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

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

SUMMARY OF CHANGES

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

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

BHV3500-301

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

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

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

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

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

_____ _____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

Title:	BHV3500-301: Phase 3: Double-Blind, Randomized, Placebo Controlled, Safety and Efficacy Trial of BHV-3500 (zavegepant) Intranasal (IN) for the Acute Treatment of Migraine
Rationale:	Zavegepant is being developed for the acute treatment of migraine. Effectiveness against migraine was demonstrated in BHV3500-201, a fully powered, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant 5 mg, 10 mg, and 20 mg via intranasal (IN) administration. The data from this study will allow characterization of the relative safety and efficacy of IN zavegepant versus placebo in the acute treatment of moderate or severe migraine measuring freedom from pain and freedom from most bothersome system (nausea, photophobia or phonophobia) as reported just prior to treatment of the migraine. Information regarding time to onset of action, the duration of action, and the sustainability of pain freedom in subjects with migraine will also be obtained.
Target Population:	The study will recruit male and female subjects 18 years of age and older with at least a 1-year history of migraine (with or without aura), consistent with a diagnosis according to the International Classification of Headache Disorders 3rd edition[1], including an age of onset prior to 50, migraine attacks that last about 4-72 hours, not more than 8 attacks of moderate or severe intensity per month within the last 3 months and not less than 2 attacks per month.
Number of Subjects:	Approximately 1,750 subjects will be screened to randomize approximately 1,400 subjects (approximately 700 per treatment group). Subjects will be randomized in a 1:1 ratio to the zavegepant or placebo treatment groups. Randomization will be stratified by prophylactic migraine medication use (yes or no).
Primary Objective:	To compare the efficacy of zavegepant with placebo in the acute treatment of migraine, as measured by co-primary endpoints of pain freedom at 2 hours postdose, and freedom from the most bothersome symptom (MBS) associated with migraine at 2 hours postdose.
Secondary Objectives:	1. To compare zavegepant with placebo for pain relief at 2 hours postdose. 2. To compare zavegepant with placebo for return to normal function at 2 hours postdose according to the Functional Disability scale.

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

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

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

STUDY SCHEMATIC