PROTOCOL BHV3500-113

Syneos Health Project Number: Number: 222025

IND Number: CCI

A PHASE 1, OPEN-LABEL, RANDOMIZED, 4-PERIOD, 4-WAY CROSSOVER, COMPARATIVE BIOAVAILABILITY STUDY OF ZAVEGEPANT (BHV-3500) ORAL FORMULATIONS UNDER FASTING CONDITIONS

Sponsor:

Biohaven Pharmaceuticals Holding Company Limited
215 Church Street
New Haven, CT
USA 06510
Tel.: 203-404-0410

Contract Research Organization:

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CONFIDENTIAL

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SPONSOR SIGNATURE PAGE

Biohaven Pharmaceuticals Holding Company Limited
215 Church Street
New Haven CT
USA 06510
Tel.: 203-404-0410

Sponsor's representative:

PPD

18 August 2022
Date

INVESTIGATOR SIGNATURE PAGE

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with the clinical site's Standard Operating Procedures (SOPs), ICH Good Clinical Practice (GCP), all other applicable regulations, and the recommendations laid down in the most recent version of the Declaration of Helsinki.

PPD

19-Aug-2022
Date

Syneos Health Clinical Research
Services, LLC (« Syneos Health »)
1951 NW 7th Avenue, Suite 400
Miami, FL 33136
USA
PPD

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{0\text{-}t}$	area under the concentration-time curve from time zero until the last observed concentration
BA	bioavailability
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CGRP	calcitonin gene-related peptide
Cl/F	apparent clearance
C_{max}	maximal observed concentration
CPK	creatine phosphokinase
CRF	case report form
CTCAE	Common Technical Criteria for Adverse Events
DAIDS	Division of Aquired Imunodeficiency Syndrome
DDM	Dodecylmaltoside
DMP	Data Management Plan
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus

HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IR	immediate release
IRB	Institutional Review Board
IV	intravenous
K_{el}	terminal elimination rate constant
LFT	liver function test
LLN	lower limit of normal
MAOI	monoamine oxidase inhibitor
Max	maximum
MDMA	3,4-methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
NOL	No Objection Letter
ODT	orally disintegrating tablet
OT	oral temperature
OTC	over-the-counter
PCP	phencyclidine
PK	pharmacokinetic(s)
PR	PR interval
PT	prothrombin time
PVG	pharmacovigilance
QA	quality assurance
QC	quality control
QRS	QRS interval of the ECG
QT	QT interval
QTcF	Fridericia's corrected QT interval

QI	Qualified Investigator
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SGC	soft gel capsule
SOP	standard operation procedure
S-STS	Sheehan suicidality tracking scale
SUSAR	suspected, unexpected, serious adverse reaction
$T_{½\ el}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time when the maximal concentration is observed
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBC	white blood cell

SYNOPSIS OF PROTOCOL

Project Number:	Biohaven Pharmaceuticals Holding Company Limited study number: BHV3500-113 Syneos Health Protocol Number: 222025 IND Number: CCI
Title:	A PHASE 1, OPEN-LABEL, RANDOMIZED, 4-PERIOD, 4-WAY CROSSOVER, COMPARATIVE BIOAVAILABILITY STUDY OF ZAVEGEPANT (BHV-3500) ORAL FORMULATIONS UNDER FASTING CONDITIONS
Study Drug:	Zavegepant (BHV-3500) 100 mg non-enteric coated soft gel capsule (SGC), oral administration: Test 1 (Treatment A). Zavegepant (BHV-3500) 100 mg immediate release (IR) tablet + Dodecylmaltoside (DDM) dosage form, oral administration: Test 2 (Treatment B). Zavegepant (BHV-3500) 200 mg IR tablet + DDM dosage form, oral administration: Test 3 (Treatment C). The dose for Treatment C may instead be administered as 2 x 100 mg IR tablets + DDM dosage form for a total zavegepant dose of 200 mg. Zavegepant (BHV-3500) 25 mg enteric coated SGC, oral administration: Reference (Treatment D).
Study Phase and Type:	Phase 1 – Comparative Bioavailability (BA) study
Objective:	The objective of this study is to compare the rate and extent of absorption of zavegepant 100 mg oral non-enteric coated SGC (Test 1), zavegepant 100 mg IR oral tablet + DDM dosage form (Test 2), zavegepant 1 x 200 mg IR oral tablet + DDM dosage form or zavegepant 2 x 100 mg IR tablets + DDM dosage form (Test 3), and zavegepant 4 x 25 mg enteric coated oral SGC (Reference), under fasting conditions.
Study Design:	This will be a Phase 1, single center, open-label, single dose, 4-period, comparative bioavailability study design. The study may be dosed in more than 1 Group. The 4 sequences will be: ACBD, CDAB, BADC, and DBCA.
Study Population:	Approximately 52 healthy male and female subjects, non-smoker (no use of tobacco products within 3 months prior to Screening), ≥ 18 and ≤ 55 years of age, with body mass index (BMI) > 18.5 and < 30.0 kg/m^2 and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females.
Inclusion Criteria:	All of the following criteria must be met in order to be considered for inclusion into the study: 1. Subjects must sign and date IEC/Institutional Review Board (IRB)-approved Informed Consent Form (ICF) obtained prior to the conduct of any study activities. 2. Male or female ≥ 18 and ≤ 55 years of age, non-smoker (no use of tobacco or nicotine products within 3 months prior to Screening), with BMI >18.5 and <30.0 kg/m2 and body weight ≥ 50.0 kg for males and ≥ 45.0 kg for females. 3. Healthy as defined by: a. The absence of clinically significant illness and surgery within 4 weeks prior to dosing. Subjects vomiting within 24 hours pre-dose will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator;

	b. The absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, hematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease in the estimation of the Investigator. 4. Subject's score on the Sheehan Suicidality Tracking Scale (S-STS) at Screening must be 0 (lifetime lookback). 5. Females must not be breastfeeding or lactating. 6. All females must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at Screening. Women of childbearing potential must have negative serum pregnancy test at admission (Day -1). 7. Females of childbearing potential (defined as premenopausal females capable of becoming pregnant [all fertile women]) who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized at least 6 months prior to Screening) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last study drug administration: a. Simultaneous use of non-hormonal intra-uterine contraceptive device placed at least 4 weeks prior to first study drug administration, and condom for the male partner; b. Simultaneous use of hormonal contraceptives, started at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner; c. Simultaneous use of diaphragm or cervical cap with intravaginally applied spermicide and male condom for the male partner, starting at least 21 days prior to the first study drug administration. 8. For females of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to dosing: a. Hysteroscopic sterilization; b. Bilateral tubal ligation or bilateral salpingectomy; c. Hysterectomy; d. Bilateral oophorectomy; e. Or be post-menopausal with spontaneous amenorrhea for at least 12 consecutive months prior to dosing and follicle-stimulating hormone (FSH) serum levels ≥40 mIU/mL consistent with post-menopausal status. 9. Male subjects who are not vasectomized for at least 6 months prior to Screening, and who are sexually active with a female partner of childbearing potential (childbearing potential females are defined as women that are neither post-menopausal nor surgically sterile) must be willing to use one of the following acceptable contraceptive methods from the first study drug administration until at least 90 days after the last study drug administration: a. Simultaneous use of a male condom and, for the female partner, hormonal contraceptives used since at least 4 weeks prior to the first study drug administration or intra-uterine contraceptive device placed since at least 4 weeks prior to the first study drug administration;

	b. Simultaneous use of a male condom with spermicide and, for the female partner, a diaphragm or cervical cap with intravaginally applied spermicide. 10. Male subjects (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from the first dosing and for 90 days after the last study drug administration. 11. Male subjects must be willing not to donate sperm for at least 90 days after the last study drug administration. 12. Subjects must be able to understand the nature of the study, agree to comply with the prescribed dosage regimens, and communicate to study personnel about AEs and concomitant medication use, as applicable.
Exclusion Criteria:	Subjects to whom any of the following applies will be excluded from the study: ***Medical History and Concurrent Diseases*** 1. Current diagnosis of viral hepatitis or a history of liver disease. 2. Any history of seizure disorder (e.g., epilepsy) other than a single childhood febrile seizure. 3. Current or recent (within 3 months of the first study drug administration) gastrointestinal disease that may interfere with drug absorption. 4. Subjects with prior gastrointestinal surgery that interferes with absorption and motility (e.g., gastric bypass, duodenectomy or gastric banding). 5. Use of medication for the timeframes specified below and throughout the study, with the exception of medications exempted by the Investigator on a case-by-case basis if they are judged unlikely to affect the PK profile of the study drug or subject safety, and occasional use of ibuprofen: a. Prescription medication within 30 days or 5 half-lives (whichever is longer) days prior to the first dosing; b. Use of any over-the-counter (OTC) medications including acetaminophen-containing products within at least 14 days or 5 half-lives (whichever is longer) prior to the first dosing except for the occasional use of ibuprofen; c. Use of any natural health products (including herbal remedies such as Butterbur root extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins [ascorbic acid is not allowed], minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 14 days or 5 half-lives (whichever is longer) prior to the first dosing; d. Use of any drug known to induce or inhibit hepatic drug metabolism, including St. John's wort, from 30 days prior to the first dosing until after the last pharmacokinetic (PK) blood sample for the study is obtained; e. A depot injection or an implant of any drug within 3 months prior to the first dosing; f. Small molecule calcitonin gene-related peptide (CGRP) receptor antagonists within 1 month prior to the first dosing; g. Biologic CGRP receptor antagonist within 6 months prior to the first dosing; h. Receipt of any vaccination, including COVID-19 vaccine, within 30 days prior to first dosing.

	i. Monoamine oxidase inhibitors (MAOI) within 30 days prior to the first dosing. 6. History of significant alcohol abuse or regular use within 6 months prior to Screening that exceeds (more than 10 units of alcohol per week for women and 15 units for men [1 unit = 140 mL of wine 12%, 340 mL of beer, or 45 mL of 40% distilled alcohol]). 7. History of drug abuse within 6 months prior to the Screening visit or recreational use of soft drugs (such as marijuana) within 1 month prior to the Screening visit or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year prior to Screening. 8. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant reaction to any drug. 9. History of anaphylactic reaction, a documented hypersensitivity reaction, or a clinically important reaction to any drug, or to any of the excipient supporting the zavegepant formulations. 10. Donation of plasma within 7 days prior to dosing, or donation or loss of blood (excluding volume drawn at Screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to dosing. 11. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the dosing, administration of a biological product in the context of a clinical research study within 90 days prior to the dosing, or concomitant participation in an investigational study involving no drug or device administration. 12. Inability or difficulty to swallow tablets or capsules. 13. Poor venous access and/or inability to tolerate catheter venous access. 14. Any reason which, in the opinion of the Investigator, would prevent the subject from participating in the study. ***Physical and Laboratory Test Findings*** 15. Subjects with any clinically significant abnormality or significant abnormal laboratory test results found during medical screening or Day-1. 16. Subject has a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody during medical screening. 17. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, 12-lead electrocardiogram (ECG), or clinical laboratory determinations beyond what is consistent with the target population. 18. Estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) study equation $\leq$ 60 mL/min/1.73 m^2 at Screening. 19. Any of the following laboratory parameters greater than the upper limit of normal (ULN) values at Screening or Baseline (Day -1): alkaline phosphatase (ALP) aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, and indirect bilirubin, and alkaline phosphatase. Only abnormal values between 1-1.5 x ULN may be repeated once for confirmation to less than the ULN. 20. Any of the following abnormalities on 12-lead ECG or blood pressure (BP) at Screening or Baseline (Day -1):

	a. PR (PR interval) ≥ 210 msec; b. QRS (QRS complex) ≥ 120 msec; c. QT (QT interval) ≥ 500 msec; d. QTcF (Fridericia's corrected QT interval) ≥ 450 msec; e. Sitting (for at least 5 minutes) systolic BP > 140 mmHg, confirmed by repeat; f. Sitting (for at least 5 minutes) diastolic BP > 90 mmHg, confirmed by repeat. 21. Any of the following abnormal laboratory test values at Screening or Baseline (Day -1): a. Hemoglobin < 12.8 g/dL for males and < 11.5 g/dL for females; b. Hematocrit < 37% for males and < 32 % for females; c. Total white blood cells (WBC) < 3.0 x 10^9/L; d. Platelet count <100 x 10^9/L; e. Neutrophils < 1.4 x 10^9/L and < 1.0 x 10^9/L for Afro-American volunteers; f. Creatine phosphokinase (CPK) > 2 x ULN. 22. Positive test for COVID-19 performed on Day -1 of each period. 23. Positive urine drug screen, alcohol breath test, or urine cotinine test at Screening or any Day -1 visit.
Study Treatments:	In each period, each subject will receive one of the following single oral dose of zavegepant (BHV3500) according to the randomization scheme: Treatment A: 1 x zavegepant 100 mg non-enteric coated SGC Treatment B: 1 x zavegepant 100 mg IR tablet + DDM dosage form Treatment C: 1 x zavegepant 200 mg IR tablet (total dose of 200 mg) + DDM dosage form. The dose for Treatment C may instead be administered as 2 x 100 mg IR tablets + DDM dosage form for a total zavegepant dose of 200 mg. Treatment D: 4 x zavegepant 25 mg enteric coated SGC (total dose of 100 mg) In each period, no food will be allowed from at least 10 hours before dosing until at least 4 hours after dosing. Except for 240 mL of water given with study drug administration, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose.
Study Procedures:	Blood samples for PK analysis will be collected and safety procedures will be performed at pre-defined times throughout the study as specified in Table 1. Subjects will be monitored throughout the study by the clinical staff for adverse events (AEs) and concomitant medications.
Statistical Analyses:	**Safety and tolerability:** Safety and tolerability data will be reported using descriptive statistics. Treatment-emergent adverse events (TEAEs) will be summarized descriptively by treatment. Safety and tolerability to treatments will be evaluated through the assessment of AEs (e.g., seriousness, severity, relationship to the study medication, outcome, duration, and management), vital signs, 12-lead ECG, and clinical laboratory parameters. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

	Any finding or absence of finding relative to each subject's baseline physical examination will be documented. Any abnormal finding noted after dosing will be documented as an AE if judged as a clinically significant change from baseline. Changes from baseline values in vital signs, 12-lead ECG, and clinical laboratory parameters will be evaluated. Clinically significant laboratory abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in the latest version of Common Technical Criteria for Adverse Events (CTCAE) if available, otherwise according to the latest version of Division of Aquired Imunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. A complete description of the statistical analyses to be performed on the safety and tolerability data will be presented in the Statistical Analysis Plan (SAP). **Pharmacokinetics (PK):** For zavegepant, using the MIXED procedure in Statistical Analysis System (SAS), with Sequence, Treatment, and Period as fixed effects, and Subject within Sequence as random effect, analysis of variance (ANOVA) will be performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. If the study is dosed in more than 1 Group, the statistical model may be modified to reflect the multi-Group nature. In case of a non-statistically significant Treatment by Group interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. The ratio of geometric means and 90% confidence intervals (A/D), (B/D), and (C/D), based on least-squares means from the ANOVA of the ln-transformed data will be calculated for AUC_{0-inf}, AUC_{0-t}, and C_{max}. Other ratio of geometric means among treatments may be explored. Untransformed T_{max} will be analyzed using the MIXED model with the difference of least-squares means from the ANOVA calculated for (A-D), (B-D), and (C-D). Other differences between treatment least-squares means may be explored. The K_{el}, and $T_{½}$ el will be summarized descriptively. PK data of treatment C will be dose normalized to 100 mg.

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

PROCEDURE	Screening (Day -28 to -2)	Periods 1 to 4			Study Exit or Early Termination[9]
		D-1	D1	D2	
Informed Consent	X				
Demographic Data	X				
Medical and Medication Histories	X				
Confinement		X	X		
Discharge				X	
Study Drug Administration					
Zavegepant [1]			X		
Pharmacokinetics					
Blood samples for PK analysis[2]			X	X	
Safety					
Physical Examination	X	X[3]			X[3]
Body Measurements (weight, height, and BMI)	X				
S-STS	X				X
Vital Signs (BP, HR, RR, OT)[4]	X	X	X		X
12-lead ECG	X	X			X
Serology (HIV and Hepatitis B and C)	X				
COVID-19 Test[5]		X			
Clinical laboratory tests[6]	X	X			X
Drug, cotinine, and alcohol screens	X	X			
FSH (for post-menopausal females)	X[7]				
Pregnancy Tests[8]	X	X			X
Review and Monitoring of AEs and Concomitant Medications	←				→

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; PK = pharmacokinetic; RR = respiratory rate; S-STS = Sheehan suicidality tracking scale; OT = oral temperature.

1. In each period, following a fasting period of at least 10 hours, subjects will receive a single oral dose of either Treatment A, B, C or D, according to the randomization scheme. Subjects will continue fasting for at least 4 hours post-dose. There will be a washout period of at least 7 days between doses.

2. A total of 16 blood samples will be collected for zavegepant concentration analysis: pre-dose (within 1 hour prior to dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose. The time tolerance window for post-dose PK blood samples will be ±1 minute for all samples collected before 8 hours post-dose and ±3 minutes for all samples collected at 8 hours post-dose through 24 hours post-dose.
3. A complete physical examination will be performed at Screening, and a brief physical examination will be performed on Day -1 of each period and at Study Exit or early termination (ET).
4. Vital signs will be measured after the subjects have been resting for at least 5 minutes in a seated position. BP, HR, RR, and OT will be measured at Screening, Day -1 of each period and Study Exit or ET. In each period, BP and HR will be measured within 1 hour before study treatment administration on Day 1 and at 2 ± 0.25 hours post-dose.
5. A COVID-19 PCR test will be performed on Day -1 of each period. If results are not available prior to admission, a COVID-19 rapid test will be performed upon admission. COVID-19 testing may be repeated during the subject's participation at the Investigator's discretion (e.g., if a subject has signs or symptoms suggestive of a COVID-19 infection).
6. Biochemistry, hematology,* and urinalysis will be performed following a fasting period of at least 8 hours at Screening, on Day -1 of each period, and at Study Exit or ET. *Haptoglobin and reticulocyte count will be performed only in the case of a decrease in hemoglobin levels below the lower limit of normal (LLN) on Day -1 of each period and at Study Exit or ET. If the haptoglobin and reticulocyte count results come back normal but the hemoglobin levels results are still abnormal after the repeat, the haptoglobin and reticulocyte count tests may be repeated upon Investigator's judgement. Coagulation tests will be performed only in case of abnormal liver function tests (LFTs) (i.e., ALP, AST, or ALT is >3x ULN) on Day -1 of each period and at Study Exit or ET. If the coagulation test results come back normal but the LFT results are still abnormal after the repeat, the coagulation tests may be repeated upon Investigator's judgement.
7. FSH levels will be measured at Screening to confirm post-menopausal status.
8. For all females, a urine pregnancy test will be performed at Screening. For women of childbearing potential females a urine pregnancy test will be performed at Study Exit or ET and a serum pregnancy test will be performed on Day -1 of each period. Subjects with a positive pregnancy test will not be enrolled or will be discontinued.
9. Study Exit procedures will be performed after the last assessment on the morning of Day 2 of Period 4. In case of ET, Study Exit procedures will be performed as soon as possible.

1 INTRODUCTION

1.1 Background Information

Zavegepant is a selective, high-affinity, small molecule CGRP receptor antagonist in development for the treatment of migraine. CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents and is thought to play a causal role in migraine. Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine; 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief; and 3) intravenous (IV) CGRP infusion produces lasting pain in non-migraineurs and migraineurs. Treatment with a CGRP receptor antagonist is thought to relieve migraine by: 1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal); 2) halting the cascade of CGRP-induced neurogenic inflammation; and/or 3) inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.[1] Efficacy and safety were determined in 2 positive pivotal trials assessing intranasal administration of zavegepant for the acute treatment of migraine. A favorable safety profile was seen during a 1 year open-label safety study with up to 8 doses per month of intranasal zavegepant for the acute treatment of migraine.

A summary of the nonclinical investigational programs can be found in the current Investigator's Brochure (IB).[1]

1.2 Summary of Clinical Experience with Zavegepant

Details regarding the clinical experience with zavegepant can be found in the IB.[1]

1.2.1 BHV3500-103: Comparative Bioavailability Study (Oral Formulations)

BHV3500-103 is a completed Phase 1, open-label, fixed-sequence, 3-period, comparative, bioavailability study of zavegepant administered as a single 50 mg oral soft gelatin capsule or a single 50 mg orally disintegrating tablet (ODT) with or without DDM in healthy subjects. A total of 12 subjects were treated in this study. Overall, all the 3 treatments of a single oral dose of 50-mg zavegepant administered to healthy adult subjects under fasting conditions were well tolerated and exhibited a favorable safety profile.

1.2.2 BHV3500-106: Safety and Tolerability Study (Soft Gelatin Capsule)

Study BHV3500-106 is a concluded Phase 1, multi-center, open-label safety study in which healthy subjects were dosed with zavegepant oral soft gelatin capsules (4 x 25 mg) every day for 8 weeks. A total of 364 subjects received zavegepant in this study. Based on preliminary data: there were no deaths in this study and a total of 13 (3.6%) subjects discontinued the study due to AEs during the on-treatment period.

1.2.3 BHV3500-302: Clinical Safety from Safety and Efficacy Dose-ranging Study for Preventive Treatment of Migraine (Oral Formulation)

BHV3500-302 is an ongoing Phase 3, double-blind, randomized, placebo-controlled, safety and efficacy dose-ranging study of zavegepant administered as an oral soft gelatin capsule for the preventive treatment of migraine.

As of the data cut-off, 17 subjects have been treated with blinded study drug (zavegepant 100 mg soft gelatin capsules: 6; zavegepant 200 mg soft gelatin capsules: 5; placebo for 100 mg: 3; placebo for 200 mg: 3 [estimated based on 2:2:1:1 randomization]). Based on preliminary data: There have been no deaths in this study. One subject experienced 2 serious adverse events (SAEs) (abdominal pain, migraine) during the observation period before receiving any blinded study drug. No subjects discontinued the study due to AEs.

1.3 Rationale for Study Design

CCI [redacted] This study will evaluate the rate and extent of absorption of zavegepant from these new commercially viable 100 mg oral formulations with pharmaceutical acceptability when administered to healthy volunteers. The safety and tolerability of single oral doses of zavegepant will also be assessed in this population.

In accordance with the FDA Guidance on *Bioavailability Studies Submitted in NDAs or INDs*,[2] the current study aims to compare the rate and extent of absorption of zavegepant 100 mg oral non-enteric coated SGC (Test 1), zavegepant 100 mg IR oral tablet + DDM dosage form (Test 2), zavegepant 1 x 200 mg IR oral tablet + DDM dosage form (Test 3) (the dose for Test 3 may instead be administered as 2 x 100 mg IR tablets + DDM dosage form), and zavegepant 4 x 25 mg enteric coated oral SGC (Reference), under fasting conditions.

1.3.1 Dose Selection

Zavegepant will be administered once in each period at a dose of 1 x 100 mg non-enteric coated SGC (Treatment A), 1 x 100 mg IR tablet + DDM dosage form (Treatment B), 1 x 200 mg IR tablet + DDM dosage form (Treatment C) (the dose for Treatment C may instead be administered as 2 x 100 mg IR tablets + DDM dosage form), and 4 x 25 mg enteric coated SGC (Treatment D) for each subject in accordance with the randomization scheme.

1.3.2 Rationale for the Study Population

A healthy volunteer population has been selected for the study because healthy subjects with no concomitant diseases and using no concomitant medications represent a homogenous population allowing for proper evaluation of the PK, safety, and tolerability of a drug without confounding factors.

No evidence of embryo lethality and teratogenicity were found in animal embryofetal development studies in rats and rabbits with zavegepant.[1] Women of childbearing potential must use effective methods of contraception before and during exposure to zavegepant in order to prevent pregnancy. No data are available on the potential in vivo transfer of zavegepant or its metabolites into human breast milk; therefore, lactating women must not receive zavegepant. Therefore, only male and non-pregnant / non-lactating female subjects will be included in the study.

1.4 Benefit/Risk Assessment

The inclusion and exclusion criteria have been chosen to select subjects who are known to be free from any significant illness, history of autoimmune diseases, and from any condition that could impact their safety or interfere with meeting the study objectives. The proposed safety screening and monitoring assessments are deemed to be sufficient to monitor potential risks of zavegepant administration. There is no anticipated therapeutic benefit for the healthy subjects in this study.

2 OBJECTIVES

The objective of this study is to compare the rate and extent of absorption of zavegepant 100 mg oral non-enteric coated SGC (Test 1), zavegepant 100 mg IR oral tablet + DDM dosage form (Test 2), zavegepant 1 x 200 mg IR oral tablet + DDM dosage form or zavegepant 2 x 100 mg IR tablets + DDM dosage form (Test 3), and zavegepant (BHV-3500) 4 x 25 mg enteric coated oral SGC (Reference), under fasting conditions.

3 STUDY DESIGN

This is a Phase 1, single center, open-label, single dose, 4-period, crossover study designed to compare the PK of zavegepant from the Test and Reference products. The study may be dosed in more than 1 Group.

The 4 sequences will be: ACBD, CDAB, BADC, and DBCA.

In each period, subjects will receive one of the following: Treatment A, B, C, or D on Day 1, followed by 24 hours of PK and safety assessments. On Day 2 subjects will be discharged from the unit and instructed to return after at least a 7 day washout time has passed for subsequent periods of treatment.

The study will include a screening visit from Day -28 to Day -2. Eligible subjects will be admitted to the clinical site on Day -1 and will be confined until completion of the assessments on Day 2. There will be a washout period of at least 7 days between doses. Study Exit procedures will be performed after the last assessment on the morning of Day 2 of Period 4. Study Exit procedures will be performed as soon as possible in case of ET.

The total duration of study participation for each subject from Screening through Study Exit is anticipated to be approximately 6.5 weeks.

This study is intended for filing under FDA regulations.

4 STUDY POPULATION

4.1 Number of Subjects

It is planned to enroll approximately 52 subjects for participation in this study. The proposed number of subjects is considered sufficient to achieve the study objectives.

4.2 Inclusion Criteria

All of the following criteria must be met in order to be considered for inclusion into the study:

1. Subjects must sign and date IEC/Institutional Review Board (IRB)-approved ICF obtained prior to the conduct of any study activities.

2. Male or female ≥ 18 and ≤ 55 years of age, non-smoker (no use of tobacco or nicotine products within 3 months prior to Screening), with BMI >18.5 and <30.0 kg/m2 and body weight ≥50.0 kg for males and ≥45.0 kg for females.
3. Healthy as defined by:
    a. The absence of clinically significant illness and surgery within 4 weeks prior to dosing. Subjects vomiting within 24 hours pre-dose will be carefully evaluated for upcoming illness/disease. Inclusion pre-dosing is at the discretion of the Investigator;
    b. The absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, hematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease in the estimation of the Investigator.
4. Subject's score on the S-STS at Screening must be 0 (lifetime lookback).
5. Females must not be breastfeeding or lactating.
6. All females must have a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at Screening. Women of childbearing potential must have negative serum pregnancy test at admission (Day -1).
7. Females of childbearing potential (defined as premenopausal females capable of becoming pregnant [all fertile women]) who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized at least 6 months prior to Screening) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last study drug administration:
    a. Simultaneous use of non-hormonal intra-uterine contraceptive device placed at least 4 weeks prior to first study drug administration, and condom for the male partner;
    b. Simultaneous use of hormonal contraceptives, started at least 4 weeks prior to study drug administration and must agree to use the same hormonal contraceptive throughout the study, and condom for the male partner;
    c. Simultaneous use of diaphragm or cervical cap with intravaginally applied spermicide and male condom for the male partner, starting at least 21 days prior to the first study drug administration.
8. For females of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to dosing:
    a. Hysteroscopic sterilization;
    b. Bilateral tubal ligation or bilateral salpingectomy;
    c. Hysterectomy;
    d. Bilateral oophorectomy;
    e. Or be post-menopausal with spontaneous amenorrhea for at least 12 consecutive months prior to dosing and FSH serum levels ≥40 mIU/mL consistent with post-menopausal status.

9. Male subjects who are not vasectomized for at least 6 months prior to Screening, and who are sexually active with a female partner of childbearing potential (childbearing potential females are defined as women that are neither post-menopausal nor surgically sterile) must be willing to use one of the following acceptable contraceptive methods from the first study drug administration until at least 90 days after the last study drug administration:
    a. Simultaneous use of a male condom and, for the female partner, hormonal contraceptives used since at least 4 weeks prior to the first study drug administration or intra-uterine contraceptive device placed since at least 4 weeks prior to the first study drug administration;
    b. Simultaneous use of a male condom with spermicide and, for the female partner, a diaphragm or cervical cap with intravaginally applied spermicide.
10. Male subjects (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from the first dosing and for 90 days after the last study drug administration.
11. Male subjects must be willing not to donate sperm for at least 90 days after the last study drug administration.
12. Subjects must be able to understand the nature of the study, agree to comply with the prescribed dosage regimens, and communicate to study personnel about AEs and concomitant medication use, as applicable.

4.3 Exclusion Criteria

Subjects to whom any of the following applies will be excluded from the study:

Medical History and Concurrent Diseases

1. Current diagnosis of viral hepatitis or a history of liver disease.
2. Any history of seizure disorder (e.g., epilepsy) other than a single childhood febrile seizure.
3. Current or recent (within 3 months of the first study drug administration) gastrointestinal disease that may interfere with drug absorption.
4. Subjects with prior gastrointestinal surgery that interferes with absorption and motility (e.g., gastric bypass, duodenectomy or gastric banding).
5. Use of medication for the timeframes specified below and throughout the study, with the exception of medications exempted by the Investigator on a case-by-case basis if they are judged unlikely to affect the PK profile of the study drug or subject safety, and occasional use of ibuprofen:
    a. Prescription medication within 30 days or 5 half-lives (whichever is longer) prior to the first dosing;

b. Use of any OTC medications including acetaminophen-containing products within at least 14 days or 5 half-lives (whichever is longer) prior to the first dosing except for the occasional use of ibuprofen;

c. Use of any natural health products (including herbal remedies such as Butterbur root extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins [ascorbic acid is not allowed], minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 14 days or 5 half-lives (whichever is longer) prior to the first dosing;

d. Use of any drug known to induce or inhibit hepatic drug metabolism, including St. John's wort, from 30 days prior to the first dosing until after the last PK blood sample for the study is obtained;

e. A depot injection or an implant of any drug within 3 months prior to the first dosing;

f. Small molecule CGRP receptor antagonists within 1 month prior to the first dosing;

g. Biologic CGRP receptor antagonist within 6 months prior to the first dosing;

h. Receipt of any vaccination, including COVID-19 vaccine, within 30 days prior to first dosing.

i. MAOI within 30 days prior to the first dosing.

6. History of significant alcohol abuse or regular use within 6 months prior to Screening that exceeds (more than 10 units of alcohol per week for women and 15 units for men [1 unit = 140 mL of wine 12%, 340 mL of beer, or 45 mL of 40% distilled alcohol]).

7. History of drug abuse within 6 months prior to the Screening visit or recreational use of soft drugs (such as marijuana) within 1 month prior to the Screening visit or hard drugs (such as cocaine, PCP, crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year prior to Screening.

8. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically significant reaction to any drug.

9. History of anaphylactic reaction, a documented hypersensitivity reaction, or a clinically important reaction to any drug, or to any of the excipient supporting the zavegepant formulations.

10. Donation of plasma within 7 days prior to dosing, or donation or loss of blood (excluding volume drawn at Screening) of 50 mL to 499 mL of blood within 30 days, or more than 499 mL within 56 days prior to dosing.

11. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the dosing, administration of a biological product in the context of a clinical research study within 90 days prior to the dosing, or concomitant participation in an investigational study involving no drug or device administration.

12. Inability or difficulty to swallow tablets or capsules.

13. Poor venous access and/or inability to tolerate catheter venous access.

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

Physical and Laboratory Test Findings

15. Subjects with any clinically significant abnormality or significant abnormal laboratory test results found during medical screening or Day-1.
16. Subject has a positive test for HIV, HBsAg, or HCV antibody during medical screening.
17. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, 12-lead ECG, or clinical laboratory determinations beyond what is consistent with the target population.
18. eGFR according to the MDRD study equation $\leq$ 60 mL/min/1.73 m^2 at Screening.
19. Any of the following laboratory parameters greater than the ULN values at Screening or Baseline (Day -1): ALP, AST, ALT, total bilirubin, direct bilirubin, and indirect bilirubin, and alkaline phosphatase. Only abnormal values between 1-1.5 x ULN may be repeated once for confirmation to less than the ULN.
20. Any of the following abnormalities on 12-lead ECG or BP at Screening or Baseline (Day -1):
    a. PR (PR interval) $\geq$ 210 msec;
    b. QRS (QRS complex) $\geq$ 120 msec;
    c. QT (QT interval) $\geq$ 500 msec;
    d. QTcF (Fridericia's corrected QT interval) $\geq$ 450 msec;
    e. Sitting (for at least 5 minutes) systolic BP > 140 mmHg, confirmed by repeat;
    f. Sitting (for at least 5 minutes) diastolic BP > 90 mmHg, confirmed by repeat.
21. Any of the following abnormal laboratory test values at Screening or Baseline (Day -1):
    a. Hemoglobin < 12.8 g/dL for males and < 11.5 g/dL for females;
    b. Hematocrit < 37% for males and < 32 % for females;
    c. Total white blood cells (WBC) < 3.0 x 10^9/L;
    d. Platelet count <100 x 10^9/L;

e. Neutrophils < 1.4 x 10^9/L and < 1.0 x 10^9/L for Afro-American volunteers;

f. CPK > 2 x ULN;

22. Positive test for COVID-19 performed on Day -1 of each period.

23. Positive urine drug screen, alcohol breath test, or urine cotinine test at Screening or any Day -1 visit.

4.4 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or designee may withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with the clinical site's Standard Operating Procedure (SOP):

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation;
- Positive pregnancy test, drug screen, cotinine test, or alcohol breath test;
- Vomiting within 4 hours post-dose;
- Positive test result for COVID-19 (during any study period).

Clinical laboratory results will be reviewed by the Investigator or designee prior to each dosing and subjects will be withdrawn from the study if it is deemed that the subject's safety may be at risk on the basis of these test results.

Subjects excluded from dosing in one period as per criteria listed above, may be invited to participate in subsequent periods of the study if deemed appropriate by the Investigator and appropriate from a statistical standpoint (i.e., would permit adequate statistical comparison). However, subjects with positive pregnancy test, COVID-19 test, drug screen, cotinine test, or alcohol breath test, will be definitively withdrawn from the study.

Subjects who withdraw prior to dosing may be replaced.

Subjects who withdraw or are withdrawn after study drug administration will be asked to remain at the clinic until the Investigator or designee agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped. A PK blood sample may be collected at the time of withdrawal if deemed required by the Investigator. Study Exit or ET procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

5 STUDY TREATMENTS

5.1 Drug Supplies and Accountability

It is the responsibility of the Sponsor to ensure that study drugs provided for this study are manufactured under Good Manufacturing Practice (GMP) and are suitable for human use. The Sponsor is responsible to ship a sufficient amount of dosage units to allow the clinical site to maintain an appropriate sampling for the study and for drug retention.

The study drugs will be stored at the clinical site as per applicable requirements. Labels will be provided in appropriate languages as required by the country in which the study is conducted. The content of the labeling will be in accordance with local regulatory specifications and requirements. The study drugs will be stored in a locked, environmentally-controlled medication room with restricted access. Container(s) will bear a label containing at least the name of the study drug, lot and/or batch number, and manufacturing and/or expiry/retest date.

Individual doses for each subject and period will be dispensed at the clinical site pharmacy, as per clinical site SOP and according to the randomization scheme, in appropriate envelopes/containers labeled with at least the project number, the period number and the subject number/spare number.

All study drug received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability record according to the relevant clinical site SOP(s). Upon completion of the study, the remaining drug products will be maintained at the clinical site, discarded, or returned to the Sponsor, as per Sponsor's request.

5.2 Identification of Treatments

Treatment A (Test 1): 1 x 100 mg zavegepant non-enteric coated SGC (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.

Treatment B (Test 2): 1 x 100 mg zavegepant IR tablet + DDM dosage form (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.

Treatment C (Test 3): 1 x 200 mg zavegepant IR tablet (total dose of 200 mg) + DDM dosage form. The dose for Treatment C may instead be administered as 2 x 100 mg IR tablets + DDM dosage form for a total zavegepant dose of 200 mg (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.

Treatment D (Reference): 4 x 25 mg zavegepant enteric coated SGC (total dose of 100 mg) (Biohaven Pharmaceuticals Holding Company Limited) administered under fasting conditions.

5.3 Randomization and Blinding

This study will be an open-label study due to the objective nature of the data. Subjects will be administered each treatment according to the 4-period, block randomization scheme produced by Syneos Health. The 4 sequences will be: ACBD, CDAB, BADC, and DBCA. The randomization code will not be available to the bioanalytical facility until the clinical and analytical phases of the study have been completed. Since Treatments B and C includes a DDM dosage form as compared to Treatments A and D, and Treatment D includes 4 capsules, the bioanalytical staff cannot be completely blinded to treatment assignment.

5.4 Study Drug Administration

For all treatments, the zavegepant will be administered to each subject with 240 mL of water and a hand and mouth check will be performed to ensure consumption of the medication. The volume of water may be increased if needed, however, must be documented within the source documentation.

Time of dosing ("0") will be set equal to the time when the first tablet or capsule is administered to the subject. The complete dosing procedure must be completed within 2 minutes.

For each treatment A, B, C, and D no food will be allowed from at least 10 hours before dosing until at least 4 hours post-dose.

Except for water given with study drug administration, no fluids will be allowed from 1 hour before dosing until 1 hour post-dose. Water will be provided *ad libitum* at all other times.

Meals will be standardized and similar in composition between periods.

6 STUDY RESTRICTIONS

6.1 Concomitant Medications

Subjects will be required to avoid receiving any vaccination (including COVID-19 vaccine) and using prescription medications, OTC medications (including acetaminophen-containing products), and natural health products (including herbal remedies such as Butterbur root or extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins [including ascorbic acid], minerals, amino acids, essential fatty acids, and protein supplements used in sports) for the period of time specified in exclusion criterion no. 5 and throughout the study.

No concomitant medications will be allowed during the study, with the exception of hormonal contraceptives, medications required for the medical management of an AE, medications exempted by the Investigator on a case-by-case basis that are judged unlikely to affect the PK profile of the study drugs or subject safety, and occasional use of ibuprofen.

If vaccination is required for any reason, it must first be discussed with and exempted by the Investigator on a case-by-case basis to ensure that it does not compromise the PK profile of the study drug or the subject safety.

All medications taken by subjects after Screening through the last study day will be documented as concomitant medications. Any concomitant medication use, other than the allowed medications stated above, will be reviewed and evaluated on a case-by-case basis by the Investigator to determine if they affect a subject's eligibility or continued participation in the study, or for potential impact on the study results.

6.2 Drugs, Nicotine, and Alcohol

Subjects will be required to abstain from using soft or hard drugs, or any tobacco, or nicotine products from Screening and throughout the study. Consumption of alcohol-based products will be prohibited from 24 hours prior to each admission until after the last PK blood sample collection of each period. A urine drug screen, an alcohol breath test, and a urine cotinine test will be performed at Screening and on Day-1 of each period.

6.3 Diet

In each period, no food will be allowed from at least 10 hours before dosing until at least 4 hours after dosing. Except for water given with study drug administration, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose. Water will be provided *ad libitum* at all other times.

In addition, subjects will be required to abstain from:

- Food or beverages containing grapefruit, starfruit, pomegranate, pineapple or pomelo from 14 days prior to the first study drug administration until the last PK blood sample collection of the study;
- Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to each dosing until after the last PK blood sample collection of each period;
- Food containing poppy seeds from 24 hours prior to each admission.

6.4 Posture and Physical Activity

Subjects will be required to remain seated and avoid lying down or sleeping, unless medically necessary or procedurally required, for 2 hours after study drug administration. Subjects will be allowed to engage in normal activity outside of these requirements.

Because excessive physical activity may increase the level of CPK above the upper normal limit value, subjects will be advised to avoid performing such activity at all times during the study. Vigorous activity will be prohibited at all times during the confinement.

7 STUDY PROCEDURES

Subjects must provide written informed consent prior to initiation of any study procedures.

Unless otherwise specified, study procedures will be conducted in accordance with clinical site SOPs. From Screening through Study Exit, subjects will undergo study procedures at pre-defined times as specified in Table 1 and as described in sections 7.1 and 7.2.

Every effort will be made to schedule and perform the procedures as close to the nominal time as possible, giving considerations to appropriate posture conditions, practical restrictions, and other procedures to be performed at the same time point.

PK blood sample collection will be performed closest to the nominal time. When vital signs measurement or ECG recording coincide with a blood collection, they should preferably be performed before the blood collection, whenever possible.

Study exit procedures will be performed on Day 2 of Period 4 or within 14 days after the last participation of the subject in the study in case of ET.

7.1 Pharmacokinetic Assessments

7.1.1 Pharmacokinetic Blood Sample Collection and Processing

In each period, blood samples for PK analysis will be collected via an intravenous catheter or by direct venipuncture at the time points indicated in Table 1. Applicable time tolerance windows for PK blood samples are defined in Table 2.

Table 2 Time Tolerance Windows for PK Blood Samples

Day	Time point	Time window
1	Pre-dose	Within 1 hour prior dosing
	0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours post-dose	±1 minute
1	8, 10, 12, and 16 hours post-dose	±3 minutes
2	24 hours post-dose	±3 minutes

Sample collections done outside the pre-defined time windows will not be considered as protocol deviations since actual post-dose sampling times will be used for PK and statistical analyses.

The planned volume of blood to be collected for this study, including that collected for eligibility and safety purposes, should not exceed 300 mL. Additional tests or blood draws could be performed, if deemed required by the Investigator or study staff.

Procedures for collection, and processing, of PK blood samples will be detailed in a separate document.

Plasma concentrations of the study drug will be determined using a validated analytical method. Details of the analytical method will be provided in a separate document.

7.2 Safety and Tolerability Assessments

Subjects will be monitored throughout the study by the clinical staff for AEs. The Investigator or designee will be on site for drug administration and until 4 hours post-dose, and available on call for the remainder of the study. If necessary, the Investigator or designee at the clinical site or a healthcare professional in a nearby hospital will administer treatment for any AE(s). A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

Safety parameters, including laboratory results and ECG, will be assessed by the Investigator or designee, using the clinical site acceptance ranges as suggested guidelines in making the medical assessment.

For eligibility purposes, abnormal vital signs measurements or clinical laboratory test results may be repeated once if an abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside of the prescribed screening window, outdated Screening procedures can be repeated.

Safety assessments scheduled during the study will be repeated according to the clinical site SOPs or upon request from the Investigator or designee. Any abnormal repeated measurement

will be evaluated and repeated, if judged necessary. Further action may be taken upon the Investigator or designee's request.

7.2.1 Physical Examination

Physical examinations will be performed at the times specified in Table 1.

A complete physical examination will include assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

A brief physical examination will include assessments of the following: HEENT, chest, lungs, abdomen, dermatological, cardiovascular/peripheral vascular, and areas of note elicited from the subject.

7.2.2 Body Measurements

Body measurements will be performed at Screening and will include body weight and height measurements, as well as BMI calculation.

7.2.3 Sheehan Suicidality Tracking Scale

The S-STS is a prospective rating scale to track both treatment-emergent suicidal ideation and behaviors.[3,4]

The scale will be administered at the times specified in Table 1 by a member of the medical team, completed on site, and will be in paper. The source document will be provided by the Sponsor. If the Investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. In such case, the subject will not be eligible to participate in the study. If determined at the Study Exit or ET procedures, the event should be recorded as either an AE or a SAE as determined by the Investigator and reported within 24 hours to the Sponsor.

7.2.4 Vital Signs

BP, HR, RR, and OT will be measured after the subjects have been resting for at least 5 minutes in a sitting position at Screening, Day -1 and Study Exit or ET. BP and HR will be measured within 1 hour before study treatment administration and at 2 ± 0.25 hours post-dose, having rested in a seated position for at least 5 minutes.

7.2.5 12-lead ECG

Standard 12-lead ECG will be recorded after the subjects have been resting for at least 5 minutes in a semi-recumbent or supine position at Screening, Day -1 of each period and Study Exit or ET.

7.2.6 Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the clinical site SOPs at the times specified in Table 1. The clinical laboratory assessments to be performed are listed in Table 3.

Table 3 Laboratory Assessments

Biochemistry	Hematology	Urinalysis
Albumin ALP ALT AST Calcium Chloride CPK Creatinine eGFR (calculated using the MDRD equation) GGT Glucose Phosphorus Potassium Sodium Total, direct and indirect bilirubin[1] Total protein Urea (BUN)	Haptoglobin[2] Hematocrit Hemoglobin[2] Platelet count RBC count Reticulocyte[2] WBC count and differential: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Bilirubin Blood (occult) Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (in the event of abnormal findings including urobilinogen)
	Coagulation[3]	**COVID-19[4]**
	aPTT PT INR	COVID-19 test
Serology	**Drug, cotinine, and alcohol screens**	**Hormone panel - females only**
HBsAg HCV antibody HIV antigen/antibody	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine MDMA Methadone Opiates PCP THC Urine cotinine test Alcohol breath test	FSH (post-menopausal females only) Serum pregnancy test Urine pregnancy test

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MDMA = 3,4- methylenedioxymethamphetamine; MDRD = Modification of Diet in Renal Disease; PCP = phencyclidine; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; THC = tetrahydrocannabinol; WBC = white blood cell.

1. Considering that indirect bilirubin is calculated from total and direct bilirubin values, indirect bilirubin result would not be available in case of direct bilirubin below the limit of quantification.
2. Haptoglobin and reticulocyte count will be performed only in case of decrease in hemoglobin levels below the LLN on Day -1 of each period and at Study Exit. If the haptoglobin and reticulocyte count results come back normal but the hemoglobin levels results are still abnormal after the repeat, the haptoglobin and reticulocyte count tests may be repeated upon Investigator's judgement.
3. Coagulation tests will be performed only in case of abnormal LFTs (i.e., ALP, AST, or ALT is >3x ULN) on Day -1 of each period and at Study Exit. If the coagulation test results come back normal but the LFT results are still abnormal after the repeat, the coagulation tests may be repeated upon Investigator's judgement.
4. A COVID-19 PCR test will be performed on Day -1 in each period. If results are not available prior to admission, a COVID-19 rapid test will be performed upon admission. COVID-19 testing may be repeated during the subject's participation at the Investigator's discretion (e.g., if a subject has signs or symptoms suggestive of a COVID-19 infection).

7.3 Adverse Events

7.3.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.3.2 Recording of Adverse Events

AEs will be recorded and evaluated for their seriousness, severity, and relationship to the study drug. AEs will be collected and documented from the time of signing the ICF and throughout the study. AEs will be followed-up until complete resolution, or until the Investigator or designee judges safe to discontinue follow-up. The severity of AEs and relationship to the study drug will be classified according to the sections below.

7.3.3 Assessment of Severity

The severity of non-serious AEs and serious AEs will be described and documented using the following definitions in Table 4:

Table 4 Description of Severity of Adverse Events

Severity	Description
Mild	Awareness of signs and symptoms, but are easily tolerated; are of minor irritant type; causing no limitations of usual activities. Signs or symptoms may require minor action.
Moderate	Discomfort severe enough to cause some limitations of usual activities and may require action.
Severe	Incapacitating with inability to carry out usual activities or significantly affects clinical status, and requires specific action and/or medical attention.

An event is defined as 'Serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

7.3.4 Assessment of Relationship to Study Drug

Each AE must be classified based on medical judgement and according to the following relationship categories: probable, possible, remote, and unrelated. The definitions for the relationship categories are as follows:

- **PROBABLY RELATED** (must have first three points)**:** This category applies to AEs that are considered, with a high degree of certainty, to be related to the investigational product. An AE may be considered probable, if:

  1) It follows a reasonable temporal sequence from the administration of the drug.

  2) It cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors or other modes of therapy administered to the participant.

  3) It disappears or decreases on cessation or reduction in dose (there are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias).

  4) It follows a known pattern of response to the suspected drug.

  5) It reappears upon re-challenge.

- **POSSIBLY RELATED** (must have first two points)**:** This category applies to AEs in which the connection with the investigational product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when:

  1) It follows a reasonable temporal sequence from the administration of the drug.

  2) It may have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant.

3) It follows a known pattern of response to the suspected drug.

- **REMOTELY RELATED** (must have first two points)**:** In general, this category is applicable to an AE that meets the following criteria:

  1) It does not follow a reasonable temporal sequence from the administration of the investigational product.

  2) It may readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant.

  3) It does not follow a known pattern of response to the suspected drug.

  4) It does not reappear or worsen when the investigational product is re-administered.

- **UNRELATED (NOT RELATED):** This category is applicable to AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.), and do not meet the criteria for medication relationship listed under remote, possible, or probable.

Determination of the relationship of non-serious AEs to the study drug:

	Probably related	**Possibly related**	**Remotely related**	**Unrelated (not related)**
Clearly due to extraneous causes	–	–	–	+
Reasonable temporal association with drug administration	+	+	–	–
May be produced by participant clinical state, etc.	–	+	+	+
Known response pattern to suspected drug	+	+	–	–
Disappears or decreases on cessation or reduction of the dose	+	–	–	–
Reappears on re-challenge	+	–	–	–

Serious AEs will be determined to be "Related" or "Unrelated" to study drug by the Qualified Investigator (QI) and reported on the SAE reporting forms.

7.3.5 Definition of Serious Adverse Event

A SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death;

- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect, or;
- Is otherwise considered to be an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Medical and scientific judgement should be exercised in deciding whether an event should be considered as an Important Medical Event. Examples of such medical events include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home;
    - Blood dyscrasias or convulsions that do not result in hospitalization;
    - Development of drug dependency or drug abuse.

7.3.5.1 Definition of Terms

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

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

In general, hospitalization signifies that the participant 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.

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

7.3.6 Reporting of Adverse Events

7.3.6.1 Serious Adverse Event Reporting to the Sponsor

Any SAE will be reported to the Sponsor (or representative) within 24 hours of learning of the event, and then a written report will be completed and provided as soon as possible, but no later than 7 calendar days of first knowledge of the event.

The notification to the sponsor should be directed to:

PPD

Biohaven Pharmaceuticals Holding Company Limited
PPD

7.3.6.2 Serious Adverse Event Reporting to Sponsor's Pharmacovigilance (PVG) Vendor

Any SAE must be reported (using the SAE reporting forms) immediately or no later than 24 hours after awareness of the event to both the Sponsor and 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), within 24 hours after awareness of the event:

24 Hour Safety Hotline 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:

24 Hour Safety Hotline Phone: +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 investigational product or if new information becomes available, a follow-up SAE report should be sent within 24 hours of the QI 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: (Investigator name)
- Participant identification: (participant number)
- Protocol Identifier: BHV3500-113
- SAE term: (if an SAE is being reported)

For all SAEs, the QI must provide the following:

- Appropriate and requested follow-up information in the time frame detailed above
- Causality of the serious event(s)
- Action taken with the investigational product (e.g., increased, reduced, unchanged, permanently discontinued, interrupted)
- Treatment of/intervention for the SAE(s)
- Outcome of the serious event(s)
- Medical records and laboratory/diagnostic information

The QI will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

7.3.6.3 Serious Adverse Event Reporting to the IEC and Regulatory Agency(ies)

It is the responsibility of the clinical site to report suspected, unexpected, serious adverse reactions (SUSARs) to the IEC responsible for the study per their policies. Report of fatal or life-threatening SUSARs must be made as soon as possible, but no later than 7 calendar days after first knowledge of the event. Report of SUSARs that are neither fatal nor life-threatening must be made as soon as possible, but no later than 15 calendar days after first knowledge of the event.

The Sponsor (or PVG representative) is responsible for notifying the regulatory agency(ies) of SUSARs observed during the study conduct per their regulations, as soon as possible but no later than 7 calendar days after becoming aware of the information when fatal or life-threatening, or 15 calendar days when neither fatal nor life-threatening. The Sponsor (or representative) is responsible to comply with any other applicable regulatory requirement(s) related to the reporting of SAE to other regulatory authority(ies).

7.4 Pregnancy

If a female participant or a female partner of a male participant in the study becomes pregnant during the study, the Investigator must report the pregnancy to the Sponsor and the Sponsor's PVG vendor. The pregnancy should be reported using the paper Pregnancy Form, which should be faxed to PPD PVG by facsimile (fax), within 24 hours after Investigator/site awareness of the event (see Section 7.3.6.2 for fax number). If the form cannot be faxed it should be reported via phone to the PPD Safety Hotline as described above in Section 7.3.6.3. Once the paper form is available, the data must be reported per standard procedures.

A participant becoming pregnant while on study drug will immediately be withdrawn from the study and ET study procedures will be performed.

The participant or female pregnant partner of a male participant should be followed by the Investigator (after obtaining the consent of the female partner, when applicable) until completion of the pregnancy. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must also be reported to PPD on a Pregnancy Follow-up Report Form. If the pregnancy ends for any reason before the anticipated delivery date, the Investigator should notify the Sponsor and PPD.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE as described in Section 7.3.6.3.

7.5 Premature Termination of the Study

The study may be prematurely terminated by the Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Investigator will promptly inform the active study subjects and the IEC/IRB responsible for this trial, stating the reasons for discontinuation of the study. It is the responsibility of the Sponsor (or representative) to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

8 STATISTICAL ANALYSES

A complete description of the statistical analyses to be performed on PK as well as safety and tolerability data will be presented in a SAP.

8.1 Determination of Sample Size

CCI [redacted] Thus, assuming a CV of 40%, and under the scenario of test vs. reference ratio of geometric means of 1.0, the width of the 90% CI for the ratio of geometric means is expected to approximately be 0.25 with 52 subjects. The expected width of the 90% CI for the ratio of geometric means will slightly decrease/increase from 0.25 as the ratio of geometrics means decrease/increase from 1.0.

8.2 Analysis Populations

8.2.1 Safety Population

The safety population is defined as all subjects who receive at least one dose of any study drug.

8.2.2 Pharmacokinetic Population

The PK population will include all subjects from the safety population who receive at least one dose of zavegepant, and for whom the PK profile can be adequately characterized.

8.2.3 Pharmacokinetic Statistical Population

The PK statistical population will include all subjects from the PK population who complete at least one period of treatment for at least one PK parameter and who have not experienced any protocol deviations or other circumstances to exclude the subject from the PK statistical analysis.

A subject with pre-dose concentrations may be excluded from descriptive statistics and ANOVA if the pre-dose concentration is greater than 5% of the C_{max} value for that subject.

A subject may be excluded from the descriptive statistics and ANOVA if the subject has experienced emesis within 2 times median T_{max} for a given treatment.

8.3 Pharmacokinetic Parameters

The following PK parameters will be calculated based on the PK population by standard non-compartmental methods for zavegepant.

- AUC_{0-t}: Area under the concentration-time curve from time zero until the last observed concentration
- AUC_{0-inf}: Area under the concentration-time curve from time zero to infinity (extrapolated)
- Residual area: Percentage of AUC_{0-inf} due to extrapolation from the time of the last observed concentration to infinity, calculated as $[1 – (AUC_{0-t}/AUC_{0-inf})] \times 100$
- C_{max}: Maximal observed concentration
- T_{max}: Time when the maximal concentration is observed
- $T_{½\ el}$: Terminal elimination half-life
- K_{el}: Terminal elimination rate constant
- Cl/F: Apparent clearance
- V_z/F: Apparent volume of distribution

PK of Treatment C will be normalized to a dose of 100 mg.

Additional PK parameters may be calculated.

8.4 Pharmacokinetic Statistical Analysis

Statistical analysis described in this section will be based on the PK statistical population.

Individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation

[SD], CV%, minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented as well for the PK parameters.

For zavegepant, using the MIXED procedure in SAS, with Sequence, Treatment, and Period as fixed effects, and Subject within Sequence as random effect, ANOVA will be performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. No adjustments will be made to alpha for multiple pairwise comparisons. If the study is dosed in more than 1 Group, the statistical model may be modified to reflect the multi-Group nature. In case of a non-statistically significant Treatment by Group interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. The ratio of geometric means and 90% confidence intervals (A/D), (B/D), and (C/D) based on least-squares means from the ANOVA of the ln-transformed data will be calculated for AUC_{0-inf}, AUC_{0-t}, and C_{max}. Other ratio of gemometric means among treatments may be explored. Untransformed T_{max} will be analyzed using the MIXED model with the difference of least-squares means from the ANOVA calculated for (A-D), (B-D), and (C-D). Other differences of least-square means between treatments may be explored. The K_{el}, and $T_{½\ el}$ will be summarized descriptively.

If the study is dosed in more than one Group the following terms will be included in the model: Group, Sequence, Sequence by Group, Period within Group, Treatment, and Treatment by Group. A random effect of Subject within Sequence by Group will also be included. If the term of Treatment by Group is found to be not statistically significant (i.e., $p > 0.05$), then the Treatment by Group term specified in the previous model would be removed from the model to calculate the ratio and 90% CI for each AUC parameter specified above and C_{max}, as applicable.

Additional PK statistical analysis may be performed.

8.5 Safety and Tolerability Analysis

Demographic parameters will be summarized descriptively. TEAEs will be summarized descriptively by treatment. Safety and tolerability analysis will be performed for all subjects in the safety population. No inferential statistical analysis of safety data is planned.

Safety and tolerability to treatments will be evaluated through the assessment of AEs (e.g., seriousness, severity, relationship to the study medication, outcome, duration, and management), vital signs, 12-lead ECG, and clinical laboratory parameters. AEs will be coded using the latest version of the MedDRA.

Any finding or absence of finding relative to each subject's baseline physical examination will be documented. Any abnormal finding noted after dosing will be documented as an AE if judged as a clinically significant change from baseline.

Changes from baseline values in vital signs, ECG, and clinical laboratory parameters will be evaluated. Clinically significant laboratory abnormalities will be identified as Grade 3 to 4 laboratory test results graded according to numeric laboratory test criteria in the latest version of CTCAE if available, otherwise according to the latest version of DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version.

Additional safety and tolerability data analysis may be performed.

9 DATA COLLECTION

The electronic source data capture system is the primary data collection instrument for the study. Collection screen in the electronic source data capture system will be utilized for the collection of all data. Data will be entered using the English language and should be kept current to enable the monitor to review the subjects' status throughout the course of the study. The case report forms (CRFs) will automatically be populated using the electronic source data capture system.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Source documents will be maintained in order to maintain data integrity. The Investigator and/or the clinical staff have the responsibility of ensuring the accuracy, completeness, legibility, and timeliness of the source data.

Details on the data management process will be described in a Data Management Plan (DMP).

10 REGULATORY CONSIDERATIONS AND QUALITY ASSURANCE

10.1 IEC/IRB Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the IEC/IRB 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 IEC/IRB favorable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the clinical site and a copy will be given to the subject.

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

The 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 Compliance

This study will be conducted in compliance with the protocol, GCP, all applicable regulations, and any IEC/IRB 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. As required by the Canadian regulatory agency, a Clinical Trial Application will be submitted before the beginning of the study and a No Objection Letter must be received prior to dosing.

10.3 Quality Assurance and Monitoring

The Sponsor or its designee will perform the quality assurance (QA) and quality control (QC) activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data. When applicable, QA procedures will be performed according to the site SOPs.

The study will be monitored according to the site monitoring plan and SOP to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The Sponsor may arrange audits as part of the implementation of QA to ensure that the study is being conducted in compliance with the protocol, SOPs, GCP, and all applicable regulatory requirements. In such case, audits will be independent of and separate from the routine monitoring and QC functions.

10.4 Confidentiality and Retention of Study Records

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a subject obtained during the conduct of the study will be kept confidential. Subjects will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor's authorized representatives, monitor(s), auditor(s), IEC/IRB, and regulatory authority(ies) will be granted direct access to the subject's original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. Consent from the subject for disclosure of such information will be obtained in writing in the ICF. In addition, should a subject require medical care or hospitalization during the course of the study, the clinical site may contact the treating physician with the subject's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the subject's identity will remain confidential.

The clinical site will maintain adequate study records according to applicable regulatory requirements. The Sponsor will be notified prior to the destruction of study records.

11 REFERENCES

1. Zavegepant (BHV-3500). Investigator Brochure. Biohaven Pharmaceuticals Inc. Version 5.0, Dated 23-Nov-2021.
2. Center for Drug Evaluation and Research (CDER), FDA. Draft Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA. April 2022.
3. Sheehan, D.V., et al. Comparative Validation of the S-STS, the ISST-Plus, and the C SSRS for Assessing the Suicidal Thinking and Behavior FDA 2012 Suicidality Categories. Innov Clin Neurosci, 2014. 11(9-10):32-46.
4. Sheehan, D.V., J.M. Giddens, and I.S. Sheehan. Status Update on the Sheehan Suicidality Tracking Scale (S-STS), 2014. Innov Clin Neurosci, 2014. 11(9-10):93-140.