DRUG:	Zavegepant (BHV-3500)
STUDY NUMBER(S):	BHV3500-302
PROTOCOL TITLE:	A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Zavegepant in Migraine Prevention
IND NUMBER:	151,524
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	15-January-2021
VERSION NUMBER:	v 6.0
VERSION DATE:	16-May-2022

SUMMARY OF CHANGES

Version Number	Brief Description Summary of Changes	Date
Version 1.0 – Original	Not Applicable	15-January-2021
Version 2.0	Updated dosing to during the DBT Phase, subjects will be instructed to follow one of the following 2 dosing regimens: • Take four (4) 25 mg soft gelatin capsules of blinded study drug every calendar day, if randomized to the zavegepant 100 mg or placebo matching zavegepant 100 mg treatment group • Take eight (8) 25 mg soft gelatin capsules of blinded study drug every calendar day, if randomized to the zavegepant 200 mg or placebo matching zavegepant 200 mg treatment group. Updated subject screening numbers to 2900 and randomization to 1440. Updated study schematic. Removed MIDAS scale at the 4 and 8 Week Visits. Corrected inconsistencies, typographical errors throughout the protocol.	5-February-2021
Version 3.0	Switched the primary objective with a secondary objective. Added an exploratory objective. Updated LFTs to include CK at every visit. Corrected formatting in Exclusion criteria 6h-j. Changed the central laboratory. Corrected typographical errors and clarified wording throughout the document.	18-May-2021

	Revised the target population of the study to subjects with chronic migraine. Updated the introduction and study rationale to include background on chronic migraine. Updated the primary objective to reference chronic migraine. Revised the inclusion and exclusion criteria require subjects to have a history of chronic migraine prior to age 65. Revised the inclusion and exclusion criteria to require subjects to have at least 8 migraine days per month, at least 15 headache days per month, and at least 1 headache-free day per month, during the 3 months prior to the screening visit. Subjects must also have at least 15 headache days, at least 8 migraine days, and at least one headache-free day during the Observation Phase. Modified exclusion criterion to exclude subjects with chronic pain syndromes. Removed history of use of analgesics (e.g., NSAIDs or acetaminophen on > 15 days per month during the 3 months (12 weeks) prior to the Screening Visit from list of prohibited concomitant medications. History of use of analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) on ≥ 15 days per month during the 3 months (12 weeks) prior to the Screening Visit. Modified use of devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections) for headache to prohibit acute treatment or prophylaxis 2 months prior to screening and during the study through week 12/EOT. Removed verapamil as an allowed prophylactic migraine treatment as it is a P-gp inhibitor.	
Version 4.0	Changed schedule of HbA1c collection to	28-Jun-2021

	screening and EOT. Corrected typographical errors and added clarification where needed.	
Version 5.0	Added 52 week Open-Label Extension (OLE) phase to the protocol to allow subjects who completed the Double-blind Treatment (DBT) phase and have not entered the Follow-up phase to receive the same assigned zavegepant dose from the the DBT phase (either 100 mg or 200 mg) for up to 52 weeks in an OLE phase. All corresponding and relevant sections of the protocol were updated to reference this addition including the schedule of events and statistical sections. Reordered the 3 safety secondary objectives and endpoints to be last. Added 2 exploratory objectives. Corrected typographical errors and added clarification where needed.	16-Nov-2021
Version 6.0	Added exploratory PK objective. Corrected observation phase from screening or baseline. Revised inclusion and exclusion criteria for clarity around use of CGRP monoclonal antibodies. Added exclusion criterion 6l. Removed St John's Wort, as it is covered under CYP3A4 and P-gp inducers categories. Corrected typographical errors and added clarification where needed.	16-May-2022

BHV3500-302

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Zavegepant in Migraine Prevention

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to zavegepant (BHV-3500) are the confidential and proprietary information of Biohaven Pharmaceuticals, Inc.

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

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Biohaven Pharmaceuticals, Inc. or specified designees. I will discuss the material with them to ensure that they are fully informed about zavegepant (BHV-3500) and the study.

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

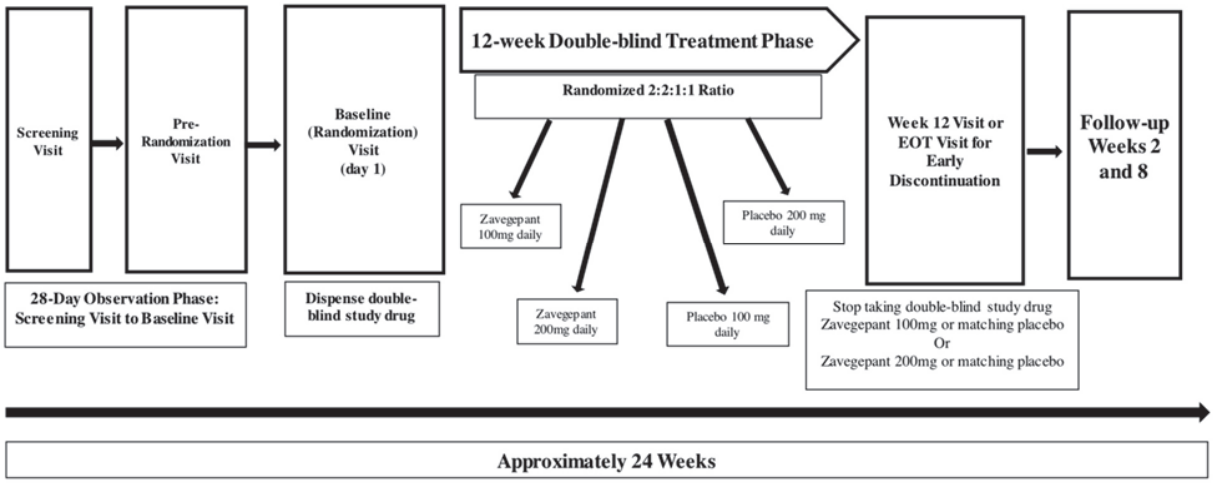
STUDY SUMMARY (SYNOPSIS)

Title:	BHV3500-302: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Zavegepant in Migraine Prevention
Rationale:	Intranasal zavegepant is being developed for the acute treatment of migraine. Effectiveness for the acute treatment of migraine was initially demonstrated in a Phase 2/3 dose-ranging study. In this study, subjects were treated with intranasal (IN) zavegepant 5 mg, 10 mg, 20 mg and placebo. In the 10 mg and 20 mg treatment groups, statistically significant efficacy versus placebo was demonstrated on both of the coprimary endpoints of freedom from pain and freedom from MBS at 2 hours postdose in the zavegepant 10 and 20 mg groups. Early studies with oral zavegepant, including a first-in-human oral formulation study, BHV3500-103, examined 50 mg single doses of a soft gelatin capsule (SGC), CCI [redacted]. All formulations have been found to be well tolerated and resulted in clinically relevant exposures. This study is being conducted to evaluate the efficacy, safety, and tolerability of oral zavegepant as a preventive treatment in subjects with chronic migraine.
Target Population:	This study will recruit male and female subjects, who are at least 18 years of age, and who have at least a one-year history of chronic migraine (with or without aura). The migraine diagnosis must be in accordance with the International Classification of Headache Disorders, 3rd edition. Per subject report, subjects must have migraine onset prior to age 50, history of chronic migraine onset prior to age 65, migraine attacks that last 4-72 hours (if not treated), and at least 15 headache days per month over the last 3 months before Screening, of which at least 8 are migraine days, and with at least one non-headache day per month during the last 3 months before Screening.
Number of Subjects:	Approximately 2900 subjects will be screened in order to randomize approximately 1440 subjects. It is estimated that approximately 1200 subjects will be entered into the OLE Phase.
Objectives (Primary):	To compare the efficacy of oral zavegepant to placebo as a preventive treatment for chronic migraine, as measured by the mean reduction from the Observation Phase in the number of migraine days per month over the entire DBT Phase. (In this study, a month is defined as 28 days or 4 weeks.)

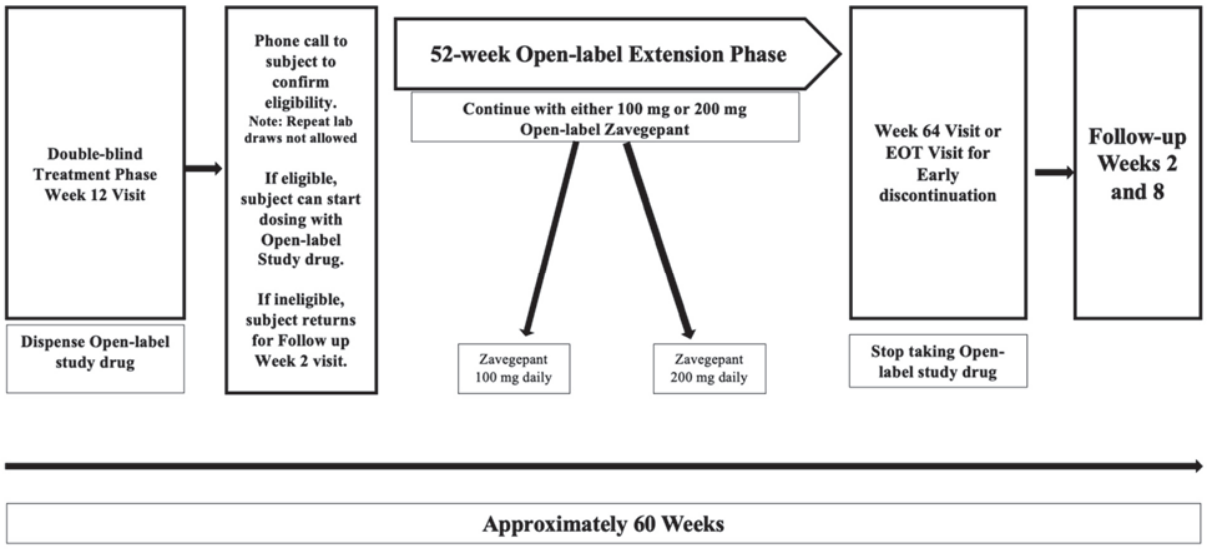
Study Design:	All subjects will participate in a 28-day Observation Phase. During the Observation Phase, subjects will treat migraines with standard of care migraine medications. Subjects will report migraine occurrence, migraine pain features and associated symptoms (e.g., pain intensity, nausea, photophobia and phonophobia), and will document use of acute migraine medication in an electronic diary (eDiary). Eligible subjects will be randomized 2:2:1:1 across 4 treatment groups in the DBT Phase: zavegepant 100 mg (n = 480); zavegepant 200 mg (n = 480); placebo matching zavegepant 100 mg (n = 240); or placebo matching zavegepant 200 mg (n = 240). Subjects will take the assigned study drug every day for 12 weeks. Subjects participating in PK draws will be required to dose in person at the study site to assess PK at the Week 4 and Week 8 Visits. Subjects will report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary during the DBT Phase. Upon completion of the DBT Phase, subjects may enter the 52-week OLE Phase and receive the assigned dose from the DBT Phase (either zavegepant 100 mg or 200 mg). If subjects do not enter the OLE Phase, they will have visits in the Follow-up Phase at approximately 2 weeks and 8 weeks after the last visit in the DBT Phase. Subjects who complete the OLE Phase or who discontinue early during the OLE Phase will also have visits in the Follow-up Phase at approximately 2 weeks and 8 weeks after the last visit in the OLE Phase. Subjects will also report concomitant medication, including standard of care migraine medication (both prophylactic and acute), taken throughout the entire study in the concomitant medication paper diary.

STUDY SCHEMATIC

Observation, DBT, and Follow-up Phases



OLE and Follow-up Phases



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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
bid	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant medication
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTSdatabase	Clinical Trial Subject Database
DAIDS	Division of AIDS
DBT	Double-blind Treatment
CCI	CCI
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eDiary	Electronic subject diary
GCP	Good Clinical Practice
GLMEM	Generalized linear mixed effect model
HR	Heart rate
ICF	Informed consent form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IN	Intranasal
INR	International normalized ratio
IRB	Institutional Review Board
iv	Intravenous
kg	Kilogram
L	Liter
MBS	Most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
mg	Milligram
min	Minute
mmHg	Millimeters mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
NO	Nitric oxide
ODT	Orally disintegrating tablet
OLE	Open-label Extension
PBO	Placebo
PK	Pharmacokinetic
P-gp	P-glycoprotein
po	By mouth, orally
qd	Once daily
SAE	Serious adverse event
SGC	Soft gelatin capsule
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It 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] Roughly one third (38%) of migraine sufferers have more than 4 attacks per month or have a migraine attack that is incapacitating,[2] and are candidates for preventive migraine therapy.

In the United States, as many as 38% of migraineurs of all types qualify for preventive therapy but fewer than 13% utilize such therapy. Similar and even lower utilization is noted in other countries that suffer comparable migraine burden.[2] Chronic migraine affects about 1-3% of the world's population, but the burden to these patients is high.[3] Both direct and indirect costs (healthcare, lost productivity, disability, related comorbidities) for the chronic migraine patient are often 3 to 4 times higher than those of the episodic migraine patient.[3,4] Reduction of migraine burden with preventative therapy for the patient with chronic migraine can be acheived by decreasing either attack frequency or level of impairment when migraines occur.[2] The role of CGRP in migraine has been well-documented,[5] and CGRP antagonists have been shown to be effective and well-tolerated acute treatment for migraine attacks as well as preventive treatment; including in patients with chronic migraine.[6] CGRP antagonists have been shown to be effective for acute and preventative treatments for migraine as well as for chronic migraine.[7] Increasing the number of preventive options for patients with chronic migraine will help reduce the personal and public health burden of this disease.

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

1.2 CGRP's Role in Migraine

CGRP receptor antagonists have been shown to be effective for both the acute and preventive treatment of migraine.[5,8,9] The efficacy of CGRP receptor antagonists against migraine is believed to be effected through the following mechanisms:

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

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

- **Inhibiting Pain Transmission:** Binding of CGRP receptor antagonists to CGRP receptors located on post-synaptic cells would inhibit the transmission of exaggerated pain signals in the brainstem.

1.3 Product Development Background

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

1.3.1 Clinical Experience

1.3.1.1 Single Ascending Dose (SAD) BHV3500-101

Administration of IN zavegepant in the Phase 1, double-blind, placebo-controlled 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 zavegepant or matching placebo as a single intranasal dose of 0.1 mg to 40 mg and completed the study. Dose escalation to the highest planned dose of 40 mg was completed and no dose limiting toxicity was observed. A Maximum Tolerated Dose (MTD) was not identified. Intranasal 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[1,10].

Additional details can be found in the Investigator's Brochure.

1.3.1.2 Multiple Ascending Dose Study (MAD) BHV3500-102

The Phase 1, multiple ascending dose (MAD) study evaluating the safety, tolerability, and PK of zavegepant following IN administration of MADs (placebo, 5 mg, 10 mg, or 20 mg) in normal healthy subjects has concluded. In this study, a total of 36 healthy subjects (3 cohorts) were administered multiple ascending doses of IN zavegepant (planned doses of 5 mg, 10 mg or

20mg; N = 12 per treatment group [3:1 zavegepant:PBO]) with the first 3 cohorts receiving a once daily dose for 14 days. Cohort 4 received two sequential 20 mg zavegepant doses (n=9) or placebo (n=3) separated by 2 hours (40 mg total daily) for 8 consecutive days. Two additional alternate dosing cohorts received 2 repeated IN administrations of zavegepant 20 mg or placebo on a single day. Safety data from BHV3500-102 indicated that zavegepant was well tolerated at all dose levels and a maximum tolerated dose was not identified. No deaths or serious adverse events (SAEs) were reported in this study. Additional details can be found in the Investigator's brochure.

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

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

No deaths were reported in the study. SAEs were reported in 2 subjects on-treatment including: thrombosis reported in 1 subject from the 10 mg group; and vestibular migraine reported in 1 subject in the placebo group. Both events were moderate in intensity and judged by the investigator as not related to study therapy. The SAE of thrombosis was reported 13 days after the single dose of zavegepant as post trauma from an automobile accident. Additional details can be found in the Investigator's Brochure.

1.3.1.4 BHV3500-103

This was a Phase 1 single dose of 50 mg in 3 different oral formulations of zavegepant in healthy subjects to evaluate the safety and tolerability and characterize the PK. Additional details can be found in the Investigator's Brochure.

1.3.1.5 BHV3500-107

This is a recently concluded Phase 1, placebo-controlled, multiple ascending dose (MAD) study that evaluated the safety, tolerability, and PK of single and multiple ascending doses of oral zavegepant using 50 mg to 300 mg for up to 14 days. Preliminary blinded data from the BHV3500-107 trial has shown to date that multiple dose administrations of 50 mg, 100 mg, 200 mg or 300 mg daily for 14 days have been well tolerated. No deaths or SAEs were reported in the study. Thus far, the adverse events (AEs) reported have been predominantly mild in intensity, and there have been no clinically significant findings on ECG, lab assessments or vital signs.

1.3.2 Summary of Animal Data with Oral and Sublingual Zavegepant

Oral (capsule) administration of 50 mg zavegepant to dogs for 14 days was well tolerated with no effects on clinical or physical examination findings, body weights, food consumption, ophthalmic and electrocardiograph (ECG) assessments, clinical pathology parameters

(hematology, clinical chemistry, coagulation, and urinalysis), organ weights, or macroscopic findings.

Summary of animal safety and PK data with oral and sublingual formulations can be found in the Investigator's brochure.[10]

1.4 Study Rationale

Biohaven Pharmaceuticals is developing a new oral soft gelatin capsule (SGC) of zavegepant (BHV-3500) as a preventive treatment in subjects with chronic migraine.

The goal of this study is to assess the efficacy and safety of daily (qd) dosing of zavegepant.

This study is being conducted to evaluate the efficacy, safety, and tolerability of zavegepant for the preventive treatment of chronic migraine. It will also further define the safety profile of zavegepant administration for as long as 64 weeks (12 weeks of double-blind and 52 weeks of open-label). Approximately 1440 subjects will dose with double-blind study drug every day for a period of approximately 12 weeks. Randomization will be stratified by stable prophylactic migraine medication use through randomization (yes or no; see Section 7.2.1). Subjects who complete the 12-week DBT Phase may continue to the 52-week OLE Phase. In the OLE Phase, subjects will continue to take the dosing regimen they were randomized to during the DBT Phase (i.e., zavegepant 100 mg or 200 mg daily).

1.4.1 Study Design Rationale

This is a 12-week multicenter, randomized, double-blind, placebo-controlled evaluation of the efficacy and safety of zavegepant tablet taken every day for the prevention of migraine in subjects with a history of chronic migraine. Eligible subjects who complete the 12-week DBT Phase may continue to the 52-week OLE Phase.

Approximately 1440 subjects will be randomized and assigned treatment in the DBT Phase. Subjects will be randomized in a 2:2:1:1 ratio across 4 treatment groups: zavegepant 100 mg (n = 480); zavegepant 200 mg (n = 480); placebo matching zavegepant 100 mg (n = 240); or placebo matching zavegepant 200 mg (n = 240). Randomization will be stratified by use of stable prophylactic migraine medication through randomization (yes or no; see Section 7.2). Upon completion of the 12-week DBT Phase, eligible subjects may continue to the 52-week OLE Phase. In the OLE Phase, subjects will continue to take the dosing regimen they were randomized to during the DBT Phase (i.e., zavegepant 100 mg or 200 mg daily).

During the DBT Phase, subjects will be instructed to follow one of the following 2 dosing regimens:

- Take four (4) 25 mg soft gelatin capsules of blinded study drug every calendar day, if randomized to the zavegepant 100 mg or placebo matching zavegepant 100 mg treatment group

- Take eight (8) 25 mg soft gelatin capsules of blinded study drug every calendar day, if randomized to the zavegepant 200 mg or placebo matching zavegepant 200 mg treatment group.

If subjects have a migraine, they may treat the migraine with permitted acute migraine medication (see Section 5.5.2) and continue to take study drug on their regular schedule.

Subjects who enter the OLE Phase will continue to take the dosing regimen they were randomized to during the DBT Phase (i.e., 100 mg zavegepant daily or 200 mg zavegepant daily).

1.4.2 Dose Selection Rationale

The oral soft gelatin formulation of zavegepant was selected based on safety and PK data from the single dose BHV3500-103 study and the multiple dose study, BHV3500-107. The preliminary exposures at steady state from the soft gelatin 100 mg oral dose (4 x 25 mg capsules) administered QD are a geometric mean (GM) C_{max} of 9.0 ng/mL and AUC of 36.6 ng*hr/mL, similar to slightly higher than the AUC, and 30% lower than the C_{max} following 10 mg QD by the IN route; 10 mg is the IN dose progressed into pivotal studies in treatment of acute migraine headache.

Preliminary results from the soft gelatin 200 mg oral dose (8 x 25 mg capsules) administered QD produced a GM C_{max} of 23.6 ng/mL and AUC of 91.2 ng*hr/mL, 1.8- and 2.8-fold higher in C_{max} and AUC, respectively, than that produced by the 10 mg IN dose. Relative to the multiple-dose PK from the highest dose studied in Phase 2/3 acute migraine treatment study BHV3500-201, 20 mg IN, the 200 mg oral soft gelatin dose yielded a C_{max} that was 42% lower, and a comparable AUC.

1.4.3 Other Rationale Related to the Compound / Study

Not applicable.

1.4.4 Research Hypothesis

Zavegepant 100 mg or zavegepant 200 mg soft gelatin capsule (SGC) oral dose taken daily is safe and effective for the prevention of migraine.

2 STUDY OBJECTIVES

A month is defined as 4 weeks (28 days) for the purpose of this protocol.

2.1 Primary Objective(s)

To compare the efficacy of zavegepant to placebo as a preventive treatment for chronic migraine, as measured by the mean reduction from the Observation Phase in the number of migraine days per month over the entire DBT Phase.

2.2 Secondary Objective(s)

1. To compare the efficacy of zavegepant to placebo on the proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire DBT Phase.

2. To compare the efficacy of zavegepant to placebo on the mean reduction from the Observation Phase in the number of migraine days per month in the last 4 weeks of the DBT Phase.

3. To compare the efficacy of zavegepant to placebo on the mean reduction from the Observation Phase in the number of migraine days per month in the first 4 weeks of the DBT Phase.

4. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine-specific medication days per month over the entire DBT Phase.

5. To compare the mean change from baseline in the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ) restrictive role function domain score at Week 12 of the DBT Phase between zavegepant and placebo.

6. To compare the mean change from baseline in the Migraine Disability Assessment (MIDAS) total score at Week 12 of the DBT Phase between zavegepant and placebo.

7. To evaluate the safety and tolerability of zavegepant during the DBT and OLE Phases.

8. To evaluate the frequency of ALT or AST > 3x upper limit of normal (ULN) concurrent with total bilirubin > 2x ULN in subjects treated with zavegepant during the DBT and OLE Phases.

9. To evaluate the frequencies of hepatic-related adverse events and hepatic-related adverse events leading to study drug discontinuation in subjects treated with zavegepant during the DBT and OLE Phases.

2.3 Exploratory Objective(s)

1. To compare the efficacy of zavegepant to placebo on the mean reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.

2. To compare the efficacy of zavegepant to placebo on the proportions of subjects with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from the Observation Phase in the number of migraine days per month and number of headache days per month by pain intensity (total; moderate or severe) in each month and over the entire DBT Phase.

3. To compare the efficacy of zavegepant to placebo on the mean reduction from the Observation Phase in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.

4. To compare the efficacy of zavegepant to placebo on the proportions of subjects with ≥ 50% reduction from the Observation Phase in the number of migraine days per week and number of headache days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.

5. To compare the efficacy of zavegepant to placebo on the proportions of subjects with a migraine day and headache day by pain intensity (total; moderate or severe) on each day of the first week of the DBT Phase.

6. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine-specific medication days per month in each month and over the entire DBT Phase.

7. To compare the efficacy of zavegepant to placebo on the mean number of acute migraine medication days per month in each month and over the entire DBT Phase.

8. To evaluate the frequency of liver function test (LFT) elevations (AST, ALT, or total bilirubin) based on fold changes above ULN in subjects treated with zavegepant during the DBT and OLE Phases.

9. To evaluate the frequency of ALT or AST > 3x ULN in temporal association with nausea, vomiting, anorexia, abdominal pain or fatigue in subjects treated with zavegepant during the DBT and OLE Phases.

10. To compare the mean changes from baseline in the MSQ preventive role function and emotional function domain scores at Week 12 of the DBT Phase between zavegepant and placebo.

11. To compare the mean changes from baseline in the MIDAS absenteeism and presenteeism scores at Week 12 of the DBT Phase between zavegepant and placebo.

12. To evaluate the mean changes from baseline in MSQ domain scores and MIDAS scores during the OLE Phase.

13. To evaluate the Preference of Medication (PoM) scale during the DBT and OLE Phases.

14. To evaluate the Satisfaction with Medication (SM) scale during the DBT and OLE Phases.

15. To evaluate the Clinical Global Impression – change (CGI-c) scale during the DBT and OLE Phases.

16. To evaluate the pharmacokinetics of zavegepant 100 mg and 200 mg.

3 STUDY ENDPOINTS

Migraine days per month and acute migraine-specific medication days per month are derived from eDiary data.

Adverse events (AEs) are determined from case report forms (CRFs).

MSQ domain scores and MIDAS total score are derived from CRFs.

Grade 3 to 4 laboratory test abnormalities are determined from laboratory test values graded using standardized criteria. Laboratory tests are identified from CRFs and central laboratory data.

3.1 Primary Endpoint(s)

Mean change from the Observation Phase in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).

3.2 Secondary Endpoint(s)

1. Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate to severe migraine days per month over the entire DBT Phase (Weeks 1 to 12).

2. Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.

3. Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase.

4. Mean number of acute migraine-specific medication days per month over the entire DBT Phase (Weeks 1 to 12). Acute migraine-specific medications are triptans and ergotamine (see Section 3.3).

5. Mean change from baseline in the MSQ restrictive role function domain score at Week 12 of the DBT Phase.

6. Mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase.

7. Number and percentage of subjects with AEs by intensity, SAEs, AEs leading to study drug discontinuation, and grade 3 to 4 laboratory test abnormalities during the DBT and OLE Phases.

8. Number and percentage of subjects with AST or ALT elevations > 3x ULN concurrent (i.e., on the same laboratory collection date) with total bilirubin > 2x ULN during the DBT and OLE Phases.

9. Number and percentage of subjects with hepatic-related AEs by intensity, and hepatic-related AEs leading to study drug discontinuation during the DBT and OLE Phases.

3.3 Definition of Migraine Days

A Migraine Day is defined as any calendar day which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting at least one of the following criteria (A and/or B):

A. ≥ 2 of the following pain features:

   a. Unilateral location,
   b. Pulsating quality (throbbing),
   c. Moderate or severe pain intensity,
   d. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

B. ≥ 1 of the following associated symptoms:

   a. Nausea and/or vomiting
   b. Photophobia and phonophobia

During the DBT Phase, if the subject takes an acute migraine-specific medication (~~i.e.,~~ e.g., triptan or ergotamine) during aura or to treat a headache, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

For the full definition of Migraine Days, please refer to Section 17.3 Appendix #3.

3.4 Definition of Headache Days

A Headache Day is any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- A qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- A qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- A headache of any duration for which acute headache treatment is administered (see Section 5.5.2).
- For the full definition of Headache Days, please refer to Section 17.3 Appendix #3.

4 STUDY PLAN

4.1 Study Design and Duration

This is a multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of zavegepant in migraine prevention with a 52-week OLE Phase.

The 28-day (+3 days) Observation Phase includes a Screening Visit and a Pre-randomization Laboratory Visit. Note that the +3 days should only be used for scheduling in cases of holidays or weekends. For subjects to be eligible for the study, they must have a one-year history of chronic migraine according to International Classification of Headache Disorders, 3rd Edition,[11] as well as a history of one headache-free day per month during the last 3 months before Screening. Additionally, the subjects must have at least 15 headache days, at least 8 migraine days, and at least 1 headache-free day during 28 days in the Observation Phase which will be documented in the eDiary.

Upon the completion of the Screening Visit, subjects will be provided an electronic diary (eDiary) to document the following on each day of the Observation Phase: migraine occurrence; migraine pain features and associated symptoms (see Section 3.3); and use of acute migraine medication (e.g., triptans; see Section 5.5.2). In addition, subjects will record all concomitant medications, including standard of care migraine medications (both prophylactic and acute), taken in the concomitant medication paper diary (see Sections 5.5.1 and 5.5.2). After completing the Observation Phase, the subject will return to the clinic with the eDiary and concomitant medication paper diary for the Baseline (Randomization) Visit.

Subjects will have blood drawn for baseline laboratory profiles at the Pre-randomization Laboratory Visit; this visit must occur within 96 hours (4 days +2 days) of the Baseline Visit. Note that the +2 days should only be used for scheduling in cases of holidays or weekends. Subjects will then return for the Baseline Visit but cannot be randomized until the pre-randomization laboratory results are reviewed and determined to meet eligibility.

At the Baseline Visit, eligibility for continued participation in the study will be assessed before randomization occurs and study drug will be dispensed. Subjects will be instructed that they must take 4 or 8 soft gelatin capsules (SGC) of blinded study drug every calendar day. If subjects have a migraine during the DBT Phase, they may, if needed, treat the migraine with their standard of care medication and must continue to take study drug.

During the DBT Phase, subjects will record their migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication on each day in the eDiary. Subjects will also use the eDiary only during the DBT Phase to complete the Preference of Medication (PoM) questionnaire and the Satisfaction with Medication (SM) questionnaire.

Subjects will also record all concomitant medications, including standard of care migraine medications (both prophylactic and acute), taken during the DBT, OLE, and Follow-up Phases in the concomitant medication paper diary.

At select study visits, subjects will complete or will be administered the Migraine-Specific Quality-of-Life Questionnaire v 2.1 (MSQ v 2.1), the Migraine Disability Assessment (MIDAS), Clinical Global Impression – change (CGI-c) scale, PoM (OLE Phase only), SM (OLE Phase only), and the Columbia-Suicide Severity Rating Scale (C-SSRS) on paper forms.

At the DBT Week 4 and Week 8 Visits, subjects participating in PK draws will be required to dose in person at the study site to assess PK (predose and at least 1 hour after dose; exact time of PK collection relative to the dose will be documented). Additional assessments and visit schedule are outlined in Table 1. Procedures include study personnel review of the eDiary data and concomitant medication paper diary data with the subject, assessment of study drug compliance, and monitoring of tolerability and safety (including collection of adverse events, physical exam, vital signs, laboratory tests, and electrocardiography).

During the Observation Phase, study visits will occur at Screening (Enrollment) and Pre-randomization Laboratory.

During the DBT Phase, study visits will occur at Baseline, Week 2, Week 4, Week 8, and Week 12. Subjects who are not eligible to enter the OLE Phase should continue to the Follow-up Phase.

Upon completion of the 12-week DBT Phase, eligible subjects may continue the same dosing regimen (zavegepant 100 mg or 200 mg daily) in the OLE Phase for up to 52 weeks (64 total weeks between DBT Phase and OLE Phase). During the OLE Phase, study visits will occur at Week 14, Week 16, and every 4 weeks thereafter until Week 64. If subjects have a migraine during the OLE Phase, they may, if needed, treat the migraine with their standard of care medication and must continue to take study drug.

During the Follow-up Phase, study visits will occur at Follow-up Week 2 and Follow-up Week 8 for assessment of AEs and laboratory assessments. All randomized subjects should complete the Follow-up Week 2 and Follow-up Week 8 Visits, regardless of completing either treatment phase.

To closely monitor for potential drug induced liver injury, guidance on reporting potential drug-induced liver injury (DILI) events is provided in the protocol. Lab results that meet predefined LFT abnormality criteria as DILI should be reported as an SAE. See Section 8.4, Potential Drug Induced Liver Injury (DILI).

4.2 Study Schematic

Figure 1: Study Schematic: Observation, DBT, and Follow-up Phases

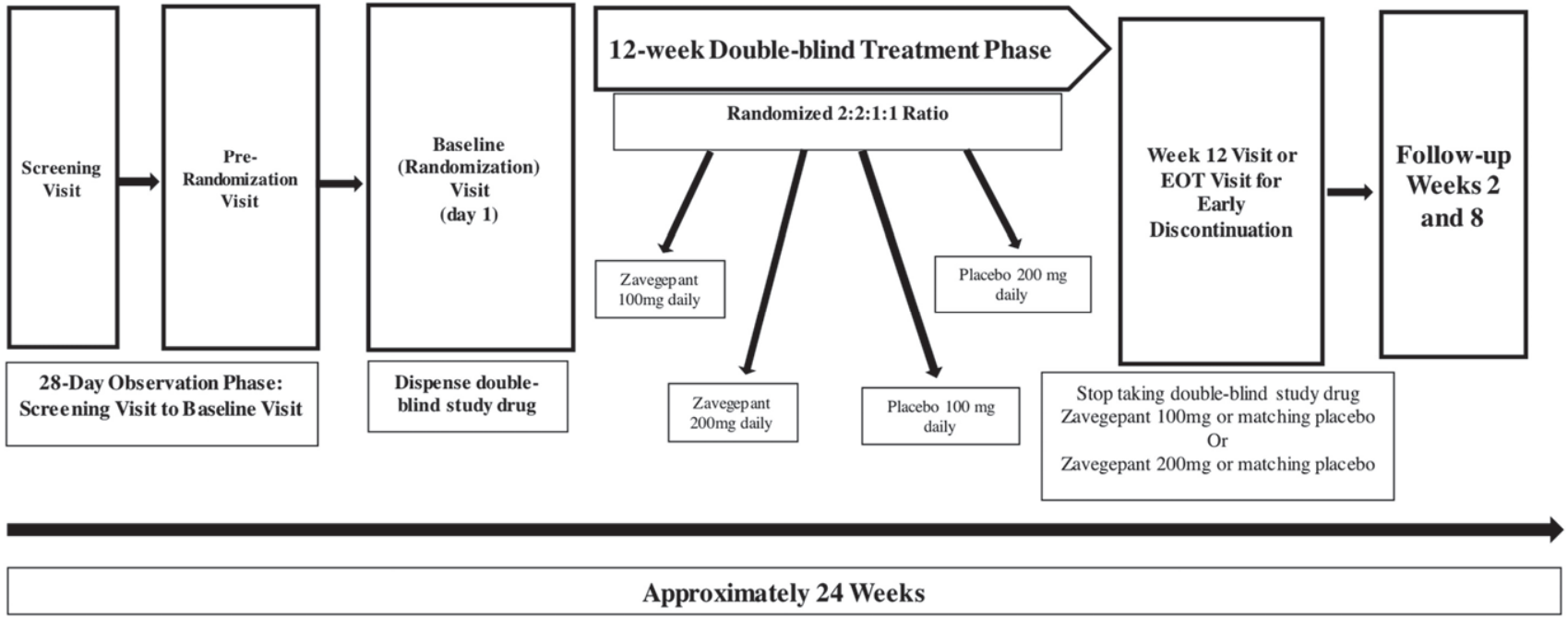
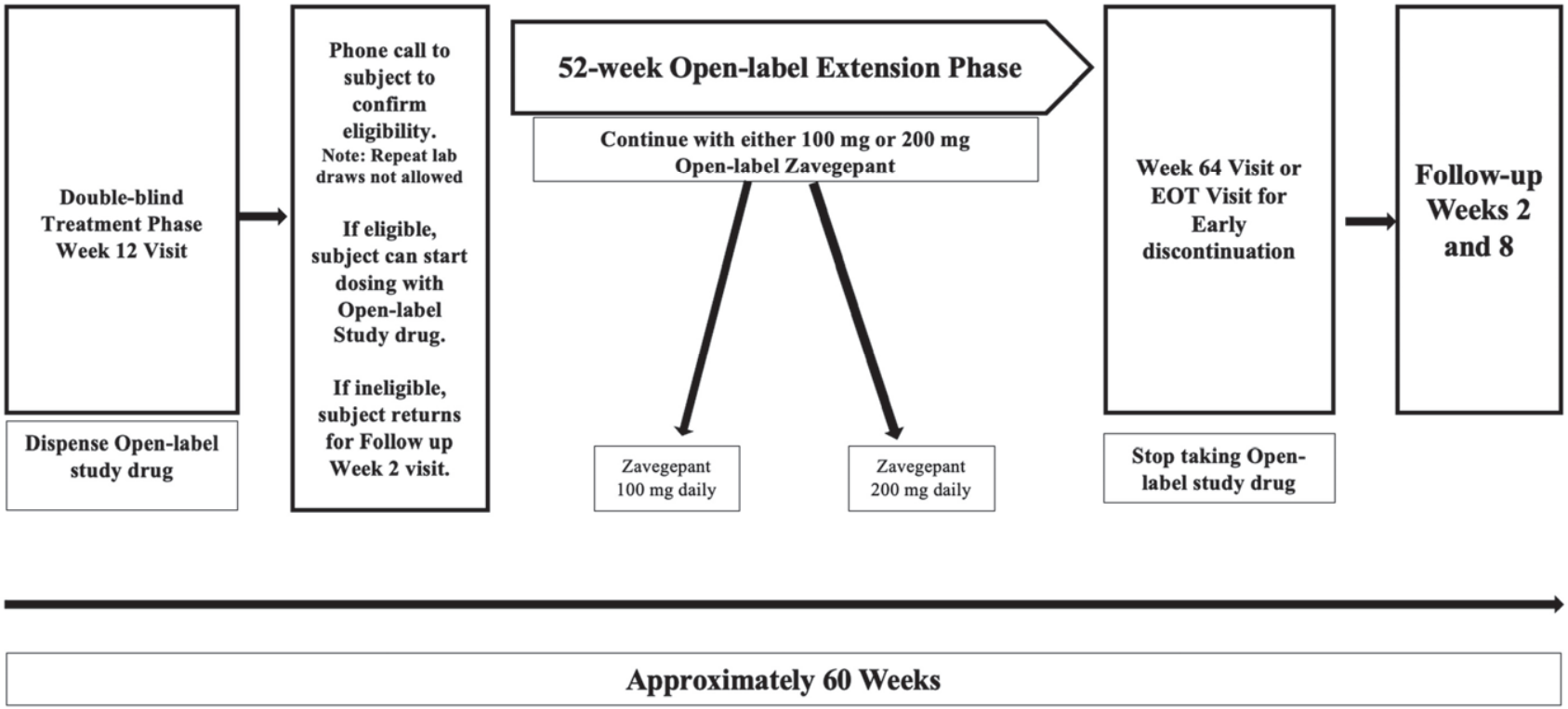


Figure 2: Study Schematic: OLE and Follow-up Phases



4.3 Schedule of Assessments

Table 1: DBT Phase Schedule of Assessments

	Observation Phase (28 days, +3 days)		**DBT Phase (12 weeks)[1,2]**				**Follow-up Phase**
Procedure	**Screening Visit**	**Pre-randomization Laboratory Visit:[3]** must occur within 96 hours before Baseline (Randomization) Visit[4]	**Baseline (Randomization) Visit[5] (Day 1 of DBT Phase)**	**Week 2 Visit (Day 15 +/- 2 days)**	**Week 4 Visit (Day 29), Week 8 Visit (Day 57)** **(both visits +/- 2 days)**	**Week 12 (Day 86 + 3 days) or EOT Visit for early discontinuation**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[6]**
Informed Consent	X						
Duplicate subject check (in CTSdatabase)	X						
Inclusion/ Exclusion Criteria	X	X	X				
Medical History	X						

[1] Subjects who do not complete the DBT Phase should complete the EOT, Follow-up Week 2, and Follow-up Week 8 Visits.
[2] While on-study, all visit windows are used for scheduling purposes and all efforts should be made to return subjects to the 28-day schedule if scheduling changes are made at any previous visit(s).
[3] If the laboratory results are not acceptable per protocol, the subject is determined to be a screen failure and must return to the study site to return the eDiary. Repeat testing of liver function test (LFT) abnormalities will **not** be permitted at this visit.
[4] The duration between the Pre-randomization Laboratory Visit and the Baseline Visit is 4 days. The "+2" days window is included ***for scheduling purposes only***. Every effort should be made to collect the Pre-randomization Laboratory Visit samples as close to, and within, the 4 days prior to the Baseline Visit as possible. However, for scheduling convenience, this window may be up to 6 days between the Pre-randomization Laboratory Visit and the Baseline Visit.
[5] Subjects should take their first dose of study drug the day after the Baseline Visit to ensure the subject is fasting appropriately (dose 4 hours after a meal and 1 hour before a meal). Review section 4.3 where phases and visits are described.
[6] Follow-up visits are based off the DBT Week 12/EOT Visit, for subjects who do not enter the OLE Phase.

	Observation Phase (28 days, +3 days)		**DBT Phase (12 weeks)[1,2]**				**Follow-up Phase**
Procedure	**Screening Visit**	**Pre-randomization Laboratory Visit:[3]** must occur within 96 hours before Baseline (Randomization) Visit[4]	**Baseline (Randomization) Visit[5] (Day 1 of DBT Phase)**	**Week 2 Visit (Day 15 +/- 2 days)**	**Week 4 Visit (Day 29), Week 8 Visit (Day 57) (both visits +/- 2 days)**	**Week 12 (Day 86 + 3 days) or EOT Visit for early discontinuation**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit (both visits +/- 2 days)[6]**
Migraine History (signs/symptoms/prior treatment/frequency/intensity/MBS)	X						
Concomitant medication paper diary[7]	X	X	X	X	X	X	X
Randomize subject in IWRS			X[8]				
Physical Examination[9]	X		X		X	X	X
Vital Signs / Physical Measurements	X	X	X		X	X	X
PK Sample Collection [10]					X		

[7] Concomitant medications, including standard of care migraine medications (both prophylactic and acute), taken throughout the study should be recorded by subjects in the concomitant medication paper diary and reviewed by study personnel at each visit.
[8] The actual Baseline Visit date should be used for IWRS enrollment date and eligibility date.
[9] Height measured at Screening Visit only. Weight, body temperature, respiratory rate, blood pressure, and heart rate will be collected at all timepoints where indicated. Sitting arterial systolic and diastolic blood pressure and radial artery pulse rate will be measured. Recommend that subjects sit at rest for 5-10 minutes prior to measurement of blood pressure and pulse. Full physical exam required at the screening, Week 12/EOT, and Follow-up Week 2 visits. Targeted physical exam of heart, lungs, and abdomen; plus other systems based on signs and symptoms is required at the Baseline, Week 4, Week 8, and Follow-up Week 8 visits.
[10] PK will be collected only at the DBT Week 4 and Week 8 Visits. Subjects will be instructed to not take study drug until they are at the study site. Subjects will have PK drawn predose and at least 1 hour postdose; exact time of PK collection relative to the dose will be documented. Subjects should fast for duration of PK assessments.

	Observation Phase (28 days, +3 days)		**DBT Phase (12 weeks)[1,2]**				**Follow-up Phase**
Procedure	**Screening Visit**	**Pre-randomization Laboratory Visit:[3]** must occur within 96 hours before Baseline (Randomization) Visit[4]	**Baseline (Randomization) Visit[5] (Day 1 of DBT Phase)**	**Week 2 Visit (Day 15 +/- 2 days)**	**Week 4 Visit (Day 29), Week 8 Visit (Day 57) (both visits +/- 2 days)**	**Week 12 (Day 86 + 3 days) or EOT Visit for early discontinuation**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit (both visits +/- 2 days)[6]**
Clinical Safety Laboratory Testing	X	X			X (Week 4 only)	X	
Liver Function Tests	X	X[11]		X	X	X	X
HbA1c	X					X	
Lipid Panel	X					X	
ECG	X				X (Week 4 only)	X	
Urinalysis	X					X	
Urine Drug Screen for drugs of abuse	X						
FSH, if applicable, to determine WOCBP status	X						
Pregnancy Test	X (serum)	X (serum)	X (urine)		X (urine)	X (urine)	X (urine – FU week 2, serum – FU week 8)

[11] Repeat testing of liver function test (LFT) abnormalities will not be permitted at this visit.

	Observation Phase (28 days, +3 days)		**DBT Phase (12 weeks)[1,2]**				**Follow-up Phase**
Procedure	**Screening Visit**	**Pre-randomization Laboratory Visit:[3]** must occur within 96 hours before Baseline (Randomization) Visit[4]	**Baseline (Randomization) Visit[5] (Day 1 of DBT Phase)**	**Week 2 Visit (Day 15 +/- 2 days)**	**Week 4 Visit (Day 29), Week 8 Visit (Day 57) (both visits +/- 2 days)**	**Week 12 (Day 86 + 3 days) or EOT Visit for early discontinuation**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit (both visits +/- 2 days)[6]**
AE, SAE and Concomitant Procedure assessment[12]	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale	X		X	X	X	X	X
Dispense Study Drug[13]			X	X	X		
Administer Study Drug[14]				X	X		
Dispense Electronic Diary (eDiary)	X						
Return used and unused study drug to site for compliance check[15]				X	X	X	

[12] SAEs, AEs, and Concomitant Procedures must be reported after subject signs informed consent. SAEs should be reported from signing of consent through the Follow-up Week 8 Visit. Non-serious AEs should be reported from signing of consent through the Follow-up Week 2 Visit.
[13] Subjects randomized to zavegepant 100 mg or matching placebo will be assigned 2 wallets at the Baseline Visit and Week 2 Visit. These subjects will then be assigned 4 wallets at Week 4 and Week 8 Visits. Subjects randomized to zavegepant 200 mg or matching placebo will be assigned 4 wallets at the Baseline Visit and Week 2 Visit. These subjects will then be assigned 8 wallets at Week 4 and Week 8 Visits.
[14]Subjects must take their study drug every day, regardless of whether they have a migraine. Doses are not required to be taken in the office on days of a study visit (with the exception of PK visits), however dosing requirements and compliance should be discussed with subjects at all visits. **Zavegepant oral soft gel capsules should be taken fasting, at least 1 hour before breakfast/first meal of the day (and at least 4 hours after the previous meal).**
[15] The Observation Phase to determine eligibility is 28 days +3 days**.** The "+3" days window is included for scheduling purposes only. Subjects in the DBT Phase who demonstrate poor compliance will be discussed with the Sponsor and corrective training will be completed by the site with the subject.

	Observation Phase (28 days, +3 days)		**DBT Phase (12 weeks)[1,2]**				**Follow-up Phase**
Procedure	**Screening Visit**	**Pre-randomization Laboratory Visit:[3]** must occur within 96 hours before Baseline (Randomization) Visit[4]	**Baseline (Randomization) Visit[5] (Day 1 of DBT Phase)**	**Week 2 Visit (Day 15 +/- 2 days)**	**Week 4 Visit (Day 29), Week 8 Visit (Day 57)** **(both visits +/- 2 days)**	**Week 12 (Day 86 + 3 days) or EOT Visit for early discontinuation**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[6]**
eDiary reviewed for completeness / returned		X	X	X	X	X	
Daily Report of migraine occurrence, migraine pain feature and associated symptoms, and use reported by subject in eDiary[16]	X	X	X	X	X	X	
Migraine-Specific Quality of Life Questionnaire (MSQ) v 2.1			X			X	
Preference of Medication (PoM) reported by subject in eDiary						X	
Satisfaction with Medication (SM) reported by subject in eDiary						X	
Satisfaction with Medication/ Clinical Global Impression Change (CGI-c)						X	
Migraine Disability Assessment (MIDAS)			X			X	

[16] The eDiary will be dispensed at the Screening Visit, after all screening procedures are completed. The subject will use the eDiary every day during the Observation Phase and DBT Phase to report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication.

Table 2: OLE Phase Schedule of Assessments

	OLE Phase (up to 52 Weeks)				Follow-up Phase
Procedure	**Phone call with subject to confirm eligibility for OLE[17]**	**Week 14 Visit (Day 99 +/- 2 days)**	**Week 16 (Day 113) Visit, Week 20 (Day 141) Visit, and every 4 weeks until Week 60 (Day 421)** **(all visits +/- 2 days)**	**Week 64 (Day 449 +/- 2 days) or EOT Visit for early discontinution**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[22]**
Inclusion/ Exclusion Criteria	X				
Concomitant medication paper diary[18]		X	X	X	X
Physical Examination		X[19]	X[19]	X[19]	X[19]
Vital Signs / Physical Measurements		X	X	X	X
Clinical Safety Laboratory Testing			X (Weeks 16, 24, and 48 only)	X	

[17] Subject eligibility for the OLE Phase will be assessed based on the DBT Week 12 laboratory results (repeats not permitted) prior to taking the first dose of open-label study drug, which is dispensed at the DBT Week 12 Visit. Once the DBT Week 12 laboratory results are received and eligibility is confirmed, the subject should be contacted by telephone and instructed to start taking open-label study drug. Subjects who (1) discontinue early from the DBT Phase or (2) have already entered the Follow-up Phase are not eligible to enter the OLE Phase. If the subject is not eligible, subject must be instructed to not take study drug and return to site for the Follow-up Week 2 Visit with unused study drug.

[18] Concomitant medications, including standard of care migraine medications (both prophylactic and acute), taken throughout the study should be recorded by subjects in the concomitant medication paper diary and reviewed by study personnel at each visit.

[19] Full physical exam required at Week 14, Week 64/EOT, and Follow-up Week 2. Targeted physical exam of heart, lungs, and abdomen; plus other systems based on signs and symptoms at Weeks 16, 20 and every 4 weeks until Week 60, and at Follow-up Week 8.

	OLE Phase (up to 52 Weeks)				**Follow-up Phase**
Procedure	**Phone call with subject to confirm eligibility for OLE[17]**	**Week 14 Visit (Day 99 +/- 2 days)**	**Week 16 (Day 113) Visit, Week 20 (Day 141) Visit, and every 4 weeks until Week 60 (Day 421)** **(all visits +/- 2 days)**	**Week 64 (Day 449 +/- 2 days) or EOT Visit for early discontinution**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[22]**
Liver Function Tests		X	X	X	X
HbA1c				X	
Lipid Panel				X	
ECG			X (Weeks 16, 24 and 48 only)	X	
Urinalysis				X	
Pregnancy Test			X (urine)	X (urine)	X (urine – FU Week 2, serum – FU Week 8)
AE, SAE and Concomitant Procedure assessment		X	X	X	X
Columbia-Suicide Severity Rating Scale		X	X	X	X

	OLE Phase (up to 52 Weeks)				Follow-up Phase
Procedure	**Phone call with subject to confirm eligibility for OLE[17]**	**Week 14 Visit (Day 99 +/- 2 days)**	**Week 16 (Day 113) Visit, Week 20 (Day 141) Visit, and every 4 weeks until Week 60 (Day 421)** **(all visits +/- 2 days)**	**Week 64 (Day 449 +/- 2 days) or EOT Visit for early discontinution**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[22]**
Dispense Study Drug[20]	X	X	X		
Administer Study Drug[21]	X[17]	X	X		
Return used and unused study drug to site for compliance check		X	X	X	
Migraine-Specific Quality of Life Questionnaire (MSQ) v 2.1			X (Week 24 only)	X	
Preference of Medication (PoM) reported by subject on paper				X	
Satisfaction with Medication (SM) reported by subject on paper				X	

[20] Subjects randomized to zavegepant 100 mg or matching placebo in the DBT Phase will receive open-label zavegepant 100 mg in the OLE Phase. Subjects randomized to zavegepant 200 mg or matching placebo in the DBT Phase will receive open-label zavegepant 200 mg in the OLE Phase. Subjects will be assigned sufficient study drug to last until the next dispensing visit.

[21] Subjects must take their study drug every day, regardless of whether they have a migraine. Doses are not required to be taken in the office on days of a study visit, however dosing requirements and compliance should be discussed with subjects at all visits. **Zavegepant oral soft gel capsules should be taken fasting, at least 1 hour before breakfast/first meal of the day (and at least 4 hours after the previous meal).**

[22] Follow-up visits are based off the Week 64/EOT Visit, for subjects who enter the OLE Phase.

	OLE Phase (up to 52 Weeks)				Follow-up Phase
Procedure	**Phone call with subject to confirm eligibility for OLE[17]**	**Week 14 Visit (Day 99 +/- 2 days)**	**Week 16 (Day 113) Visit, Week 20 (Day 141) Visit, and every 4 weeks until Week 60 (Day 421)** **(all visits +/- 2 days)**	**Week 64 (Day 449 +/- 2 days) or EOT Visit for early discontinution**	**Follow-up Week 2 Visit, Follow-up Week 8 Visit** **(both visits +/- 2 days)[22]**
Satisfaction with Medication/ Clinical Global Impression Change (CGI-c)				X	
Migraine Disability Assessment (MIDAS)			X (Week 24 only)	X	

4.3.1 Observation Phase

The Observation Phase will be 28 days + 3 days. Note that the "+ 3 days" window is included ***for scheduling purposes only*** in cases of holidays or weekends.

The Observation Phase will have 2 scheduled visits, Screening and Pre-randomization Laboratory, which should be completed in person.

Subjects will report migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary every day during the Observation Phase.

All subjects will continue to use their standard of care migraine medications (both prophylactic and acute) during the Observation Phase. Subjects will record all concomitant medications, including standard of care migraine medications (both prophylactic and acute, prescribed and OTC), taken during the entire Observation Phase in a concomitant medication paper diary.

After completing the Observation Phase, subjects will return to the study site for the Baseline (Randomization) Visit, and both their eDiary and paper diary will be reviewed for completeness.

4.3.1.1 Screening Visit

Before any study procedures are performed, subjects must sign informed consent. After informed consent is obtained, subjects will be enrolled in the IWRS system. The subject's migraine history and medical history will be collected at the Screening Visit.

Subjects will undergo all screening procedures as detailed in Table 1. After the screening procedures are completed, subjects will be provided an eDiary to document occurrence, pain intensity, and characteristics of migraines each day during the Observation Phase. The Screening Visit starts at day 1 of the Observation Phase. Subjects with fewer than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary. This will be assessed at the Baseline (Randomization) Visit.

During this period, and within 96 hours (4 days + 2 days; note that the +2 days should only be used for scheduling in cases of holidays or weekends) of the Baseline Visit, subjects must return to the study site for the Pre-randomization Laboratory Visit. See Table 1 for laboratory tests performed. Subjects then return to the site for the Baseline Visit; if the subject is not eligible, the subject will be considered a screen failure and should be recorded as such in IWRS.

If the subject meets inclusion/exclusion criteria, the subject may enter the DBT Phase.

4.3.1.2 Pre-randomization Laboratory Visit

Within 96 hours (4 days + 2 days; note that the +2 days should only be used for scheduling in cases of holidays or weekends) of the Baseline Visit, subjects must return to the study site for the Pre-randomization Laboratory Visit.

LFTs, CK and a serum pregnancy test for WOCBP will be obtained and compliance with the eDiary will be assessed. If the subject continues to meet study entry criteria and laboratory test results are acceptable per protocol, the subject will be randomized at the Baseline Visit into the DBT Phase.

If the laboratory results are not acceptable per protocol, the subject is determined to be a screen failure and must return to the study site to return the eDiary.

Repeat testing of LFT abnormalities will not be permitted at this visit.

4.3.2 Double-blind Treatment (DBT) Phase

The DBT Phase will be up to 12 weeks from the Baseline (Randomization) Visit through the Week 12 or End of Treatment (EOT) Visit.

Zavegepant oral soft gel capsules should be taken fasting, at least 1 hour before breakfast/first meal of the day (and at least 4 hours after the previous meal).

Subjects should take their first dose of study drug the day after the Baseline Visit to ensure the subject is fasting appropriately.

Subjects will be instructed that they **must take four (4) or eight (8) capsules of study drug (depending on randomized treatment group assignment) every calendar day**, regardless of whether they have a migraine on that day. If subjects have a migraine during the DBT Phase, they may treat the migraine with their standard of care medication.

The electronic subject diary will be completed by subjects to capture frequency and severity of migraines during the DBT Phase. Subjects will also use the eDiary to complete the Preference of Medication (PoM) and Satisfaction with Medication (SM) questionnaire. The Migraine-Specified Quality-of-Life Questionnaire v 2.1 (MSQ), the Columbia-Suicide Severity Rating Scale (C-SSRS), Migraine Disability Assessment (MIDAS), and Clinical Global Impression (CGI-c) will be completed, or administered by the investigator, on paper at specified study visits (Table 1).

Study visits will be approximately every 2 weeks during the first month and then every 4 weeks, through Week 12 (Table 1). At each visit, the eDiary will be reviewed by site staff for completeness and compliance; study drug wallet will be reviewed for compliance at each visit and concomitant medication use will be reviewed (and compared to the eDiary and concomitant medication paper diary entries, where applicable). Subjects will be dispensed additional study drug as needed. Additional safety assessments (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 1.

Due to the COVID-19 Pandemic, visits may be conducted remotely (ex: telephone, telemedicine) and must be documented within the source records as being conducted remotely. All procedures not able to be completed due to a visit being conducted remotely must be reported as a protocol deviation and can be performed at the next visit, where appropriate to do so based on subject presentation.

4.3.2.1 Baseline (Randomization) Visit

After completing the Pre-randomization Laboratory Visit in the Observation Phase, subjects will return to the study site for the Baseline (Randomization) Visit (i.e., Day 1 of the DBT Phase, approximately Day 29 of Observation Phase), which should be completed in person. Subjects who continue to meet all inclusion/exclusion criteria and have been compliant with the eDiary may enter the DBT Phase, pending review of additional laboratory test results; see Section 4.3.1.2. Subjects with fewer than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary.

At the Baseline Visit, eligible subjects will be randomized randomized 2:2:1:1 across 4 treatment groups in the DBT Phase: zavegepant 100 mg (n = 480); zavegepant 200 mg (n = 480); placebo matching zavegepant 100 mg (n = 240); or placebo matching zavegepant 200 mg (n = 240).

4.3.2.2 *Week 12 or EOT Visit*

Subjects will return to the study site at the Week 12 Visit (Day 86 + 3 days) or at the EOT Visit for early discontinuation, for review of the electronic diary, assessment of medication compliance, assessment of tolerability and safety (including physical exam, vital signs, laboratory tests, and ECGs) (Table 1). Subjects will return the unused blinded study drug and eDiary to the study site.

All randomized subjects ***who discontinue early from the DBT Phase*** should complete the EOT Visit. Otherwise, subjects should complete the Week 12 Visit.

If the Week 12 or EOT Visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 Pandemic, the subject should return to the site for the Follow-up Week 2 Visit to complete all procedures that could not be completed remotely. Procedures completed at the Week 12 or EOT Visit occurring remotely do not need to be repeated.

After the DBT Phase, subjects should enter the OLE or Follow-up Phase. Subjects who discontinue early from the DBT Phase or are otherwise not eligible for the OLE Phase should enter the Follow-up Phase.

Open-label zavegepant will be dispensed at the Week 12 Visit to be taken in the OLE Phase. **Subjects should be instructed to NOT take open-label zavegepant until they have received a phone call from the site confirming their eligibility for the OLE Phase (see Section 4.3.3).**

4.3.3 Open-label Extension (OLE) Phase

The OLE Phase will be up to 52 weeks through the Week 64 or EOT Visit.

Note that the OLE Phase was added to the study design after some subjects already entered the Follow-up Phase after the DBT Phase. ***Subjects who complete 12 weeks of the DBT Phase and have not entered the Follow-up Phase*** may be offered to enter the OLE Phase. Subjects must meet the same laboratory eligiblilty criteria assessed prior to randomization in

the DBT Phase in order to be eligible for the OLE Phase. Repeat labs will not be allowed at the week 12 visit to determine OLE eligibility. The DBT Week 12 laboratory results will be used to assess eligibility for the OLE Phase. Once the Week 12 laboratory results are received and eligibility is confirmed, the subject should be contacted by telephone and instructed to start taking open-label study drug.

Subjects who (1) discontinue early from the DBT Phase or (2) have already entered the Follow-up Phase are not eligibile to enter the OLE Phase.

Eligible subjects will have study visits approximately every 2 weeks during the first month of the OLE Phase and then every 4 weeks, through Week 64. See Table 2 for schedule of procedures.

Subjects randomized to zavegepant 100 mg or matching placebo in the DBT Phase will receive open-label zavegepant 100 mg in the OLE Phase. Subjects randomized to zavegepant 200 mg or matching placebo in the DBT Phase will receive open-label zavegepant 200 mg in the OLE Phase.

At each visit, the study drug wallet will be reviewed for compliance and concomitant medication use will be reviewed (and compared to concomitant medication paper diary entries, where applicable). Subjects will be dispensed additional study drug as needed. Additional safety assessments (including laboratory tests and ECGs) will be performed per the schedule outlined in Table 2.

Subjects will not use the eDiary in the OLE Phase.

Subjects must continue to record use of concomitant medications in the concomitant medication paper diary through the entire OLE Phase.

4.3.3.1 Week 64 or EOT Visit

Subjects will return to the study site at the Week 64 Visit (Day 449 +/- 2 days), or at the EOT Visit for early discontinuation, for assessment of medication compliance and assessment of tolerability and safety (including vital signs, laboratory tests, and ECG) (Table 2). Subjects must return the unused study drug to the study site.

All randomized subjects ***who discontinue early from the OLE Phase*** should complete the EOT Visit. Otherwise, subjects should complete the Week 64 Visit.

If the Week 64 or EOT Visit occurs remotely in order to be completed during the protocol required window and due to the COVID-19 pandemic, the subject should return to the site for the Follow-up Week 2 Visit to complete all procedures that were not able to be completed remotely. Procedures completed at the Week 64 or EOT Visit occurring remotely do not need to be repeated.

4.3.4 Follow-up Phase

The Follow-up Phase will have 2 scheduled visits, Follow-up Week 2 and Follow-up Week 8. These visits should occur approximately 2 weeks and 8 weeks, respectively, after the last visit

in the last treatment phase (i.e., Week 12/EOT Visit [+3 days] if the subject did not enter the OLE Phase; Week 64/EOT Visit [+/- 2 days] if the subject entered the OLE Phase).

All randomized subjects should complete both follow-up visits, regardless of completing either treatment phase.

Subjects will continue to record all concomitant medications, including standard of care migraine medications (both prophylactic and acute, prescribed and OTC), taken during the entire Follow-up Phase in a concomitant medication paper diary.

4.3.4.1 Follow-up Week 2 Visit

Subjects will return to the study site approximately 2 weeks (14 days +/- 2 days) after the last visit in the last treatment phase to collect LFTs, CK, vital signs, electrocardiography, and assessment of AEs/ SAEs. Subjects will return the concomitant medication paper diary which should be reviewed one final time by study staff.

Investigators should assess subjects for AEs consistent with study drug dependency or withdrawal effects and report as appropriate (see Section 7.4).

4.3.4.2 Follow-up Week 8 Visit

Subjects will return to the study site approximately 8 weeks (56 days +/- 2 days) after the last visit in the last treatment phase to collect LFTs, CK, vital signs, assessment of SAEs, and to have a serum pregnancy test performed (WOCBP). Subjects will return the concomitant medication paper diary for documenting concomitant medications.

4.4 Post Study Access to Therapy (if applicable)

At the conclusion of this study, subjects or investigators will not have access to the study drug. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

5 POPULATION

5.1 Number of Subjects

It is anticipated that up to approximately 2900 subjects may be screened in order to randomize up to approximately 1440 subjects to study drug (zavegepant 100 mg, zavegepant 200 mg, placebo matching zavegepant 100 mg, or placebo matching zavegepant 200 mg) in the DBT Phase. It is estimated that approximately 1200 subjects will enter the OLE Phase.

5.2 Inclusion Criteria

1. Signed Written Informed Consent

    a. Written informed consent must be obtained from the subject in accordance with requirements of the study center's institutional review board (IRB) or ethics committee, prior to the initiation of any protocol-required procedures.

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:

    Subject has at least 1 year history of chronic migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition[11], including the following:

    a. Age of onset of migraines prior to 50 years of age

    b. Age of onset of chronic migraine prior to 65 years of age

    c. Migraine attacks, on average, lasting 4 – 72 hours if untreated

    d. Per subject report, the occurrence of at least 15 headache days per month, at least 8 migraine days per month, and at least 1 headache-free day per month during the last 3 months prior to the Screening Visit (month is defined as 4 weeks for the purpose of this protocol)

    e. 8 or more ***migraine days (as defined in Appendix 3)*** during 28 days in the Observation Phase

    f. 15 or more ***headache days*** (***as defined in Appendix 3)*** during 28 days in the Observation Phase

    g. 1 or more ***non-headache day*** during 28 days in the Observation Phase

    h. Ability to distinguish migraine attacks from tension/cluster headaches

i. Subjects on one prophylactic migraine medication are permitted to remain on therapy if the dose has been stable for at least 3 months (12 weeks) prior to the Screening Visit, and the dose is not expected to change during the course of the study.

   i. Subjects may remain on one (1) medication with migraine-prophylactic effects, excluding CGRP antagonists [monoclonal antibody or small molecule], during the DBT Phase.

   ii. Subjects who previously discontinued prophylactic migraine medication must have done so at least 90 days prior to the Screening Visit. Specifically CGRP monoclonal antibodies must be discontinued 6 months (24 weeks) prior to the Screening Visit and are prohibited during the study.

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

5. Age and Reproductive Status

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

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

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

   d. At the Baseline Visit, prior to dispensing investigational study drug, WOCBP must have a negative 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 included only if the investigator considers the finding not clinically significant, that it will not introduce additional risk factors, nor interfere with the study assessments of safety or efficacy (not including exclusion criteria listed in Section 5 below).

5.3 Exclusion Criteria

1. Target Disease Exclusion

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

2. Medical History and Concurrent Diseases

   a. Subjects with a history of HIV disease

b. Subjects with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia during the 6 months (24 weeks) prior to the Screening Visit. Subjects with history of 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 (high blood pressure), or uncontrolled diabetes. However, subjects can be included who have stable hypertension and/or stable diabetes for at least 3 months (12 weeks) prior to the Screening Visit. Blood pressure measurement of greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest is exclusionary. This may be repeated once at screening once during visit to confirm reproducibility.

d. Subjects with major depressive (MDD) or any anxiety disorder (AD) which require more than 1 daily medication for each disorder or subjects with major depressive episode (MDE) within the last 12 months of the Screening Visit. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening visit.

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

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

g. History of gallstones or cholecystectomy.

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

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

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

k. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months (48 weeks) or subjects who have met DSM-V criteria[12] for any significant substance use disorder within the past 12 months (48 weeks) from the date of the Screening Visit according to PI assessment.

l. History of use of opioid- or barbiturate- (e.g., butalbital) containing medication for 4 or more days per month during the 3 months (12 weeks) prior to Screening Visit.

m. 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. Retesting is not allowed.

   ii. 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 (12 weeks) prior to the Baseline Visit until the EOT Visit occurs.

   iii. 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[12] 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. Subject must agree to refrain from marijuana use during the trial.

n. Malignancy diagnosis within 5 years prior to the Screening Visit, with the exception of a history of localized basal cell or squamous cell skin cancer. Subjects are eligible for the study if they are cancer-free prior to the Screening Visit in this study.

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

p. Body mass index $\geq$ 33.0 kg/m^2

3. History of anaphylaxis to any substance or a clinically important reaction to any drug.

4. Sex and Reproductive Status

   a. Females of child-bearing potential who are unwilling or unable to use an acceptable contraceptive method or abstinence to avoid pregnancy for the entire study period and for 90 days after the study. See Section 5.6 for acceptable contraception methods.

   b. Women who are pregnant, lactating, or breastfeeding.

   c. Women with a positive pregnancy test.

5. ECG and Laboratory Test Findings

   a. Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (4-variable) Modification of Diet in Renal Disease (MDRD) Study equation $\leq$ 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) > 1x ULN.

(Only abnormal values between 1-1.5x ULN obtained at the Screening Visit may be repeated once for assessment of eligibility during the Observation Phase. Abnormal bilirubin results obtained at the Pre-randomization Laboratory Visit may not be repeated and will result in the subject being a screen failure.)

g. AST (SGOT) or ALT (SGPT) > 1x ULN.

(Only abnormal values between 1-1.5x ULN obtained at the Screening Visit may be repeated once for assessment of eligibility during the Observation Phase. Abnormal AST or ALT results obtained at the Pre-Randomization Laboratory Visit may not be repeated and will result in the subject being a screen failure.)

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

i. HbA1c ≥ 6.5%

6. Other Exclusion Criteria

a. Prisoners or subjects who are involuntarily incarcerated.

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

c. Non-compliance with or inability to complete eDiary during Observation Phase. Subjects with fewer than 24 completed eDiary reports during 28 days in the Observation Phase will not be considered for participation due to non-compliance with the eDiary.

d. Exposure to non-biological investigational agents (other than zavegepant) within 30 days prior to the Screening Visit.

e. Exposure to biological investigational agents such as monoclonal antibodies within 6 months (24 weeks) prior to the Screening Visit.

f. Subjects who meet criteria for C-SSRS Suicidal Ideation Items 4 or 5 within the last 12 months prior to the Screening Visit, OR subjects who endorse any of the 5 C-SSRS Suicidal Behavior Items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behavior) within the last 10 years prior to the Screening Visit, OR subjects who, in the opinion of the investigator, present a serious risk of suicide (See Section 6.2.5).

g. Previous enrollment in any multi-dose BHV-3500 (zavegepant) study. Note that subjects who were considered screen failures in a past BHV-3500 study may be considered after discussion with the Sponsor and written approval is received.

h. No therapeutic response with > 2 of the 8 medication categories for prophylactic treatment of migraine listed in Appendix 4 after an adequate therapeutic trial. Additional details can be found in Section 17.4 (Appendix 4).

i. Past participation in a clinical trial within 30 days prior to the Screening Visit. Note that subjects who were considered screen failures within the last 30 days should not be considered as excluded.

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

k. Subjects with an exclusionary match found in the CTSdatabase.

l. Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study.

7. Prohibited Medications

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

a. Use of ergotamine on ≥ 10 days per month on a regular basis for ≥ 3 months (≥ 12 weeks) in the year prior to the Screening Visit.

b. Use of CGRP monoclonal antibodies (e.g., Emgality® [galcanezumab], Aimovig® [erenumab], Ajovy® [fremanezumab], Vyepti® [eptinezumab]) within 6 months (24 weeks) prior to the Screening Visit.

c. Use of FDA-approved gepants (e.g. Nurtec ODT® [rimegepant], Ubrelvy® [ubrogepant]) within 2 weeks prior to the Screening Visit.

d. Use of a prohibited medication or device during the Observation Phase (refer to Section 5.4).

5.4 Prohibited and Restricted Concomitant Medications and Devices

All medications taken by subjects after screening until the last study day will be documented as concomitant medications including vaccinations.

The medications and devices listed below are prohibited starting at the Baseline Visit and during the course of this study or as specified.

1. The use of CGRP monoclonal antibodies (e.g., Emgality® [galcanezumab), Aimovig® [erenumab], Ajovy® [fremanezumab], Vyepti® [eptinezumab]) is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit.

2. The use of FDA-approved gepants (e.g., Nurtec ODT® [rimegepant], Ubrelvy® [ubrogepant]) is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit.

3. Butterbur root or extracts should not be taken 14 days prior to the Baseline Visit and throughout the study, including the Follow-up Week 8 Visit.

4. Use of ergotamine is prohibited from the Screening Visit through the Follow-up Week 8 Visit.

5. Use of narcotic medication, such as opioids (e.g., morphine, codeine, oxycodone, and hydrocodone) or barbiturates, is prohibited starting from 2 days prior to the Baseline Visit and throughout the study, including the Follow-up Week 8 Visit.

6. Use of 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.

7. Use of marijuana and all forms of ingested or inhaled cannabidiol (CBD) and THC-containing products are prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit.

8. Use of strong CYP3A4 inhibitors is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit. If use of a strong CYP3A4 inhibitor is required, dosing should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inhibitor. Refer to Section 17.2, Appendix #2.

9. Use of strong CYP3A4 inducers is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit. If use of a strong CYP3A4 inducer is required, dosing should be stopped and should not start again until 14 days after the last dose of the strong CYP3A4 inducer. Refer to Section 17.2 Appendix #2.

10. Use of potent P-glycoprotein (P-gp) inhibitors from the Screening Visit through the Follow-up Week 8 Visit. If use of a P-gp inhibitor is required, dosing should be stopped and should not start again until 14 days after the last dose of the P-gp inhibitor. Refer to Section 17.2 Appendix #2.

11. Use of potent P-glycoprotein (P-gp) inducers from the Screening Visit through the Follow-up Week 8 Visit. If use of a P-gp inducer is required, dosing should be stopped and should not start again until 14 days after the last dose of the P-gp inducer. Refer to Section 17.2 Appendix #2.

12. Use of atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone) or

Depakote/Depakene (divalproex/valproic acid/valproate) is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit.

13. Use of LAMICTAL (lamotrigine) is prohibited during the study from the Screening Visit through the Follow-up Week 8 Visit.

14. Use of acetaminophen or acetaminophen-containing products for the treatment of migraine on >2 consecutive days per month or use of more than 1000 mg/day of acetaminophen are both prohibited for duration of the trial.

15. Devices, neuromodulation, neurostimulation, or injectable therapy (trigger point injections) for headache acute treatment or prophylaxis are prohibited 2 months prior to the Screening Visit and during the study through Week 64/EOT.

16. Use of any investigational agent other than zavegepant from the Screening Visit through the Follow-up Week 8 Visit.

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

5.5 Standard of Care Migraine Medications

Use of standard of care migraine medication during the Observation Phase and through the Follow-up Week 8 Visit will be recorded by the subject on the concomitant medication paper diary and reported to the site. Migraine medications include both prophylactic and acute migraine medications.

5.5.1 Prophylactic Migraine Medications

Subjects may use no more than 1 of the following medications with possible migraine-prophylactic effects, regardless of indication, if not otherwise prohibited by the protocol. Doses must be stable **within 3 months (12 weeks) prior to the Screening Visit** and throughout the study. Use of more than 1 of the following medications is prohibited within 3 months (12 weeks) prior to the Screening Visit and throughout the study.

Prophylactic migraine medications that are permitted during the study include:

- Topiramate, gabapentin
- Beta blockers (such as: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- Tricyclic antidepressants (such as: amitriptyline, nortriptyline, protriptyline)
- Venlafaxine, desvenlafaxine, duloxetine, milnacipran
- Flunarizine, lomerizine
- Lisinopril, candesartan

- Clonidine, guanfacine
- Cyprohepatdine
- Methysergide
- Pizotifen
- Feverfew, magnesium (≥ 600 mg/day), riboflavin (≥ 100 mg/day)
- Botox®

The above listed medications are the only prophylactic migraine medications allowed.

5.5.2 Acute Migraine Medications

Subjects may use their permitted standard of care medication if needed for acute treatment of a migraine throughout the study.

Acute migraine medications that are permitted during the study include the following:

- Triptans (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)
- Aspirin
- Ibuprofen
- Baclofen
- Acetaminophen up to 1000 mg/day for a maximum of 2 consecutive days at a time (this includes Excedrin Migraine and any other acetaminophen-containing products)
- Naprosyn (or any other type of non-steroidal anti-inflammatory (NSAID))
- Antiemetics (e.g., metoclopramide or promethazine)
- Muscle relaxants.

The above listed medications are the only acute migraine medications allowed.

If a subject experiences a migraine after dosing with study drug for the day during the DBT or OLE Phase, the subject may take their ***acute migraine medication*** as described above in this section of the protocol.

5.6 Women of Childbearing Potential and Contraception

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal. Tubal ligation

is considered one form of contraception; therefore, one additional form of contraception must be used to fulfill contraception requirements for the study. Essure, tubal occlusion and endometrial ablation are not acceptable methods of contraception. Menopause is defined as:

- Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL
- NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to 1 year

  OR

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

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

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

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

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

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

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

5.7 Other Restrictions and Precautions (if applicable)

Not applicable.

5.8 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion/exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/IEC at the frequency required by your IRB/IEC. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

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

- Investigator File/Study Binder
- Pharmacy Binder
- Drug Accountability Logs
- Sample source documents, where applicable
- Concomitant medication paper diary (take home for subject)
- Investigator Brochure
- Interactive Web-based Response System (IWRS) manual
- Electronic Case Report Forms (eCRF) instructions
    - Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields
    - All sites will use an Electronic Data Capture (EDC) tool to submit study data to the CRO. Electronic Case Report Forms (eCRFs) will be prepared for all data collection fields including Serious Adverse Events (SAE) Reporting. SAE data (including queries) will be submitted to the CRO using eCRFs.
- Electronic Clinical Outcome Assessment (eCOA) Handheld devices (eDiary)
    - The eDiary will be used daily during the Observation Phase and DBT Phase to record migraine occurrence, migraine pain features and associated symptoms, use of acute migraine medication (i.e., triptans, ergotamine, or other). The eDiary will be used during the DBT phase to record select subject-rated scales (PoM and SM). Any assessment completed by the subject in the eDiary will be transferred from the site/subject to the vendor and from the vendor to the CRO and Sponsor. No additional source documents are required for scales and assessments completed by the subject on the eDiary. In the OLE Phase, the PoM and SM will be reported on paper forms at the site.
- Laboratory kits and laboratory manual
    - Safety laboratory, plasma, urinalysis and serum instructions for all specimens collected will be provided by a designated central laboratory.
- ECG Machine and instructions

  - ECG equipment, supplies, instructions and training materials will be supplied by a centralized ECG vendor.

- SAE forms and SAE Reporting instructions
- Pregnancy surveillance forms
- C-SSRS documents
- MIDAS forms
- MSQ v 2.1 forms
- PoM forms (OLE Phase only)
- SM forms (OLE Phase only)
- CGI-c forms
- Study system access:
  - Electronic Data Capture (EDC) tool to submit study data to Sponsor / CRO
  - IWRS
  - Central Laboratory
  - Central ECG Vendor

6.2 Safety Assessments

6.2.1 Vital Signs and Physical Measurements (Height and Weight)

Vital signs, body weight and height will be recorded at the scheduled visits as outlined in Table 1.

6.2.2 Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the Observation Phase and at all scheduled visits as outlined in Table 1 and Table 2. 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 whether any ECG abnormalities are clinically significant based on the overread from the central ECG vendor.

6.2.3 Physical Exam

Subjects will undergo a complete physical examination during the Observation Phase and brief and symptom-directed physical exam at all scheduled visits as outlined in Table 1 and Table 2. Targeted physical examinations to include examination of heart, abdomen, and lungs; plus review of any other system to be guided by signs and symptoms.

6.2.4 Laboratory Tests

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. 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 participant's condition.

6.2.4.1 Safety Laboratory Testing

Blood and urine samples will be obtained as outlined in Table 1 and Table 2 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 before laboratory tests.** 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.

1. 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, BUN (urea), serum creatinine, uric acid, LDH, total protein, albumin.

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

2. **LFTs**: AST, ALT, Alkaline Phosphatase and Bilirubin (Total, Direct, Indirect), CK (fractionation will be ordered if CK result is > 5.0x ULN).

3. **HbA1c**

4. **Lipid panel:** Cholesterol, LDL, HDL, triglycerides.

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

6. **Urine Drug Screen:** For drugs of abuse.

7. **FSH:** At screening in female subjects to confirm postmenopausal status, if applicable.

Additional tests may be required to evaluate laboratory abnormalities and/or adverse events; please refer to the Laboratory Manual.

6.2.4.2 PK Testing

PK will be collected at the Week 4 and Week 8 Visits only. Subjects will be instructed to not take study drug until they are at the study site. Subjects will have PK drawn predose and at least 1 hour postdose. The time of dose administration in the clinic, time and date of last dose

and the exact time of PK sample collection will be documented at the clinic visit. Subjects should be fasting prior to dose administration (at least 4 hours after the last meal) and for duration of PK assessments.

6.2.4.3 Pregnancy Testing

WOCBP will complete pregnancy tests (serum and/or urine) at specified study visits, prior to taking study drug, and as outlined in Refer to Section 5.6.

6.2.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide Assessment.[13] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version"[14] will be used at subsequent visits in this study.

The C-SSRS Assessment is intended to help establish a person's immediate risk of suicide. The C-SSRS is a clinician administered scale that should be administered by a certified rater. This scale will be collected on site with a paper form. The C-SSRS should be reviewed by the Investigator or designee before the subject is allowed to leave clinic.

At the Screening Visit, the recall period for completing is 12 months for suicidal ideation and 10 years for suicidal behavior; at all other visits, the recall period for completing the C-SSRS is since the last visit (reference Table 1 and Table 2).

If the Investigator determines that a participant is at risk of suicide or self-harm, or reports a "Yes" response to any question during the course of the study, appropriate measures to ensure the participant's safety and obtain mental health evaluation must be implemented. In such circumstances, the participant must immediately be discontinued from the study. The event should be recorded as either a non-serious AE or SAE through the Follow-up Week 8 Visit as determined by the Investigator and reported within 24 hours to the Sponsor.

6.3 Efficacy Assessments

The eDiary will be used daily to record acute migraine medication dosing occurrences and migraine pain features and associated symptoms during the Observation Phase and DBT Phase.

Efficacy assessments will be derived from eDiary data and will include the number of migraine days per month by pain intensity (total; moderate or severe), and number of acute migraine-specific medication days per month, in each month by study period.

6.4 Other Assessments

6.4.1 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 Qualify-of-Life Questionnaire version 2.1 (MSQ v 2.1). The MSQ v 2.1 is a 14-item instrument that has been validated in 3 domains: role function – restrictive, role function – preventive, and emotional function.[15] The MSQ will be completed on a paper form at the site.

6.4.2 Migraine Disability Assessment

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.[16] The MIDAS will be completed on a paper form at the site.

6.4.3 Preference of Medication Scale

The Preference of Medication Scale (PoM) is a subject-rated, 5-point scale that measures preference of the study drug compared to the previous medications to treat migraine pain. The eDiary will be used to evaluate the PoM in the DBT Phase, and a paper form will be used at the site to evaluate the PoM in the OLE Phase.

6.4.4 Satisfaction with Medication Scale

The Satisfaction with Medication (SM) scale is a subject-rated, 7-point scale that measures satisfaction with the study drug to treat migraine headaches. The eDiary will be used to evaluate the SM in the DBT Phase, and a paper form will be used at the site to evaluate the SM in the OLE Phase.

6.4.5 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.[17] 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 at the site.

6.5 Early Discontinuation from the Study

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator or sponsor, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Biohaven Pharmaceuticals
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

- Poor compliance with study procedures and visits, including poor completion compliance with evening reports in eDiary; poor compliance with study drug – see Schedule of Assessments Table 1 and Table 2.

- All subjects who discontinue in the DBT Phase early should comply with protocol specified DBT EOT procedures as outlined in Table 1. All subjects who discontinue in the OLE Phase early should comply with the protocol specified OLE EOT procedures as outlined in Table 2. 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).

6.5.1 Lost to Follow-up

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

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

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

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

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

6.6 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.ctsdatabase.com and enter the last 7 digits of the subject study ID and authorized subject identifiers. An immediate report detailing matches is generated and should be printed

for source documentation. The report will specify either (1) no matches found, (2) a match was found with a subject participating in another study within 30 days or (3) the subject matches with a subject who has *pre*-screened at another site.

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

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

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

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

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

In this protocol, investigational product (study drug) is zavegepant (BHV-3500) 25 mg soft gelatin capsule (SGC) or matching placebo.

7.1.2 Non-Investigational Product

In this protocol, there are no non-investigational products.

7.1.3 Formulation

Zavegepant (BHV-3500) is formulated as a 25 mg soft gelatin capsule (SGC) taken as either 4 soft gelatin capsules (SGC) for each 100 mg daily dose (25 mg x 4 = 100 mg) or 8 SCG for each 200 mg daily dose (25 mg x 8 = 200 mg).

7.1.4 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 Pharmacy Manual/Investigator Brochure for specific conditions. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor/CRO immediately.

7.2 Dose and Administration

7.2.1 Method of Assigning Subject Identification

The Investigator or designee will need to access an Interactive Web-based Response System (IWRS) in order to register each subject. 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 DBT and OLE

Phases, 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.

At the Baseline Visit, eligible subjects will be randomized to a treatment group (see Section 1.4.1). The randomization will be stratified by stable prophylactic migraine medication use through randomization (yes or no), as determined by site review of subjects' concomitant medication paper diary. Subjects should be categorized as "yes" if they took a specified prophylactic migraine medication > 3 months (12 weeks) before the Screening Visit and through randomization, i.e., (1) the medication start date is > 12 weeks before the Screening Visit date, **and** (2) either the medication stop date is on or after the randomization date or the medication is ongoing. Otherwise, subjects should be categorized as "no".

Subjects may not be rescreened for this study.

Study drug will be assigned via IWRS; 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 Study 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 subject from participation in the study.

7.2.2 Selection and Timing of Dose and Administration

Study drug (zavegepant or matching placebo) will be assigned via the IWRS system. There are no dose adjustments in this study and subjects will receive wallets as outlined in Table 1. Subjects will be dispensed study drug at the Baseline (Randomization) Visit, and the subjects will be instructed that they must take ***4 or 8 capsules of study drug (depending on randomized treatment group assignment) every calendar day, regardless of whether they have a migraine on that day.*** This is the scheduled dosing regimen for the 12-week DBT Phase.

Zavegepant oral soft gelatin capsules should be taken fasting, at least 1 hour before breakfast/first meal of the day (and at least 4 hours after the previous meal).

Scheduled visit for Week 4 and Week 8 – subjects should not dose until they arrive at the study site and will take study drug with site staff to assess PK outlined in Table 1. PK will be drawn predose and at least 1 hour postdose; exact time of PK collection relative to the dose will be documented. At these visits, subjects should fast for the duration of PK assessments. Date and time of last meal will be collected (regardless of fasting status).

Subjects who complete 12 weeks of the DBT Phase may continue to take their assigned dose, either zavegepant 100 mg or 200 mg, in the OLE Phase for 52 weeks.

During the DBT or OLE Phase, if the subject has a migraine when they have ***already taken study drug for the day***, the subject can take their acute migraine medication in accordance with protocol restrictions (see Section 5.5.2). Subjects **must** be instructed that they CANNOT

take more than what their randomization assignment allows (4 (four) capsules, or 8 (eight) capsules of study drug every day).

7.2.3 Dose Modifications

There will be no dose adjustments in this study.

7.3 Blinding and Unblinding

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

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

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

7.4 Treatment Compliance

Responsible study personnel will dispense the study drug. Subjects should finish a wallet blister of study drug before starting a new wallet. Accountability and compliance verification should be documented in the subject's study records.

Subjects must be counseled on the importance of taking the study drug as directed (see Section 7.2.2). Treatment compliance should be completed by a thorough review of returned study drug. Treatment compliance should be assessed by site staff at each study visit. Discrepancies, review of study drug and information provided by subject must be documented in the source record. Investigators should inform subjects that involuntary termination from the study will occur in cases where non-compliance is identified. Study staff should contact a subject in between the study visits if the subject demonstrates non-compliance with the eDiary and document the contact in the source, to identify potential lost to follow-up subjects as early as possible.

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 also 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 subjects 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 subjects who discontinue treatment without returning study drug) should be documented in the source record and reported as an AE or SAE as appropriate. Overdose is defined in Section 8.3. Dosing errors (e.g., accidentally taking over the assigned number of soft gelatin capsules in one calendar day) should be reported as deviations.

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.

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) or symptom, or any disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

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

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

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

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

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

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

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

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

Assessment for Determining Relationship of AE to Study Drug:

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

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

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.

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

8.1 Serious Adverse Events

8.1.1 Definition of Serious Adverse Event (SAE)

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

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received zavegepant
- 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 8.4)
- 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 8.3

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

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

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

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

8.1.2 Collection and Reporting Serious Adverse Events

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the Observation

Phase and throughout the course of the study, up to and including the End of Treatment Visit and through the Follow-up Week 8 Visit. The investigator should report any SAE occurring after this time period that is believed to be related to study drug or protocol-specific procedures.

All SAEs should be followed to resolution or stabilization.

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

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

SAEs, whether related or not related to study drug, overdose (see Section 8.3), potential drug induced liver injury (see Section 8.4) and pregnancies (see Section 8.1.3) must be reported within 24 hours of the Investigator becoming aware of the event.

The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the SAE information into the Case Report Form (CRF) and/or system (i.e., event term, start/stop dates, causality, and severity).

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

- North America Fax – 1-888-488-9697

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

- North America Telephone – 1-800-201-8725

If only limited information is initially available, follow-up reports are required. If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the Investigator becoming aware of the updated information using the same procedure used for the transmission of the initial SAE and the same event term should be used.

The minimum information required for an initial SAE report is:

Sender of report (Site number, Investigator name)

Subject identification (subject number)

Protocol number

SAE term (if an SAE is being reported)

8.1.3 Pregnancy

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

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

- North America Fax – 1-888-488-9697
- Or if the form cannot be faxed or emailed (wilsafety@ppdi.com; subject line must include "**Biohaven Protocol BHV3500-302**"), reported via phone to the PPD Safety Hotline at North America: 1-800-201-8725 or EU EMEA: +44 1223 374 240.
- Once the paper form is available, the data must be reported per standard procedures.

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

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

8.2 Non-Serious Adverse Events

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

8.2.1 Collection and Reporting of Non-serious Adverse Events

Non-serious AE information should be collected from the start of the Observation Phase intended to establish a baseline status for a subject and should be captured through the Follow-up Week 2 Visit except for non-serious suicidality AEs which should be captured through the Follow-up Week 8 Visit (see Section 6.2.5).

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

8.2.2 Laboratory Test Abnormalities

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

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.

8.3 Overdose

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

All occurrences of medically significant overdose (suspected or confirmed and irrespective of whether it involved study drug) 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 more than 4 capsules instead of prescribed dose of 4 capsules in one calendar day) should be reported as deviations.

8.4 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. ALT or AST elevation > 3x ULN

AND

2. Total bilirubin > 2x 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.

8.5 Adverse Events of Special Interest

Not applicable.

9 STATISTICS

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

9.1 Sample Size

With a sample size of approximately 480 randomized subjects per zavegepant treatment group and 240 randomized subjects per placebo treatment group, we expect approximately 440 subjects per zavegepant treatment group and 220 subjects per placebo treatment group in the migraine analysis set. Assuming zavegepant provides a 1-day advantage over placebo pooled on the mean change in migraine days per month over the entire DBT Phase (Weeks 1 to 12), and a common standard deviation of 4.2 days, then the study will have ≥ 90% power for the primary endpoint with an alpha level of 0.025. The estimates for the migraine analysis set sample size, mean change in migraine days per month, and standard deviation are based on observed pooled data from rimegepant study BHV3000-305.

9.2 Analysis Sets

The following analysis sets will be used in this study:

- Enrolled: Subjects who sign informed consent and are assigned a subject identification number
- Randomized: Subjects in the enrolled analysis set who receive a randomized treatment group assignment (zavegepant or placebo)
- DBT safety: Subjects in the enrolled analysis set who take ≥ 1 dose of double-blind study drug (zavegepant or placebo)
- Open-label zavegepant safety: Subjects in the enrolled analysis set who take ≥ 1 dose of open-label zavegepant
- Double-blind or open-label zavegepant safety: Subjects in the enrolled analysis set who take ≥ 1 dose of double-blind or open-label zavegepant
- PK: Subjects in the DBT safety analysis set who take ≥ 1 dose of double-blind zavegepant and have ≥ 1 PK sample collected
- DBT efficacy: Subjects in the randomized analysis set who are randomized only once, and take ≥ 1 dose of double-blind study drug
- Migraine: Subjects in the DBT efficacy analysis set with ≥ 14 days (not necessarily consecutive) of eDiary efficacy data in both the Observation Phase and ≥ 1 month (4-week interval) in the DBT Phase.

9.3 Statistical Methods

Results will be summarized by treatment group and the 2 matching placebo groups pooled, where applicable.

9.3.1 Efficacy Analyses

9.3.1.1 Primary Efficacy Endpoint

The primary endpoint will be assessed for the migraine analysis set using a generalized linear mixed effect model (GLMEM) with repeated measures that will use the identity link function and include the following variables: change from the Observation Phase in the number of migraine days per month as the dependent variable; subject as a random effect; number of migraine days per month in the Observation Phase as a covariate; and fixed effects for treatment group, randomization stratum (i.e., stable prophylactic migraine medication use through randomization), month, and month-by-treatment group interaction. Migraine days are of any pain intensity. Months are defined using 4-week intervals as Month 1 (Weeks 1 to 4), Month 2 (Weeks 5 to 8), and Month 3 (Weeks 9 to 12). The number of migraine days per month is prorated to 28 days account for days with missing migraine data. The difference estimate (zavegepant – placebo), standard error (SE), 97.5% confidence interval (CI), and p-value will be reported for the entire DBT Phase (Weeks 1 to 12) for each dose of zavegepant versus placebo pooled.

The repeated measures error structure is assumed to be constant across treatment groups, and will be initially specified as unstructured. If the model fails to converge or cannot be fit with an unstructured error structure, then a heterogeneous Toeplitz error structure will be attempted. If the Toeplitz fails, then an autoregressive order 1 error structure will be attempted.

The Kenward-Roger method will be used to approximate denominator degrees of freedom.

9.3.1.2 Secondary Efficacy Endpoints

The proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate or severe migraine days per month over the entire DBT Phase (Weeks 1 to 12) will be analyzed using a Cochran-Mantel-Haenszel test stratified by randomization stratum for the migraine analysis set. Missing data are imputed as non-response (i.e., failure). The difference estimate (zavegepant – placebo), SE, 97.5% CI, and p-value will be reported for each dose of zavegepant versus placebo pooled.

The mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase will be assessed for the migraine analysis set from the same GLMEM used for the primary efficacy endpoint.

The mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks (Weeks 1 to 4) of the DBT Phase will be assessed for the migraine analysis set from the same GLMEM used for the primary efficacy endpoint.

The mean number of acute migraine-specific medication days per month over the entire DBT Phase (Weeks 1 to 12) will be assessed for the migraine analysis set using a GLMEM that is

similar in structure to that used for the primary efficacy endpoint, except that the number of acute migraine-specific medication days per month is the dependent variable and there is no covariate. Acute migraine-specific medications are triptans and ergotamine.

The mean changes from baseline in MSQ restrictive role function domain score and MIDAS total score at Week 12 will be analyzed for the DBT efficacy analysis set using GLMEMs that will use the identity link function and include the following variables: Week 12 change from baseline in the score as the dependent variable; baseline score as a covariate; and fixed effects for treatment group and randomization stratum. The Week 12 difference estimate (zavegepant – placebo), SE, 97.5% CI, and p-value will be reported for each endpoint and each dose of zavegepant versus placebo pooled.

9.3.1.3 Adjustment for Multiplicity

Type 1 error is controlled through the use of hierarchical testing. The significance of the primary endpoint is evaluated at the 0.025 level for each dose of zavegepant versus placebo. If the primary endpoint is significant for a dose, then the following secondary efficacy and outcomes research endpoints will be tested hierarchically in the following order, each at the 0.025 level:

- Proportion of subjects with ≥ 50% reduction from the Observation Phase in the number of moderate or severe migraine days per month over the entire DBT Phase
- Mean change from the Observation Phase in the number of migraine days per month in the last 4 weeks of the DBT Phase
- Mean change from the Observation Phase in the number of migraine days per month in the first 4 weeks of the DBT Phase
- Mean number of acute migraine-specific medication days per month over the entire DBT Phase
- Mean change from baseline in MSQ restrictive role function domain score at Week 12 of the DBT Phase
- Mean change from baseline in MIDAS total score at Week 12 of the DBT Phase.

9.3.2 Safety Analyses

Deaths will be listed regardless of onset for the enrolled analysis set.

The frequencies of safety endpoints will be assessed descriptively as the number and percentage of subjects with events/findings separately for the 3 safety analysis sets.

The frequencies of the following safety endpoints will be tabulated on treatment: AEs by intensity (mild, moderate, severe, total); AEs by relationship to study drug (related, possibly related, unlikely related, not related); SAEs; AEs leading to study drug discontinuation; hepatic-related AEs by intensity; hepatic-related AEs leading to study drug discontinuation; clinically significant laboratory test abnormalities; and LFT elevations based on fold changes above ULN, including ALT or AST > 3x ULN concurrent (on the same laboratory test collection date) with total bilirubin > 2x ULN.

The investigators will determine the intensity of AEs and the relationship of AEs to study drug. The investigators' terms will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study. AEs will be tabulated by system organ class and preferred term. In tables by intensity, if a subject has an AE with different intensities over time, then only the greatest intensity will be reported. In tables by relationship to study drug, if a subject has an AE with different relationships over time, then the highest degree of relatedness to study drug 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

A clinical study report will be produced after the last subject completes the last visit in the DBT Phase in order to assess the primary and secondary efficacy endpoints.

An addendum study report will be produced after the last subject completes the last visit in 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 (DSMC). The study drug, zavegepant, has been tested and found to be well-tolerated. 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 CTSdatabase participation. The signed and dated ICF will be retained at the Investigator's site, with a copy provided to the study subject and date will be entered in his or her CRF or appropriate system. The IRB/IEC must review and approve all protocol versions and informed consent form versions and a copy of each version of the IRB/IEC approved protocol and informed consent form is to be retained in the Study Master file. Any revisions to the protocol or ICF will be reviewed and approved by the IRB/IEC and subjects will be informed of ICF changes and document continuing consent by signing and dating the revised version of the ICF.

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

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

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

10.6 Case Report Forms

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

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

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

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

11 RECORDS MANAGEMENT

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

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

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

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

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

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

11.1 Source Documentation

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

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

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

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

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

11.2 Study Files and Record Retention

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

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

12 AMENDMENTS

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

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

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

13 STUDY REPORT AND PUBLICATIONS

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

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

14 STUDY DISCONTINUATION

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

15 CONFIDENTIALITY

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

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

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

16 CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Zavegepant in Migraine Prevention

Study No: BHV3500-302

Original Protocol Date: 15-January-2021

Protocol Version No: V 6.0

Protocol Version Date: 16-May-2022

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

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

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

Name and Title	Signature Approval	Date
Author: PPD	PPD	
Clinical Operations: PPD		
Biostatistics PPD , PhD PPD		
Medical Lead: PPD , MD PPD		
Regulatory Affairs: PPD		

17 APPENDICES

17.1 APPENDIX 1 – Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals Refer to contact list in study binder for contact information
Medical Monitor:	PPD , MD PPD
Clinical Research Organizations:	Synteract Refer to contact list in study binder for contact information
Central Laboratory:	ACM Global Laboratories Refer to contact list in study binder for contact information
Central ECG:	Clario (formerly known as Bioclinica) Refer to contact list in study binder for contact information
eCOA:	Yprime Refer to contact list in study binder for contact information
Pharmacovigilance:	PPD Refer to SAE, Pregnancy Surveillance Forms and study binder for contact information.

17.2 Appendix 2 – Inhibitors and Inducers of CYP3A4 and Inhibitors of P-glycoprotein (not all inclusive)

The following tables present some of the inhibitors and inducers of CYP3A4 and P-glycoprotein (P-gp). This list should not be considered all-inclusive. Individual drug labels should be reviewed for specific information on propensity to inhibit or induce CYP450 or to inhibit P-gp enzymes for a specific compound.

As described in the study protocol, concomitant use of strong CYP3A4 inhibitors or inducers is prohibited.

Strong CYP3A4 Inhibitors
Clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, troleandomycin, voriconazole

Strong CYP3A4 Inducers
Apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, St. John's Wort

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

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

P-gp Inducers
Carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort

Resources:

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

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

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2

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

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

17.3 Appendix 3 – Definition of Migraine Days

Migraine Day: Any calendar day in which the subject experiences a qualified migraine headache (onset, continuation, or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura, lasting for ≥ 30 minutes, and meeting the conditions specified in at least one of the two sets of criteria specified below criteria (A and/or B)

A. ≥ 2 of the following pain features:

   a. Unilateral location,

   b. Pulsating quality (throbbing),

   c. Moderate or severe pain intensity,

   d. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

B. ≥ 1 of the following associated symptoms:

   a. Nausea and/or vomiting

   b. Photophobia and phonophobia

If the subject took a migraine-specific medication (~~i.e.,~~ e.g., triptan or ergotamine) during aura or to treat headache, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.

A moderate to severe migraine day is a migraine day with a migraine reported with moderate or severe pain intensity.

Headache Day: Any calendar day on which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as:

- a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication), or
- a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache, or
- a headache of any duration for which acute headache treatment is administered.

Acute Migraine-specific Medication Day: Any calendar day on which the subject took an acute migraine-specific medication (i.e., triptan or ergotamine).

Monthly eDiary Data: Data collected by the eDiary based on the subject's monthly study drug dosing schedule when at least 14 days of eDiary data are collected within that interval. Monthly frequency measurements will be prorated to 28-day equivalents.

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from two attacks, or to distinguish between attacks and relapses:

a) A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack and not two.

b) An attack treated successfully with medication but with relapse within 48 hours (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as one attack.

17.4 Appendix 4 – Categories of Migraine Prevention Medications

No therapeutic response with > 2 of the following 8 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

- **Category 1**: Divalproex sodium, sodium valproate
- **Category 2**: Topiramate, carbamazepine, gabapentin
- **Category 3**: Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol)
- **Category 4**: Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline)
- **Category 5**: Serotonin-norepinephrine reuptake inhibitors (for example: venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- **Category 6**: Flunarizine, verapamil (verapamil use is prohibited during the study)
- **Category 7**: Lisinopril, candesartan
- **Category 8**: Botox®

No therapeutic response is defined as no reduction in headache frequency, duration, or intensity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment.

The following scenarios ***do not*** constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

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