PROTOCOL TITLE:	A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
NCT NUMBER:	NCT04408794
PROTOCOL DATE:	10-July-2020

DRUG:	Zavegepant (BHV-3500)
STUDY NUMBER(S):	BHV3500-202
PROTOCOL TITLE:	A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
IND NUMBER:	134,120
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	3-February-2020
VERSION NUMBER:	2.0
VERSION DATE:	10-Jul-2020

BHV3500-202

A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (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

Summary of Changes

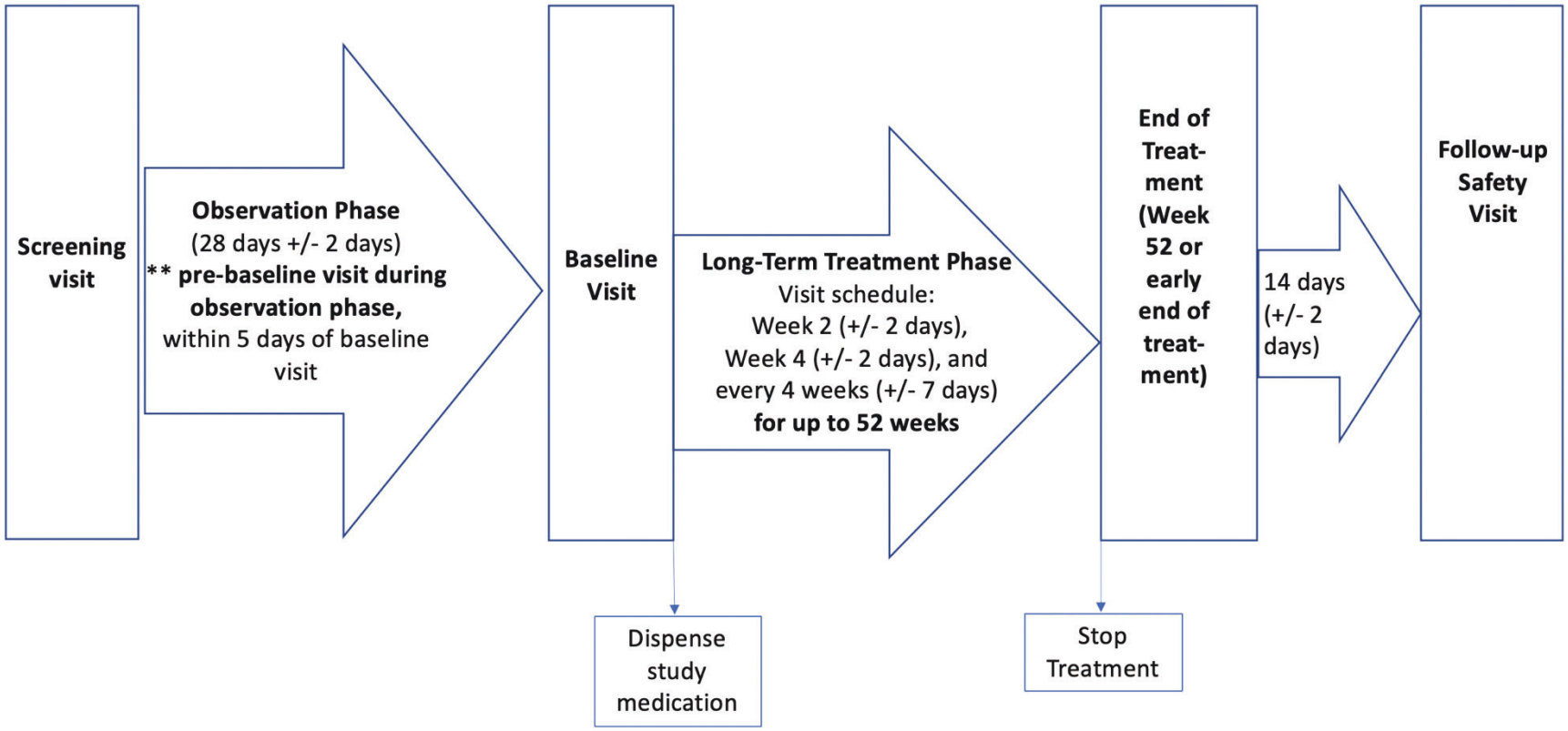
Version	Summary of Changes	Date
Version 01	Not applicable	03 Feb 2020
Version 02	Updated the drug name from vazegepant to zavegepant throughout protocol Added guidance to manage study visits that may not occur on site due to coronavirus disease 2019 (COVID-19) travel restrictions, including visit windows, which visits must be conducted in person at the site, guidance for shipping drug, etc. Updated safety information to align with Investigator Brochure version 3. Updated one exploratory objective. Clarified in the study schema that the pre-baseline visit occurs during the observation phase. Clarified the contraception guidance for subjects in same sex relationships, subjects who report abstinence, and male subjects with vasectomy. Modified exclusion criterion 6g to allow for investigator discretion regarding compliance with electronic evening reports during observation phase. Added ergotamine medications as prohibited concomitant medication. Added discontinuation rule for subjects with eGFR $\leq$ 40 ml/min/1.73m^2). Corrected inconsistencies, typographical errors throughout protocol.	10 Jul 2020

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3500-202: A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV3500 (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 of intranasal (IN) administration of zavegepant in the treatment of mild, moderate or severe migraine. Subjects will be allowed to treat up to 8 migraine attacks per month (28 days) for 1 year.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a one-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 800 subjects will be screened to achieve approximately 600 treated.
Objectives:	Primary: To evaluate the safety and tolerability of zavegepant.
Study Design:	This is a multi-center, open-label study to assess the safety and tolerability of long-term use of zavegepant, taken up to 8 times per month, in subjects with migraine. For subjects to be eligible for the study, they must have between 2-8 moderate to severe migraines per month in the 3 months prior to the screening visit. Subjects who have participated in previous BHV-3500 phase 2 and phase 3 clinical studies will be allowed to enroll in this study provided they meet all eligibility requirements. The screening phase includes a screening visit and a 28-day Observation Phase. Upon completion of the screening visit, subjects will electronically

	record migraine occurrence every day. If a migraine occurs, subjects record migraine intensity and whether the migraine was treated. Subjects will report all concomitant medications, including migraine standard of care medications, in a concomitant medication log. During the 28-day observation phase, the subject will return to the clinic for the pre-baseline visit. At the pre-baseline visit, a blood sample for laboratory tests will be collected. After the pre-baseline visit, subjects will return to the clinic for the baseline visit. At the baseline visit, eligibility for continued participation in the study will be assessed. After the investigator reviews the results of the pre-baseline laboratory assessments and all other eligibility criteria, eligible subjects may be dispensed study drug and may start dosing in the long-term treatment phase. If eligible for the long-term treatment phase, subjects will be instructed that they can take study drug at the onset of a migraine. Subjects will be instructed that they can treat a maximum of 8 migraines per month (28 days) during the long-term treatment phase and that only one administration of study drug is allowed per calendar day. Subjects are required to continue to electronically record their migraine occurrence and migraine intensity daily. If the subject administers study drug to treat a migraine, the dose of study drug must also be reported on that day. Subjects will continue to record any concomitant medication use (including migraine standard of care medications) in the paper diary throughout the course of the study. Subjects will have study visits at Week 2, Week 4 and every 4 weeks through Week 52. The Week 52 (+/- 7 days) visit is the end of treatment visit. There is a follow up visit 14 days (+/- 2 days) after the Week 52/end of treatment visit (see Table 1).

STUDY SCHEMATIC



Total study duration approximately 58 weeks

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LIST OF ABBREVIATIONS

ACS	Acute Coronary Syndrome
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AT	Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Concentration
CGRP	Calcitonin gene-related peptide
CONMED	Concomitant Medication
COVID-19	Coronavirus Disease 2019
CTS database	Clinical Trial Subject Database
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug induced liver injury
DAIDS	Division of AIDS
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
MedRA	Medical dictionary regulatory activities
mITT	Modified intent to treat
mg	Milligram
MI	Myocardial Infarction
min	Minute
mmHg	Millimeters Mercury
MSQ	Migraine-Specific Quality of Life Questionnaire v 2.1
Msecs	Milliseconds
MTD	Maximum tolerated dose
MOH	Medication-overuse headache
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
PK	Pharmacokinetic
po	By Mouth, Orally
PoM	Preference of medication
PVG	Pharmacovigilance

qd	Once Daily
QTcc	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
TB	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]

A summary of the nonclinical investigational programs can be found in the current Investigator's Brochure (IB).[11]

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 Nonclinical 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 in 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 Clinical Experience

1.2.2.1 Single Ascending Dose (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 40mg 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 SAEs or deaths reported in this study. The majority of AEs were mild in intensity and resolved spontaneously by the end of treatment. The most frequently reported treatment emergent adverse events (TEAEs) 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 (BHV3500-102)

This is an ongoing, multiple dose study to assess safety, tolerability and PK. In this study, zavegepant was administered once daily for up to 14 days or two sequential doses for up to 8 days.

1.2.3 Other Clinical / Non-clinical Studies

A series of in vitro studies have been performed to investigate CYP-mediated drug interactions. BHV-3500 has been examined for effects in a transporter study.[12] The details of these studies can be found in the zavegepant (BHV-3500) IB.[11]

1.2.3.1 Phase 1 Studies

There is a planned series of additional clinical pharmacology studies with zavegepant. Relevant information will be provided in the IB or protocol when available.

1.2.4 Clinical Adverse Event Profile

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

BHV-3500 is a concluded, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study conducted to evaluate the safety and efficacy of zavegepant (5 mg, 10 mg, or 20 mg) of zavegepant intranasal (IN) versus placebo in the acute treatment of migraine.

No deaths were reported, and no treatment-related serious adverse events (SAEs) were reported. SAEs were reported on-treatment in two subjects including post-traumatic thrombosis reported in one subject in the zavegepant 10 mg group, and vestibular migraine reported in one subject in the placebo group. Both events were moderate in intensity and judged by the investigator as not related to study drug.

The overall incidence of AEs was 26.2% (311 of 1,185 subjects) in the zavegepant groups and 15.4% (62 of 403 subjects) in the placebo group. The incidence of AEs in the zavegepant groups were as follows: 22.7% (88 of 388 subjects) in the 5 mg group, 24.6% (97 of 394 subjects) in the 10 mg group, and 31.3% (126 of 403 subjects) in the 20 mg group. The majority of AEs in all treatment groups were mild or moderate in intensity, not related to study therapy and resolved without treatment. The most frequently (≥ 2%) reported AEs in any treatment group are shown in the table below.[11]

BHV3500-201 On-treatment Adverse Events Reported in at Least Two Percent of Subjects in Any Treatment Group					
Adverse Event	**5 mg**	**10 mg**	**20 mg**	**Overall zavegepant**	**Placebo**
Dysgeusia	13.9%	13.5%	16.1%	14.5%	3.5%
Nausea	2.6%	4.1%	2.7%	3.1%	0.5%
Nasal Discomfort	1.3%	1.3%	5.2%	2.6%	0.2%
Throat Irritation	1.0%	1.0%	2.2%	1.4%	0.0%
Nasal Congestion	0.3%	0.3%	2.0%	0.8%	0.5%
UTI	0.8%	1.0%	2.0%	1.3%	1.2%

Nasal inspection conducted at screening, baseline and end of treatment showed no clinical evidence of nasal mucosal injury. No subject had AST or ALT > 3x ULN or bilirubin > 2x ULN in any treatment group.

Refer to the most recent version of the Investigator Brochure for latest clinical adverse event profile.

1.3 Study Rationale

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

This study will evaluate the safety and tolerability of BHV-3500 during longer-term acute treatment of migraine with or without aura in adults.

1.3.1 Study Design Rationale

This is a multi-center, open-label study to assess the safety and tolerability of long-term use of IN zavegepant, taken up to 8 times per month (every 28 days) in subjects with migraine. The study drug, zavegepant (BHV-3500), is formulated as a 10 mg IN dose and will be administered using an Aptar Unit Dose System (UDS) liquid spray device. Each UDS devices contains a single dose of study drug zavegepant. The subjects will be instructed to take their study drug, when they have a migraine headache, up to 8 times per month.

The study will screen approximately 800 subjects to treat approximately 600 subjects

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 the 5 mg, 10 mg, 20 mg or 40 mg dose levels.

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 post dose, 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, 10mg, 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 and received 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 demonstrated statistical superiority to placebo on both coprimary endpoints of pain freedom and freedom from most bothersome symptom (MBS) at 2 hours. Rapid onset of pain relief was seen as early as 15 minutes 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 is safe and well tolerated in the treatment of migraine.

2 STUDY OBJECTIVES

2.1 Primary Objectives

To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine.

2.2 Secondary Objectives

Not applicable.

2.3 Exploratory Objectives

1. To evaluate the frequency of AEs potentially associated with drug abuse.
2. To evaluate frequency of AEs indicating Medication-overuse headache (MOH)
3. To evaluate the frequency and intensity of hepatic-related adverse events (AEs)
4. To evaluate the frequency of local irritation AEs.
5. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, alkaline phosphatase, and total bilirubin) based on fold changes above ULN.
6. To evaluate the frequency of ALT or AST > 3x ULN concurrent with total bilirubin > 2x ULN.
7. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.
8. To evaluate Sheehan Suicidality Tracking Scale (S-STS) scores and changes from baseline.
9. To evaluate the reduction from the observation phase in the number of migraine days per month by intensity.
10. To evaluate Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQ) domain scores and changes from baseline.
11. To evaluate Preference of Medication (PoM).
12. To evaluate Satisfaction with Medication (SM).
13. To evaluate MIDAS scores and changes from baseline.
14. To evaluate Clinical Global Impression – Change (CGI-c).

3 STUDY ENDPOINTS

3.1 Primary Endpoints

The frequency and intensity of AEs that occur in at least 5% of treated subjects, the frequencies of SAEs, AEs leading to study drug discontinuation, and clinically significant laboratory test abnormalities will be assessed on treatment.

The frequency of AEs will be determined from case report forms (CRFs) and based on the number and percentage of subjects with events. The frequency of clinically significant laboratory test abnormalities will be determined from Grade 3-4 laboratory tests from CRFs and central laboratory test data, and based on the number and percentage of subjects with abnormalities.

3.2 Secondary Endpoints

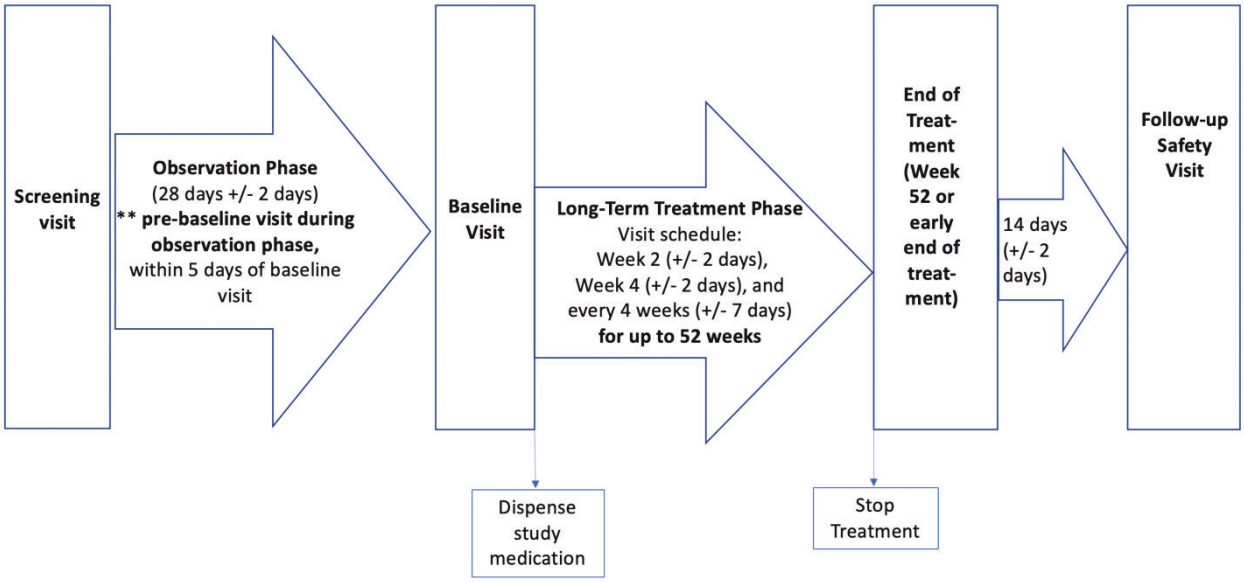
Not applicable.

4 STUDY PLAN

4.1 Study Design and Duration

This is a multi-center, open-label study to assess the safety and tolerability of long-term use of zavegepant, taken up to 8 times per month (every 28 days), in subjects with migraine. Approximately 800 subjects will be screened to treat up to approximately 600 eligible subjects. After completion of screening procedures and an observation phase, eligible subjects may participate in the study up to 52 weeks in the long-term treatment phase. Subjects who complete the 52-week long-term treatment phase or discontinue early from the long-term treatment phase will all complete a follow up visit approximately 14 days after the end of treatment visit. Subjects who do not administer study drug to treat any migraines by week 8 of the long-term treatment phase will be discontinued from this study.

4.2 Study Schematic



Total study duration approximately 58 weeks

4.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	Screening Visit	Observation Phase (28 days +/- 2 days)	Pre-Baseline Visit (up to 5 days prior to Baseline Visit)	Baseline Visit (Day 1)	Week 2 (Day 15 +/- 2 days)[1]	Week 4 (Day 29 +/- 2 days)[1]	Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or EoT) (all visits +/- 7 days)[1]	Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)[1]
Informed Consent	X							
Inclusion / Exclusion Criteria	X			X				
Medical History	X							
Migraine History (signs/symptoms/prior treatment/frequency/intensity)	X							
Concomitant medication reported by subject in paper diary[2]	X	X		X	X	X	X	X[3]

[1] Every effort should be made to conduct the study visits within the specified windows. However, if necessary due to local COVID-19 safety requirements, visits may be performed outside of these windows in order to minimize any potential risks to subject safety and to comply with governmental and institutional guidance. See sections 4.3.1 - 4.3.6 for more information.
[2] Concomitant medication, including migraine standard of care medication and prophylactic migraine medication, taken at any time during the study will be reported by subject on a medication log and reviewed by site staff at each study visit
[3] Collect if treatment with concomitant medication is required for an AE or if concomitant medication is considered related to AE

Procedure	**Screening Visit**	**Observation Phase (28 days +/- 2 days)**	**Pre-Baseline Visit (up to 5 days prior to Baseline Visit)**	**Baseline Visit (Day 1)**	**Week 2 (Day 15 +/- 2 days)[1]**	**Week 4 (Day 29 +/- 2 days)[1]**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or EoT) (all visits +/- 7 days)[1]**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)[1]**
Physical Examination[4]	X[5]		X			X	X (Weeks 24 and EoT only)	
Vital Signs/Physical Measurements[6]	X		X		X	X	X	X
Nasal Inspection	X		X		X	X	X	X
Clinical Safety Laboratory Testing	X[7]		X			X	X (Weeks 24 and EoT only)	
Liver function tests (LFTs)	X[8]		X		X	X	X	X
Lipid panel			X[9]				X (Weeks 24 and EoT only)	
ECG	X[10]					X	X (Weeks 24 and EoT only)	X
Urinalysis[11]			X				X (EoT only)	
Urine Drug Screen for drugs of abuse	X							

[4] Full physical exam at screening and EoT; targeted physical exam guided by signs and symptoms at all other specified visits.
[5] If the end of treatment physical exam from BHV3500-301 was done within 4 weeks of the screening visit for BHV3500-202, it does not need to be completed at screening. The data from the BHV3500-301 physical exam must be entered in the BHV3500-202 CRF.
[6] Height collected at screening only.
[7] **Hematology** includes hemoglobin, hematocrit, RBCs, WBCs with differential, platelets; **Chemistry** includes creatine kinase**,** sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin.
[8] **LFTs** includes AST, ALT, Alkaline Phosphatase, and bilirubin (total, direct, indirect)
[9] **Lipid panel** includes cholesterol, LDL, HDL, and triglycerides
[10] The BHV3500-301 EoT ECG can be used as the screening ECG for BHV3500-202 if the visits are done on same day.
[11] **Urinalysis** includes pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and blood. If blood, protein or leukocytes are positive, reflex to microscopic examination

Procedure	**Screening Visit**	**Observation Phase (28 days +/- 2 days)**	**Pre-Baseline Visit (up to 5 days prior to Baseline Visit)**	**Baseline Visit (Day 1)**	**Week 2 (Day 15 +/- 2 days)[1]**	**Week 4 (Day 29 +/- 2 days)[1]**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or EoT) (all visits +/- 7 days)[1]**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)[1]**
FSH, if applicable, to determine WOCBP status[12]	X							
Pregnancy Test	X (urine)		X (serum)			X (urine)	X (urine)[13]	X (urine)**Error! Bookmark not defined.**
AE and SAE assessment[14]	X		X	X	X	X	X	X
Sheehan Suicidality Tracking Scale	X		X		X	X	X[15]	X
Subject report of migraine occurrence and intensity		X	X	X	X	X	X	
Migraine-Specific Quality of Life Questionnaire (MSQ) v 2.1			X				X (Weeks 12, 24, 36, 52/EoT only)	
Preference of Medication							X (Week 52/EoT)	
Satisfaction with Medication							X (Week 52/EoT)	

[12] If WOCBP status was determined by FSH in BHV3500-301 the subject is considered to have the same status in BHV3500-202

[13] Pregnancy tests must be completed monthly for any WOCBP subjects. Pregnancy tests may be completed at home if a study visit is not conducted in person. The pregnancy test result must be reported to the site by the subject in real time and documented by site (please see Sections 4.3.4 and 7.4).
[14] SAEs and non-serious AEs must be reported after the subject signs informed consent
[15] S-STS must be completed monthly for all subject. S-STS may be completed over the phone if a study visit is not conducted in person.

Procedure	**Screening Visit**	**Observation Phase (28 days +/- 2 days)**	**Pre-Baseline Visit (up to 5 days prior to Baseline Visit)**	**Baseline Visit (Day 1)**	**Week 2 (Day 15 +/- 2 days)[1]**	**Week 4 (Day 29 +/- 2 days)[1]**	**Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52 (or EoT) (all visits +/- 7 days)[1]**	**Week 2 Follow-up Safety Visit (14 days after EOT visit +/- 2 days)[1]**
Clinical Global Impression-change (CGI-c)							X (Weeks 12, 24, 36, 52/EoT only)	
Migraine Disability Assessment (MIDAS)			X				X (Weeks 12, 24, 36, 52/EoT only)	
Dispense Study drug				X	X	X	X	
Administer study drug				X	X	X	X	
Return used and unused study drug to site for compliance assessment					X	X	X	
eCOA handheld device dispensed or personal device set up[16]	X							
CTSdatabase registration (optional)	X							

[16] Applicable if subject elects to use provisioned device. Subjects also have option to use their personal device.

4.3.1 Screening Visit and Observation Phase

Approximately 800 subjects will be screened in this study.

Before any study procedures are performed, subjects must sign informed consent. After informed consent has been signed, subjects will be entered in the IWRS. 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. Subjects will complete daily evening reports electronically (either on a provisioned device, the subject's personal smart phone, or a backup web portal) to report if a migraine occurred, the intensity of the migraine and whether or not the migraine was treated with migraine standard of care medication. Subjects will record medications on a concomitant medication log. The Observation Phase is 28 days, +/- 2 days. After completion of the Observation Phase subjects will return to the study site for the pre-baseline visit. In this study, subjects may be screened only once; rescreening is not permitted. The screening visit must be conducted in person.

4.3.2 Pre-Baseline Visit

Screened subjects will be assessed for eligibility based on data collected at the screening visit, during the observation phase, and at the pre-baseline visit. The pre-baseline visit should be completed within 5 days of the baseline visit. This visit must be conducted in person.

4.3.3 Baseline Visit

The baseline visit should occur within 28 days (+/- 2 days) of the screening visit. If the pre-baseline laboratory test results are determined to be unacceptable per protocol, the subject is considered a screen failure and must return to the study site to return the provisioned device (if applicable). Eligible subjects will be dispensed study drug at this visit. This visit must be conducted in person.

4.3.4 Long-Term Treatment Phase

Up to approximately 600 subjects will enter the long-term treatment phase. Study visits will be approximately every two weeks (14 days) during the first month, then every 4 weeks (28 days) up to week 52 (Table 1). At each visit, the electronic daily evening reports will be reviewed for completeness and compliance with reporting all doses of study drug taken by the subject. Study drug compliance will be reviewed by study site staff at each visit. Subjects will be counselled regarding compliance with: study drug dosing instructions, administration of zavegepant only to treat a migraine, and that only one dose of study drug can be taken per calendar day. Subjects will be instructed that they may treat up to 8 migraines per month (28 days). Subjects will be informed that they may be withdrawn from the study for reasons including non-compliance with the protocol, abuse of the study drug, or not treating a migraine with study medication prior to

the Week 8 visit. Subjects will complete electronic evening reports of daily migraine occurrence, migraine intensity, administration of study drug (if applicable), and administration in left or right nostril (if applicable). The MSQ, S-STS, MIDAS, and CGI-c will be completed on paper at the appropriate visits.

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. Pregnancy tests in WOCBP subjects must be completed monthly (at-home pregnancy tests may be provided) and results reported to the clinical site in real time. Subject report to the site of a negative pregnancy test is required for continued participation in the study (and must be documented) and before shipments of study medication to any subject. Any potential issues should be discussed with Sponsor/CRO and will be addressed on an individualized basis. The screening, pre-baseline, baseline, Week 4, Week 24 visits must be done in person. Other visits may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.).

4.3.5 End of Treatment (early discontinuation or Week 52)

Subjects will return to the study site at Week 52, or at End of Treatment for those subjects who discontinue early, for review of the electronic evening reports, assessment of study drug compliance, and end of treatment procedures (Table 1). The POM and SM will be completed electronically and the MSQ, S-STS, MIDAS, and CGI-c will be completed on paper. Subjects must return all used and unused study drug and the provisioned electronic eCOA handheld device (if applicable) to the study site. This visit must be conducted in person, but may be delayed if necessary due to local COVID-19 safety requirements).

4.3.6 Follow up Safety Visit

Subjects will return to the study site approximately 14 days after the Week 52/End of Treatment visit for a follow up safety visit and applicable study procedures (Table 1). Subjects will return the concomitant medication log at this visit for one final review by the study site staff. This visit must be conducted in person, but may be delayed if necessary due to local COVID-19 safety requirements).

4.3.6.1 Electronic Data Collection

Subjects will complete electronic evening reports daily. The subjects may choose to either receive a provisioned device (referred to as an eCOA handheld device, or eDiary), or use their own smartphone device and download an application to report the evening reports. Subjects will also have access to a back-up method of reporting the electronic evening reports on a password

protected website. The website should be considered a backup method for completion of the electronic evening reports.

The following data will be reported by the subjects electronically throughout the study:

- Whether or not a migraine occurred
- Migraine pain intensity (mild, moderate, or severe)
- During the observation phase, if the migraine was treated with migraine standard of care medication
- During the long-term treatment phase, if the migraine was treated with study drug and nostril of administration (left or right)
- At the end of treatment visit, the PoM and SM.

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 migraine.

5 POPULATION

Individuals entered in this trial will be subjects who suffer from migraine. 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

Up to approximately 800 subjects will be screened and up to approximately 600 subjects will treat migraines with study drug in this study. It is anticipated that enrollment will occur at approximately 65 sites in the United States over a period of approximately 5 months.

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 migraine (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) 2- 8 migraine attacks of moderate or severe intensity per month within last 3 months prior to the screening visit.

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

    e) Treatment of 2 or more migraines attacks with standard of care medication during Observation Phase.

    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 during the observation phase.

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 two acceptable methods of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. See Section 5.6 for the definition of WOCBP and contraception requirements.

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

d) At the pre-baseline visit prior to dispensing study drug, WOCBP must have a negative 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 parameters outside the reference range 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 (not including exclusion criteria listed in Section 5.3 below).

5.3 Exclusion Criteria

1) Disease Target Exclusion

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

b) Subjects with headaches occurring 15 or more days per month (migraine or non-migraine) in any of the 3 months prior to the screening visit and during observation phase

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 (24 weeks) prior to the screening visit.

c) Uncontrolled hypertension or uncontrolled diabetes (however, subjects can be included who have stable hypertension and/or stable diabetes for at least 3 months prior to being screened). 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) 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 be at a stable dose for at least 3 months prior to the screening visit.

e) Active chronic pain syndrome (such as fibromyalgia, chronic pelvic pain, complex regional pain syndrome (CRPS) or other pain syndromes including trigeminal neuralgia).

f) Current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder.

g) Dementia or significant neurological disorder (other than migraine) that, in the investigator's opinion, might interfere with study assessments.

h) 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.

i) History of gallstones or cholecystectomy.

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

k) Subjects must stop all OTC or prescription nasal sprays at the screening visit (see Section 5.4).

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

m) 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.

n) 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 of medication.

o) History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or subjects who have met DSM-V criteria[13] for any significant substance use disorder within the past 12 months from the date of the screening visit.

p) History of use of opioid- or barbiturate- (e.g. butalbital) containing medication for 4 or more days per month on average during the 3 months (12 weeks) prior to the screening visit.

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

   i) Detectable levels of cocaine, amphetamine, and phencyclidine (PCP) in the drug screen are exclusionary. Subjects who are positive for amphetamines, and who are on a prescribed amphetamine medication for an approved indication (e.g. ADHD) will be allowed into the study at the Investigator's discretion. This determination by the Investigator must be well documented in the subject's source medical records. The stimulant dose must be stable from 3 months prior to baseline until the end of treatment visit occurs.

   ii) Detectable levels of marijuana in the drug screen are not exclusionary, if in the Investigator's documented opinion the subject does not meet DSM-V criteria[13] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the subject or interpretation of the study results.

r) 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.

s) Body mass index $\geq$ 33 kg/m^2

t) 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 acceptable contraceptive methods (see Section 5.6) to avoid pregnancy for the entire study period and for 90 days after the last dose of study drug.

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 (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation ≤ 40 ml/min/1.73m^2.

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

c) Left Bundle Branch block.

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

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

f) Serum bilirubin (total, direct, or indirect) > 1 x ULN at pre-baseline visit (Only abnormal values of between 1-1.5x ULN at the screening visit may be repeated once for eligibility during the observation phase. Abnormal bilirubin results obtained at the pre-baseline visit may not be repeated.)

g) Neutrophil count ≤ 1000/µL (or equivalent) at screening or pre-baseline visit.

h) AST (SGOT) or ALT (SGPT) > 1 x ULN at pre-baseline visit. (Only abnormal values of between 1-1.5x ULN at the screening visit may be repeated once for eligibility during the observation phase. Abnormal AST or ALT results obtained at the pre-baseline visit may not be repeated.)

i) HbA1c ≥ 6.5% at screening visit.

6) Other Exclusion Criteria:

a) Prisoners or subjects who are involuntarily incarcerated.

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

c) Participation in clinical trial with non-biological investigational agents or investigational interventional treatments within the 30 days prior to Baseline Visit (except BHV3500-301).

d) Participation in clinical trial with biological investigational agents within the 90 days prior to the screening visit.

e) Score of > 0 on the Sheehan Suicidality Tracking Scale at the screening or pre-baseline visit.

f) Participation in any other investigational clinical trial (including observational trials) while participating in this clinical trial.

g) Non-compliance with completing the electronic evening reports during the observation phase, which in the investigator's opinion, would make the subject a poor candidate for participation in a year-long study.

h) Previous enrollment in study BHV3500-202 (re-screens are not allowed in this study).

i) Failure to complete the baseline visit within the timeframe specified in the schedule of assessments.

j) Identified as duplicate subject in CTSdatabase

7) Please see Section 5.4 for prohibited medications and Section 5.5 for allowable prophylactic and standard of care medications.

5.4 Prohibited Concomitant Medications

The below medications are prohibited on or after the baseline visit and during the course of this study or as specified.

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

2. Modafinil (PROVIGIL®) should not be taken 14 days prior to the baseline visit and throughout the study.

3. Butterbur root or extracts should not be taken 14 days prior to the baseline visit and throughout the study.

4. Concomitant use of non-narcotic analgesic medications ≥ 15 days per month (e.g. acetaminophen, NSAIDs, gabapentin etc.) is prohibited during the study.

5. Use of narcotic medication, such as opioids (e.g. morphine, codeine, oxycodone and hydrocodone) is prohibited for at least 2 days prior to the baseline visit and throughout the study including the 2-week follow up safety visit.

6. Barbiturate-containing products (e.g. Fioricet, Fiorinal, butalbital, phenobarbital) are prohibited 14 days prior to the baseline visit and throughout the study including the 2-week follow up safety visit.

7. Use of all acetaminophen or acetaminophen containing products for non-migraine indications after the baseline visit is prohibited. Any use of acetaminophen or acetaminophen containing products for non-migraine indications during the Observation Phase must be stopped at least 2 days prior to the baseline visit. Acetaminophen as a standard of care migraine medication as described in Section 5.5 is allowed during the Long-Term Treatment phase.

8. The use of triptans, lasmiditan or ergotamine medications is prohibited from at least 2 days prior to the baseline visit and throughout the study.

9. Use of marijuana is prohibited during the study including the 2-week follow up safety visit.

10. Muscle relaxants (baclofen is allowed, see Section 5.5).

11. Concomitant use of strong CYP3A4 inhibitors with zavegepant 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 zavegepant 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 zavegepant is prohibited during the study. If use of a strong CYP3A4 inducer is required, such as use of carbamazepine, phenytoin, or rifampin, dosing with zavegepant 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. All OTC or prescription topical nasal medications (e.g. steroids, oxymetazoline, topical nasal antihistamines, topical nasal anticholinergics, and topical nasal mast cell stabilizers) must be stopped at the screening visit. After the baseline visit, acute use (< 10 days/month) is permitted as needed. However, chronic use is prohibited and daily use of these products for 3 consecutive months or longer, may result in withdrawal from 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 the screening visit.

15. The use of FDA-approved gepants is prohibited from the screening visit to the last study visit (e.g. Nurtec ODT® (rimegepant), Ubrelvy® (ubrogepant)).

16. Concomitant use of atypical antipsychotics such as Abilify® (aripriprazole), Zyprexa® (olanzapine), Seroquel® (quetiapine), Geodon® (ziprasidone), or Risperdal® (risperidone), or Depakote®/Depakene® (valproic acid/valproate) is prohibited during the study.

17. Concomitant use of Lamictal® (lamotrigine).

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

5.5 Prophylactic and Standard of Care Migraine Medications

Subjects on prophylactic migraine medication are permitted to remain on the medication if the dose has been stable for at least 3 months prior to the screening visit and is not expected to change during the course of the study (including monoclonal antibodies (mAbs), e.g. Emgality® (galcanezumab), Aimovig® (erenumab)), Ajovy® (fremanezumab), Vyepti® (eptinezumab-jjmr).

Subjects may take their previously prescribed acute treatment standard of care medications unless otherwise prohibited in Section 5.4: aspirin, ibuprofen, acetaminophen up to 1000 mg/day for a maximum of 2 consecutive days at a time (this includes Excedrin Migraine) Naprosyn (or any other type of non- steroidal anti-inflammatory (NSAID)), antiemetics (e.g., metoclopramide or promethazine), or baclofen.

If a subject takes a dose of IN zavegepant and experiences a migraine later in the same calendar day, the subject should take acute treatment standard of care migraine medication as described in this section of the protocol. Subjects are not allowed to administer more than 1 spray of study drug per calendar day.

Use of standard of care medication and prophylactic migraine medication throughout the course of the study will be recorded by the subject on a concomitant medication log and it should be reviewed by site staff at each visit (review of concomitant medication log is not required at the pre-baseline visit).

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 one 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 acceptable methods of contraception to avoid pregnancy throughout the study and for 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 two 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 last dose of study drug). The two methods should include one barrier method (ex. condom with spermicidal gel, non-hormonal intrauterine device, cervical cap etc.) and one 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 requirement 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 same-sex relationships 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 to donate sperm until 90 days following the last study drug administration.

All WOCBP must complete the pregnancy test schedule (Table 1).

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 to the site:

- Investigator File/Study Binder
- Drug Accountability Logs
- Sample source documents
- Subject Concomitant Medication Log
- 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
- Provisioned electronic devices (subjects have the option to use their own smartphone and download an application to report the daily evening reports)
- Drug administration instructions
- Laboratory kits and laboratory manual
- ECG machine and instructions
- Serious Adverse Event (SAE) forms and Serious Adverse Events (SAE) Reporting instructions
- Pregnancy surveillance forms and reporting instructions
- S-STS source document
- MIDAS source document
- MSQ source document
- CGI-c source document

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

The subject will report daily evening migraine reports electronically. The primary reporting method will be either through a provisioned device supplied by the eCOA vendor or the subject's personal device. If the subject is unable to report in the provisioned device or personal device, the subject will also have the option to complete the daily evening migraine reports in a password protected web portal. The web portal should be used as the secondary or back-up reporting method. If subject compliance with the daily evening migraine reports is low, the subject may be offered a provisioned device to assist with increased compliance.

6.2 Eligibility Assessments

Informed consent, inclusion/ exclusion criteria including medical history, migraine history assessment, concomitant medications, laboratory assessments, ECG, daily electronic evening reports as outlined in Table 1.

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 at the screening visit and at the scheduled visits as outlined in Table 1. A central ECG service will be utilized for all ECGs. The over read from the central ECG vendor should be used to determine eligibility for the study. The Investigator will determine if any abnormalities are of clinical significance.

6.3.3 Physical Exam

Subjects will undergo a physical examination at screening at ET (Table 1). The directed physical exam should be guided by the subject's signs and symptoms.

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 visits specified in 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 8.3.2) . The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory test findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject'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 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 subject 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.

Clinical Safety Labs:

- **Hematology**: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelets.

- **Chemistry**: Sodium, potassium, chloride, bicarbonate, calcium; glucose, HbA1c, BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin, CK (elevations in CK >5x ULN may have further CK fractionation tests performed).

- **eGFR** using the estimated MDRD formula (calculated at central lab)

LFTs: AST, ALT, alkaline phosphatase, and bilirubin (Total, Direct, Indirect)

Lipid panel: total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides

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, barbiturates, opioids, PCP, and THC.

FSH: For WOCBP at screening, to determine WOCBP status

Reflex tests:

- If ALT or AST ≥ 3x ULN OR total bilirubin ≥ 2x 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 or urine), when appropriate and as outlined in Table 1.

6.3.5 Sheehan Suicidality Tracking Scale (S-STS) (if applicable)

The Sheehan STS (S-STS) is a prospective, subject self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors[14,15] The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is 30 days prior; at all other visits, the recall period for completing the S-STS is since the last visit. Any responses other than 0 must be immediately evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. For discussion on a study specific basis: 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.

Any subject with a response greater than 0 to any question, excluding Question 2, must be immediately discontinued from the study. Subjects with a response of 1 ("a little") to Question 2 will be discontinued per the investigator's assessment or if the response persists. Subjects with a response greater than 1 on Question 2 will be discontinued from the study immediately.

S-STS may be completed over the phone with the exception of the following visits: Screening, Pre-Baseline, Week 4, Week 24, EOT, and Follow-up Safety.

6.4 Efficacy Assessments

Not applicable.

6.5 Other Assessments

6.5.1 Daily Migraine Assessment of Intensity and Frequency

The number of migraine days and intensity of migraine attacks during the period that subjects are treated with zavegepant relative to the observation phase will be analyzed.

6.5.2 Migraine-Specific Quality of Life Questionnaire v 2.1

Impact of treatment on subject-reported quality of life will be assessed using the Migraine-Specific Quality of Life Questionnaire v 2.1 (MSQ v 2.1). The MSQ is a 14 item instrument that has been validated in 3 domains: role function – restrictive, role function – preventive, and emotional function.[16]

6.5.3 Preference of Medication

The Preference of Medication (PoM) is a subject-rated, 5-point scale that measures the preference of the study drug compared to the previous medications to treat migraine pain. The PoM will be completed electronically.

6.5.4 Satisfaction with Medication

The Satisfaction with Medication (SM) is a subject-rated 7-point scale that measures satisfaction with the study drug to treat migraine headaches. The SM will be completed electronically.

6.5.5 Migraine Disability Assessment (MIDAS) Questionnaire

The Migraine Disability Assessment (MIDAS) is a retrospective, subject-reported, 5 item questionnaire that measures headache-related disability as lost days due to headache from paid work or school, household work, and non-work activities over a 3-month period. The MIDAS will be completed on paper.[17]

6.5.6 Clinical Global Impression – Change (CGI-c) Scale

The Clinical Global Impression-change (CGI-c) scale is an observer-rated, 7-point scale that measures subject total improvement relative to the investigator's past experience with other subjects with the same diagnosis, with or without collateral information. The CGI-c will be administered by the investigator, or designee who has been trained on administration, and will be completed on a paper form.[18]

6.6 Early Discontinuation from the Study

Subjects must discontinue investigational product 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
- No migraine treated with study drug prior to the week 8 visit of the long-term treatment phase of the study
- Lack of efficacy of study medication

- Poor compliance with study procedures, including poor compliance with study medication dosing instructions.

- Infrequent study drug usage (defined as an average of <2 doses per month over 3 consecutive months).

- Please see Section 6.3.5 for guidance on study discontinuation based on results from the S-STS.

- eGFR ≤ 40 (ml/min/1.73m^2) using the estimated MDRD formula

- Termination of the study by Biohaven Pharmaceuticals

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

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

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 seven 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 (IP) also known as investigational medicinal product (IMP) in some regions, is defined as follows:

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

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

In this protocol, IP is zavegepant 10 mg IN and will be provided as single use disposable Aptar UDS devices fully prepared and ready for administration. Zavegepant is packaged as 4 devices per box.

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

7.1.2 Formulation

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

7.1.3 Packaging, Shipment and Storage

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. Please see the 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 need to 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. At the baseline visit and subsequent visits in the long-term treatment phase, container assignments will be obtained by the Investigator (or designee) via the IWRS system. This subject number must not be reused for any other participant in the study. Subjects will maintain their subject number assigned at screening, throughout the trial.

Subjects may not be rescreened for this study.

Study drug will be assigned via the IWRS system; the system will assign specific container numbers for all study drug to be dispensed to the 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 (zavegepant) will be assigned to subjects via the IWRS. There are no dose adjustments in this study. Subjects will receive 4 devices containing zavegepant in a box/container and may receive more than one box of 4 devices at a study visit. Subjects will be dispensed study drug at the baseline visit, after eligibility is confirmed based on the subject's pre-baseline laboratory tests and other screening procedures.

Subjects will be instructed to administer one spray from a single device to treat a migraine. Subjects must be instructed that they cannot administer more than one spray (or device) per calendar day. Subjects will dose for up to 52 weeks. Subjects may administer study drug a maximum of 8 times per month (every 28 days). Subjects who demonstrate poor compliance with study drug instructions or who do not administer study drug may be involuntarily discontinued from the study.

Study drug may be interrupted and re-started after consultation with the Sponsor medical monitor.

7.2.3 Dose Modifications

Not applicable

7.3 Blinding and Unblinding

Not applicable.

7.4 Study and Treatment Compliance

Responsible study personnel will dispense the study drug to the study subjects. Subjects should use all devices in one box/container before starting to use the devices in the next container. Accountability and compliance verification should be documented in the subject's study records.

Subjects must be counseled at all study visits on the importance of taking the study drug as directed. Treatment compliance, through review of study drug doses reported electronically, and review of the returned study drug, should be assessed by site staff at each study visit. Discrepancies between doses reported electronically, review of study drug, and information provided by subject, must be documented in the source record. Incorrect or missing dosing data and migraine data that are reported in the eDiary will be corrected through either a Data Clarification Record or a Medication Reconciliation Form, as appropriate.

Investigators should inform subjects that involuntary termination from the study will occur in cases where non-compliance is identified (defined as both non-compliance with the daily evening report and/or with average number of monthly doses of study drug). Study staff should contact a subject in between the monthly study visits if the subject demonstrates non-compliance the daily evening migraine report and document the contact in the source notes, to identify potential lost to follow up or non-compliant subjects as early as possible.

Investigators must monitor subjects for possible cases of abuse of study drug (patients taking study drug for non-therapeutic purposes, e.g. for psychoactive effects such as high or euphoria). Investigators should assess study drug accountability discrepancies (e.g. missing study drug, loss of drug, or non-compliance cases in which more study drug was used, as compared to expected). Investigators should obtain more information and explanation from patients when there are study drug accountability discrepancies. See Section 8.1.1.

Cases of potential study drug abuse or overdose (including cases of non-compliance with study drug dosing instructions or patients who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Dosing

errors (e.g. accidentally administering 2 sprays from 2 devices in one calendar day) should be reported as deviations.

If poor compliance continues, (i.e., non-compliance with study drug dosing instructions or instances of lost study drug during the long-term treatment phase), discontinuation of the subject from the trial will be considered.

In the event a study visit cannot be completed due to the COVID-19 pandemic, the study site may send drug via certified and tracked courier to the subject, if allowable by the policies of the study site. The sponsor should be consulted prior to shipping drug. For WOCPB subjects, a negative pregnancy test must be documented for continued participation in the study and prior to shipping 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 relate to the investigational product.

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

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

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 adverse events and serious adverse events).

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 Biohaven clinical studies (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 the 14 days after last dose. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study drug, overdose (see Section 8.1.4), potential drug induced liver injury (see Section 8.1.6) and pregnancies (see Section 8.1.5) 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 serious adverse event must be reported immediately or no later than 24 hours after awareness of the event to CCI A written description of any serious adverse event, using the CCI SAE report form, must be sent to CCI 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 number

Protocol number (BHV3500-202)

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 both **excessive** and **medically important**.

All occurrences of medically significant overdose (suspected or confirmed and irrespective of whether it involved zavegepant/BHV-3500) must be communicated to Biohaven or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any treatments administered.

Asymptomatic dosing errors (e.g. accidentally taking two sprays from two devices instead of prescribed dose of one spray per calendar day) should be reported as deviations.

8.1.5 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 study subjects to contact the Investigator if they become pregnant during the course of the study. The investigator must immediately notify the Biohaven (or designee) Medical Monitor and CCI of the event and complete the Pregnancy Form in accordance with SAE reporting procedures as described in Section 8.1.3. 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 BHV3500-202**"), reported via phone to the CCI Safety Hotline at North America: 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.

8.1.6 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 8.1.3.

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

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

8.2 Adverse Events of Special Interest

Not applicable.

8.3 Non-serious Adverse Events

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

8.3.1 Collection and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the screening visit through the Follow up Safety Visit. Non-serious AE information is reported from the start of the observation phase to establish a baseline status for a subject.

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

8.3.2 Laboratory Test Abnormalities

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

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

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

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

9 STATISTICS

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

9.1 Sample Size

With a sample size of 600 treated subjects and no events observed, the upper bound of a one-sided 95% confidence interval for zero observations is 0.005. Hence this sample size is large enough to rule out an event adverse events that occur at rates greater than 5 cases per 1,000 subjects.

9.2 Analysis Sets

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

Safety: Subjects in the enrolled analysis who take study drug (zavegepant).

9.3 Statistical Methods

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

The frequencies of the following on-treatment safety events will be presented for the safety analysis set: AEs by intensity in ≥ 5% of subjects; SAEs; AEs by relationship to study drug; AEs related to study drug by intensity; AEs leading to study drug discontinuation; clinically relevant laboratory test abnormalities; LFT elevations based on fold change above ULN; and vital sign, physical measurement, and ECG abnormalities. Frequencies of safety events will be based on the number and percentage of subjects with events.

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). AEs will be presented by system organ class and preferred term. If a subject has an AE with different intensities over time, then only the greatest intensity will be reported.

Clinically significant laboratory test abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (2017), if available. Otherwise, if CTCAE grades are not available, then results will be graded according to numeric laboratory test criteria in Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 (2017). If a subject has a laboratory test abnormality with different toxicity grades over time, then only the highest toxicity grade will be reported.

9.4 Schedule of Analyses

This is an open-label, single-arm study designed to evaluate the safety and tolerability of zavegepant. As such, safety monitoring is the primary concern. During the course of the study, laboratory, safety, and exposure data will be monitoring on an on-going basis. Summaries of these data may be produced periodically for review by the sponsor and CRO. In addition, data may be locked, analyses conducted, and interim reports produced as required to support safety monitoring, administrative concerns, and regulatory requirements. A clinical study report will be produced to support regulatory requirements after the final database lock of the study.

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.

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 Clinical Trial Subject 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/ study drug is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount of study medication 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 – Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals Refer to study reference manual 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.

16.2 APPENDIX II – Strong CYP3A4 Inhibitors and Inducers (not all inclusive)

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

Strong CYP3A Inhibitors
Boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, nefazodone, nelfinavir

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

Strong CYP3A Inducers
Carbamazepine, phenytoin, rifampin, St. John's Wort

Resources:

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

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

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/

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2/3 Open-label, Long-Term, Safety Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine

Study No: BHV3500-202

Original Protocol Date: 03 Feb 2020

Protocol Version No: V02

Protocol Version Date: 10 Jul 2020

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

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

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

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

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