded at the same time points as headache pain intensity.

- Current MBS before taking study drug.

- Migraine Quality of Life Questionnaire (MQoL) and Preference of Medication (PoM) 24 hours after taking study drug.

Subjects should be encouraged to treat their first qualifying (moderate or severe) migraine that occurs during the treatment phase. If subjects are unable to treat their first qualifying migraine, refer to Section 5.5. Rescue Medications for a list of medications that are allowed during the course of this study.

4.3.3 Extension Phase (if applicable)

Not applicable.

4.3.4 Washout Phase (if applicable)

Not applicable.

4.3.5 End of Treatment

Subjects will return to the site for their EOT Visit (after assessments in the handheld are completed) within 7 (+2) days after dosing with study drug. The "+2" day window is included for scheduling purposes only.

At the EOT 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 Visit.

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 drug and their handheld device to the investigational site.

Certain provisions may be implemented, in order to minimize potential hazards to study participants due to COVID-19. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in-home phlebotomy vendors, and shipping of study medication directly to study subjects if needed. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. The screening and randomization/baseline visits must be done in person. Components of the EOT Visit may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.) and the window visit may be extended by 5 days if circumstances warrent.

4.4 Post Study Access to Therapy (if applicable)

At the conclusion 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. Subjects may be eligible to participate in a zavegepant long-term safety study requiring approval by responsible health authorities and ethics committees. There can be no guarantee or assurance that a subject can participate in the zavegepant long-term safety 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 1,750 subjects will need to be screened in order to randomize approximately 1,400 subjects. The subjects will be randomized in a 1:1 ratio to the zavegepant or matching placebo treatment groups. It is anticipated that enrollment will occur at approximately 65 sites in the United States over a period of approximately 5 months during this trial.

5.2 Inclusion Criteria

1) Signed written informed consent. 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.

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

3) Subjects must be able to read and understand English or Spanish.

4) 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.

5) Age and Reproductive Status:

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

b) All subjects must understand the contraception requirements for this study and agree to use 2 acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 5.6 for the definition of WOCBP.

c) Women must not be pregnant, lactating or breastfeeding.

d) At the Baseline Visit prior to dispensing investigational study drug, WOCBP must have a negative urine pregnancy test.

6) Other Inclusion Criteria:

a) No clinically significant abnormality identified on the medical or laboratory evaluation. A subject with a clinical abnormality or laboratory parameter outside the reference range (not including exclusion criteria listed in Section 5.3 below) may be considered for inclusion 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.

b) Subjects who were screen failures from this study (BHV3500-301) previously, may be considered for re-screening under protocol version 4 provided the ineligibility was due to one of the eligibility items modified in this protocol version 4 or who are reasonably expected to be eligible. Subjects being considered for re-screening other than the reason listed above (e.g., previously pregnant, screening window too long) should be discussed with the Sponsor prior to re-screen.

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 with a 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) Subjects with major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening visit.

e) Chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, complex regional pain syndrome (CRPS)).

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

g) Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder.

h) The subject has a history of 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.

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

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

k) 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.

l) 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.

m) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria[11] for any significant substance use disorder within the past 12 months from the date of the screening visit.

n) 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 the Baseline Visit until the EOT 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[11] 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.

o) 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.

p) Body mass index $\geq$ 40 kg/m^2

q) 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.

5) ECG and Laboratory Test Findings

a) Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 ml/min/1.73m^2.

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

c) Left Bundle Branch block.

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

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

f) Serum bilirubin (Total, Direct or Indirect) > 1.5 x ULN are excluded. However, abnormal values of between 1-1.5x ULN may be considered but must be repeated once for confirmation during the screening period. Repeat results **must** be the same or lower than the first lab result in order to remain eligible for the study. Subjects must be excluded if repeat is > 1.5x ULN.

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

h) AST (SGOT) or ALT (SGPT) >1.5 x ULN are excluded. However, abnormal values of between 1-1.5x ULN may be considered but must be repeated once for confirmation during the screening period. Repeat results **must** be the same or lower than the first lab result in order to remain eligible for the study. Subjects must be excluded if repeat is >1.5x ULN.

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

d) Participation in clinical trial with non-biological investigational agents or investigational interventional treatments (last study visit occurring) within the 30 days prior to Baseline Visit.

e) Subjects who have previously participated in any BHV-3500 study (re-screens for this study, (BHV3500-301), may be considered, as described in inclusion criteria 6b above).

f) Participation in clinical trial with biological investigational agents (last study visit occurring) within the 90 days prior to Baseline visit.

g) Participation in any other investigational clinical trial while participating in this clinical trial. Participation in a COVID-19 mRNA vaccine study (vaccine must be authorized under FDA emergency use authorization or approval) ***who are at least 30 days post last dose*** of the vaccine are permitted to be screened for this study.

h) Identified as a duplicate subject in CTSdatabase.

i) Subjects must complete the Baseline/ Randomization visit within 3 to 28 days of the Screening visit (Table 1).

7) Please see Section 5.4 for Prohibited medications and Section 5.5 for allowable Rescue Medications.

5.4 Prohibited Concomitant Medications

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 5.5 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 5.5). 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 5.5).

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 16.2, 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 16.2, 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 antagonist biologics [e.g. Emgality® (galcanezumab), Aimovig® (erenumab)), Ajovy® (fremanezumab), Vyepti® (eptinezumab-jjmr] is prohibited during the study. CGRP antagonist biologics must be discontinued 6 months prior to screening and are prohibited throughout the study.

16. The use of FDA-approved gepants must be discontinued 2 weeks prior to screening and are prohibited throughout the study (e.g. Nurtec ODT® (rimegepant), Ubrelvy® (ubrogepant)).

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

5.5 Rescue Medications

After dosing with study drug, all other headache medication is prohibited during the first 2 hours postdose 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 drug (***and after the 2-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 postdose of study drug.***

If the migraine is relieved by study drug 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.

In all circumstances, the subject will always continue to complete the handheld entries through the 48-hour assessment after taking the study drug. Use of concomitant medication after randomization, including rescue medication, will be recorded by the subject on a paper diary and returned to the site. Subjects will record any concomitant medications taken on the Concomitant Medication paper diary. Subjects will record any rescue medications taken on the Rescue Medication paper diary. The site will record medications that were taken within 14 days of dosing with study drug (or until the EOT 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 drug, 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 in their handheld (through 48 hours and before returning to the clinical site for EOT Visit), if subjects experience a migraine they are allowed to take their prescribed standard of care medication (including triptans if not contraindicated and acetaminophen up to 1000mg/day, this includes Excedrin Migraine), provided the medication is not otherwise prohibited.

5.6 Women of Childbearing Potential

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Essure, tubal occlusion and endometrial ablation are not acceptable methods of contraception. Menopause is defined as:

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

  NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to 1 year

  or

- Woman on hormone replacement therapy (HRT) who no longer menstruate.

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

The requisite drug interaction studies to determine the interaction of zavegepant with oral contraceptives have not been performed to date. It is, therefore, not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP or men with partners who are WOCBP who are participating this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited.

It is required that all WOCBP use 2 methods of contraception to prevent pregnancy, for the duration of the study (i.e. this study begins with signed consent form through 90 days after dosing with study drug). The 2 methods should include 1 barrier method (ex. condom with spermicidal gel, non-hormonal intrauterine devices, cervical cap etc.) and 1 other method. The other method could include hormonal contraceptives (e.g. oral contraceptives, injectable contraceptives, patch, or contraceptive implant [e.g. hormonal intrauterine device]) used since at least 4 weeks prior to sexual intercourse or another barrier method.

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

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

All WOCBP must complete the pregnancy test schedule Table 1.

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 drug and should immediately contact the Investigator.

5.7 Other Restrictions and Precautions (if applicable)

Not Applicable.

5.8 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 deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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 1 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
- SAE forms and 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

6.2 Eligibility Assessments

As outlined in Table 1: Informed consent, inclusion/ exclusion criteria, medical history study procedures, migraine history assessment, concomitant medication paper diary, ECG and randomize subject in IWRS

6.3 Safety Assessments

6.3.1 Vital Signs and Physical Measurements (Height and Weight)

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

6.3.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Screening Phase and at the scheduled visits as outlined in Table 1. A central ECG service will be utilized for all ECGs and based on the central read, the Investigator will determine if any abnormalities are of clinical significance.

6.3.3 Physical Exam

Subjects will undergo a complete physical examination at the Screening visit and at the scheduled visits as outlined in Table 1. The directed physical exam should be guided by the subject's signs and symptoms. Physical exam will include nasal inspection.

If applicable, Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.3.3.1 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 EOT Visits (refer to Table 1) 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.

6.3.4 Laboratory Assessments

The investigator must review all laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF (see guidance in Section 8.2.2). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered to be clinically significant during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a reasonable period of time as judged by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and Table 1.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

6.3.4.1 Safety Laboratory Testing

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

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

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

Lipid panel: Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.

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 including but not limited to cocaine, amphetamines, opioids, PCP, THC and barbiturates.

Reflex tests:

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

  Additional laboratory tests may be required.

6.3.4.2 Pregnancy Testing

Pregnancy tests will be conducted (serum, urine, or home pregnancy test), when appropriate and as outlined in Table 1. If applicable, a FSH test will be obtained at screening to confirm WOCBP status.

6.3.5 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 [13,14]. 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 (reference Table 1). 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. In such circumstances, 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.

6.4 Efficacy Assessments

6.4.1 Pain

Subjects record their headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe) in the eCOA handheld device at the time points indicated in Table 1.

6.4.2 Nausea, Phonophobia and Photophobia

Subjects will record the status (present or absent) of their migraine associated symptoms of photophobia, phonophobia and nausea in the handheld at the time points indicated in Table 1. In addition, subjects will record the intensity of the symptom on a 4-point numeric rating scale (none, mild, moderate, or severe) in the handheld at the same time points.

Subjects will also record their current MBS (nausea, phonophobia or photophobia) in the handheld before taking study drug.

6.4.3 Rescue Medication

Subjects must not take rescue medication until 2 hours postdose with study drug. Subjects will record their use of rescue medication in a paper diary.

6.4.4 Functional Disability

Subjects will record their functional disability level using the Functional Disability scale, a 4-point numeric rating scale (normal, mild impairment, severe impairment, required bedrest), in the handheld at the time points indicated in Table 1.

6.5 Other Assessments

6.5.1 Migraine Quality of Life Questionnaire

The Migraine Quality of Life Questionnaire (MQoL) version 3.0 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 5 migraine-specific domains: work functioning, social functioning, energy/vitality, feelings and concerns, and migraine headache symptoms.[15] Subjects will evaluate the MQoL using the handheld at 24 hours postdose (see Table 1).

6.5.2 Preference of Medicine

The Preference of Medication (PoM) is a 5-point numeric rating scale that measures the subject's preference of study drug to previous medications to treat migraine pain. The 5 preference categories are: much better, I prefer this medication; slightly better than the previous medication; about the same as the previous medication; slightly worse than the previous medication; and much worse, I prefer my previous medication. Subjects will evaluate the PoM using the handheld at 24 hours postdose (see Table 1).

6.6 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 AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- See Section 6.3.5 for guidance on study discontinuation based on results from the S-STS.

All subjects who discontinue should comply with protocol specified EOT Visit 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).

6.6.1 Lost to Follow Up

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

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

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

6.7 Clinical Trial Subject Database (CTSdatabase)

CTSdatabase is a clinical trial subject registry that maintains the privacy and security of research subjects while providing sponsors and investigators with crucial information about subjects' current and/or previous study participation.

CTSdatabase has been shown to reduce the number of duplicate and professional subjects entering clinical trials.

The use of this database must be presented to all subjects participating in this protocol. If subjects refuse to provide authorization, the study team should be notified. At the time of providing the Informed Consent for the study, the Investigator or designee will explain the IRB-approved Subject Database Authorization to the subject and witness the signature.

During screening, site staff that have received training and login information should access www.ctsdatabae.com and enter the last 7 digits of the subject study ID and authorized subject identifiers. An immediate report detailing matches is generated and should be printed for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days or (3) the subject matches with a subject who has *pre*-screened at another site.

At the last subject contact, CTSdatabase staff will automatically close out subjects (SF, ET or Completer) based on IWRS information.

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.

Zavegepant or the matching placebo will be provided in single use Aptar UDS devices fully prepared and ready for administration. Zavegepant and placebo 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: standard of care medications for migraine treatment.

7.1.3 Formulation

Zavegepant (BHV-3500), is formulated as 10 mg for intranasal single dose administration using an Aptar Unit Dose System (UDS) liquid spray device.

7.1.4 Packaging, Shipment and Storage

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

7.2 Dose and Administration

7.2.1 Method of Assigning Subject Identification

The Investigator or site designee will access an Interactive Web-based Response System (IWRS) in order to register each subject. Initially, after informed consent is obtained at the Screening Visit, the Investigator or designee will enter the subject into the study and obtain a subject number assignment. If the subject is deemed eligible to participate in the study, at the Baseline visit, container assigned will be obtained by the Investigator (or designee) via the IWRS system. Randomization will be stratified by use of prophylactic migraine medication (yes or no) in IWRS at the Baseline visit.

A new subject ID should be assigned for all re-screens and will be tracked with subject's previous subject ID in EDC and IWRS. Subjects may only be re-screened one time.

Study drug will be assigned via the IWRS system; the system will assign specific container numbers for all blinded study drug to be dispensed to the subject. Once a container has been assigned it cannot be dispensed to another study subject. Sites will be responsible for recording the container numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record.

Once a subject completes the study, or if a subject is discontinued early from the study, the Investigator or designee must access the IWRS to document discontinuation of the patient from participation in the study.

7.2.2 Selection and Timing of Dose and Administration

Study drug (Aptar UDS containing zavegepant or matching placebo) will be packaged in a labeled carton. There are no dose adjustments in this study and subjects will receive study drug sufficient to treat 1 migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit). Subjects will be dispensed the study drug 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 is made to preserve the blind for remaining site personnel.

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 drug within 45 days of the Baseline Visit, they should return to the clinic for their EOT Visit and return their study drug.

7.5 Destruction and Return of Study Drug

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

8 ADVERSE EVENTS

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

Adverse events can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of 1 or more AEs.

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

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)

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

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

- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse
- Potential drug induced liver injury (see Section 8.1.6)
- Abuse or overdose of medication
  - Potential study drug abuse (including cases of excessive non-compliance with study drug dosing instructions or subjects who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Investigators must monitor subjects for possible cases of abuse of study drug (subjects taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should obtain more information and explanation from subjects when there are study drug accountability discrepancies.
  - Potential study drug overdose is defined in Section 8.1.4

Definition of Terms (the below applies to both non-serious AEs and SAEs).

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

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

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

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

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

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

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

- A visit to the emergency room or other hospital department <24 hours that does not result in an admission (unless considered “important medical event” or event that is life threatening);
- Elective surgery planned prior to signing consent;
- Admissions as per protocol for a planned medical/surgical procedure;
- Routine health assessment requiring admission (i.e., routine colonoscopy);
- Admission encountered for another life circumstance that carries no bearing on health and requires no medical intervention (i.e., lack of housing, care-giver respite, family circumstances).

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

8.1.2 Assessment for Determining Relationship of AE to Study Drug:

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

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

Possibly related (non-serious AEs only): This category applies to AEs that are considered to have an unlikely connection to study drug, but a relationship cannot be ruled out with certainty.

Unlikely related (non-serious AEs only): This category applies to AEs that do not follow a reasonable temporal sequence from the administration of the study drug. The AE may readily have been produced by the subject’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

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

8.1.3 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 the14 days after dose. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study drug, overdose (see Section 8.1.4), potential drug induced liver injury (see Section 8.1.7) and pregnancies (see Section 8.1.6) must be reported within 24 hours of the Investigator becoming aware of the event. In this study SAEs are reported in the 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, intensity).

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

- North America - PPD

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

- North America – 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)

8.1.4 Overdose

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

All occurrences of medically significant overdose (suspected or confirmed and irrespective of whether it involved zavegepant) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any treatments administered.

Asymptomatic dosing errors should be reported as deviations.

8.1.5 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.

Under no circumstance may a subject be assigned a second dose of study medication.

8.1.6 Pregnancy

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

Sites should instruct patients to contact the Investigator if they become pregnant during the course of the study. The investigator must immediately notify the Biohaven (or designee) Medical Monitor and CCI of the event and complete the Pregnancy Form in accordance with SAE reporting procedures as described in Section 8.1.2. The pregnancy should be reported using paper forms, which should be faxed to CCI by facsimile (fax), which is the preferred method of submission, within 24 hours after Investigator/site awareness of the event:

- North America - PPD

Or if the form cannot be faxed or emailed (PPD; subject line must include "**Biohaven Protocol BHV3500-301**"), reported via phone to the CCI Safety Hotline at North America: PPD or EU EMEA: PPD

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

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

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

8.1.7 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 ALT or AST elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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

8.2 Adverse Events of Special Interest

8.2.1 Non-serious Adverse Events

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

8.2.1.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the Baseline Visit through the EOT Visit.

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

8.2.2 Laboratory Test Abnormalities

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

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

2. Any laboratory abnormality that required the 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 Sample Size

It is anticipated that about 90% of the 700 subjects randomized to each treatment group will have a headache in the allotted time period, resulting in approximately 630 subjects evaluable for efficacy in each treatment group.

The sample size calculation is based on results from the Phase 2/3 dose-ranging study BHV3500-201. The response rates for the pooled zavegepant 10 mg and 20 mg groups, and for the placebo group in study BHV3500-201 were 22.8% and 15.5%, respectively, for pain freedom at 2 hours postdose, and 42.2% and 33.7%, respectively, for MBS freedom at 2 hours postdose.

A total sample size of 1,260 evaluable subjects (630 per group) will provide approximately 91% power for the co-primary endpoint of pain freedom at 2 hours postdose, approximately 88% power for the co-primary endpoint of MBS freedom at 2 hours postdose, and approximately 80% power to detect a difference between treatment groups for both endpoints jointly.

9.2 Analysis Sets:

- Enrolled: Subjects who sign informed consent and are assigned a subject identification number.
- Randomized: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo) from IWRS.
- Safety: Subjects in the enrolled analysis set who take study drug (zavegepant or placebo).
- Efficacy: Subjects in the randomized analysis set who: (1) are randomized only once; (2) have a migraine of moderate or severe pain intensity at the time of dosing; (3) take study drug; and (4) have postdose efficacy data (i.e., non-missing pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level after taking study drug).

9.3 Statistical Methods

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

9.3.1 Efficacy Analyses

The intercurrent event of rescue medication use will be handled using RM=F, i.e., subjects who take rescue medication will be classified as failures for all efficacy assessments that are reported at or after taking rescue medication. The RM=F method will apply to all efficacy endpoints, except the secondary efficacy endpoint of rescue medication use within 24 hours postdose.

9.3.1.1 Primary Endpoints

Zavegepant will be tested for superiority against placebo at an alpha=0.05 level for both co-primary endpoints using the efficacy analysis set. For each endpoint, treatment groups will be compared using a Cochran-Mantel Haenszel test to estimate the difference in percentages of subjects achieving the endpoint response criteria (zavegepant – placebo) stratified by prophylactic migraine medication use at randomization (yes or no). The percentage of subjects achieving the endpoint response criteria will be presented with a 95% confidence interval (CI) by treatment group. The difference in percentages between treatment groups will be presented with a 95% CI and p-value.

Subjects with missing data at 2 hours postdose will be classified as failures (i.e., Non-Completer = Failure; NC=F).

Sensitivity analyses will be described in the SAP.

9.3.1.2 Secondary Endpoints

If the tests of both co-primary endpoints are significant (i.e., both p-values are ≤ 0.05), then the secondary endpoints will be tested hierarchically at the alpha=0.05 level in the order shown in the Secondary Endpoints section, using the efficacy analysis set. Thus, a secondary endpoint will be tested only if the preceding secondary endpoint in the hierarchy is determined to be significant (i.e., p-value ≤ 0.05). The same statistics will be presented as those for the co-primary endpoints.

For endpoints based on a single time point, such as phonophobia freedom at 2 hours postdose, subjects with missing data at a single time point will also be classified as failures. For endpoints based on multiple time points, such as sustained pain relief from 2 to 48 hours postdose, subjects with missing data at (1) 2, 24, or 48 hours postdose, or (2) more than 1 time point from 3 to 8 hours postdose will also be classified as failures.

9.3.2 Safety Analyses

Deaths will be listed without regard to onset for the enrolled analysis set.

The frequencies of the following postdose safety endpoints will be presented by treatment group for the safety analysis set: AEs by intensity; SAEs; AEs related to study drug; clinically relevant laboratory test abnormalities; liver function test elevations; and nasal inspection abnormalities.

The investigators will determine the intensity of AEs and the relationship of AEs to study drug. The investigators' terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study. AEs will be presented by system organ class and preferred term.

Clinically significant laboratory test abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017) if available; otherwise, results will be graded according to numeric laboratory test criteria in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017), if available.

9.4 Schedule of Analyses

The final analysis will occur after the last subject has completed their last visit. No interim analyses are planned.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP), International Conference on Harmonization guidelines, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any Independent Ethics Committee (IEC) requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

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

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

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

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

10.2 Data and Safety Monitoring Committee

This study will not make use of a Data Safety Monitoring Committee (DMC). Safety will be closely monitored via oversight by the investigators, Sponsor and CRO/designee and an Institutional Review Board/Independent Ethics Committee.

10.3 Steering Committee

Not applicable to this study.

10.4 Institutional Review Board/Independent Ethics Committee

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

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

10.5 Informed Consent

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

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

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

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.

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.

10.6 Case Report Forms

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

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

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

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

11 RECORDS MANAGEMENT

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

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

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

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

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

- amount of study drug received and placed in storage area
- label ID number or batch number or Kit number as specified for the protocol
- amount dispensed to and returned from each patient
- amount transferred to another area or site for dispensing or storage if applicable
- amount of drug lost or wasted
- amount destroyed at the site if applicable
- amount returned to sponsor, if applicable
- retain samples for bioavailability/bioequivalence, if applicable
- record of dates and initials of personnel responsible for IM dispensing and accountability.

11.1 Source Documentation

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

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

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

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

11.2 Study Files and Record Retention

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

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

12 AMENDMENTS

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

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

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

13 STUDY REPORT AND PUBLICATIONS

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

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

14 STUDY DISCONTINUATION

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

15 CONFIDENTIALITY

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

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

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

16 APPENDICES

16.1 APPENDIX I: 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

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

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

16.2 APPENDIX II: Study Personnel

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

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

Study No: BHV3500-301

Original Protocol Date: 03 February 2020

Protocol Version No: V 4.0

Protocol Version Date: 02 June 2021

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 AEs, relating to treatment with the investigational product.

Name and Title	**Signature Approval**	**Date**
Author: PPD PPD		
Clinical Operations: PPD PPD PPD		
Biostatistics: PPD PPD PPD PPD		
Medical Lead: PPD PPD PPD _ PPD		
Study Director: PPD PPD PPD PPD		
Regulatory Affairs: PPD PPD PPD		

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