PROTOCOL

Project No.:	Biohaven study number: BHV4157-Open, under IND 137551
Title:	An Open Trial of BHV-4157 in Adult Subjects with Cerebellar Ataxia
Objectives:	a) Primary Objectives • To assess the efficacy of BHV-4157 (140 mg orally once daily) on ataxia symptoms in subjects with Cerebellar Ataxia after 12 weeks of treatment as measured by the total score on the Scale for the Assessment and Rating of Ataxia [SARA] b) Secondary Objectives • To assess of the safety and tolerability of BHV-4157 in subjects with Cerebellar Ataxia; including safety measures-- Beck Depression Inventory(BDI), Beck Anxiety Inventory (BAI), and Sheehan Suicidality Tracking Scale Sheehan (STS). • To assess the efficacy of BHV-4157 on the 8- meter Timed Walk test c) Exploratory Objectives • To assess the efficacy of BHV-4157 on *non- ataxia* symptoms in subjects with Cerebellar Ataxia after 12 weeks of treatment, via assessment on the INAS • To assess the efficacy of BHV-4157 on the 9- hole peg test • To assess the efficacy of BHV-4157 on health outcome assessment, EQ-5D • To assess the efficacy of BHV-4157 on patient impression via use of the PGIC • To assess the efficacy of BHV-4157 on clinician impression via use of the CGIC • In the subgroup with SCA3/dizziness-predominant, to add preliminary assessments on effects of BHV-4157 on selected patient reported measures of dizziness and its impact on quality of life. There are 4 that have been used in most studies of dizziness/vertigo posted on ClinicalTrials.gov. 1. Vertigo Symptom Scale 15 item short form. 2. Dizziness Handicap Inventory (© AMA) 3. Vestibular Disorders ADL Scale (© AMA) 4. Activities-specific Balance Confidence Scale

Study Rationale:	BHV-4157 is a glutamate modulating drug that is being developed for eventual commercial use in the treatment of spinocerebellar ataxia (SCA). There is a current Phase IIb/3, double-blind, placebo-controlled study being performed in 140 ambulatory patients with SCA 1, 2, 3, 6, 7, 8, and 10 (ClinicalTrials.gov Identifier**:** NCT0296089; IND/FDA Orphan Designation 16-5200; Compassionate IND for this proposed study—pending). There is currently no approved medication indicated for SCA. BHV-4157 is a novel tripeptide prodrug of the glutamate modulating agent riluzole. While BHV-4157 has yet to be fully studied in clinical populations, studies with riluzole in populations with ataxia provide support for the therapeutic potential of BHV-4157. Relevant pharmacologic activities of riluzole, such as increasing glutamate transporters (Cvetanovic et al. 2015; Custer et al. 2006) or potential activation of small-conductance calcium-activated potassium channels (Shakkottai et al. 2011) prompted clinical testing. Two well-designed clinical trials (Ristori et al. 2010) and (Romano et al. 2015) demonstrated preliminary safety and robust efficacy of riluzole 50 mg twice a day in patients with SCA. Since BHV-4157 is a prodrug of riluzole, it is expected to have similar therapeutic potential in SCA. BHV-4157 was developed to advance upon the limitations of riluzole that have restricted its broader clinical application. Riluzole tablets have 60% bioavailability, attributed to high first-pass metabolism in the liver. This is thought to be related to metabolism by the heterogeneously expressed CYP1A2 enzyme, which also contributes to the high PK variability associated with riluzole (Greonveld et al. 2001; Sanderink et al. 1997; Martinet et al. 1997). In addition, riluzole is associated with reduced exposure when taken with meals (i.e., a negative food effect), resulting in the guideline to take riluzole within a three hour fasting window (one hour before or two hours after a meal). Riluzole is also dosed twice a day, has dose-dependent effects on liver function tests, and the drug substance itself has other intrinsic limitations including: very low solubility in water, poor oral palatability, pH dependent chemical stability, and intense oral numbness if administered directly to the oral mucosa. In an effort to mitigate the aforementioned limitations of riluzole, several classes of prodrugs were designed, synthesized, and evaluated in multiple in vitro stability assays to predict in vivo drug levels (McDonnell et al. 2012). BHV-4157 is a third generation of prodrug development representing multiple years of chemistry effort with optimized in vivo and in vitro features based on stability while transiting the digestive system, enhanced gastrointestinal absorption, avoidance of first pass metabolism, favorable safety pharmacology, metabolic cleavage in the plasma, enhanced pharmacokinetic properties, and good oral palatability. Based on the preclinical features of BHV-4157, we anticipate the clinical pharmacology to offer favourable properties as compared to commercially available riluzole: • BHV-4157 is expected to have better oral bioavailability; • BHV-4157 is designed to release riluzole after bypassing first-pass metabolism and thus lowers the overall drug burden to the liver, which may translate into a better safety and tolerability profile, and reduces pharmacokinetic variability.

	• BHV-4157 is expected to allow for once daily dosing, thus improving regimen compliance; • BHV-4157 is expected to be readily absorbed in both the fasting and fed states; thus, the prodrug is not anticipated to require any special meal restrictions. In contrast, oral riluzole tablets require a 3-hour window of fasting around the two daily doses. • BHV-4157 will ultimately be formulated as an orally dispersible tablet (Zydis). This formulation will be amenable to patients who have difficulty swallowing. BHV-4157 is expected to have good oral tolerability and palatability when administered sublingually.
Study Design:	BHV4157-Open is a single center, open study designed to assess safety, tolerability, and efficacy signals in a population of subjects with Cerebellar Ataxia. Subjects will receive oral BHV-4157 (140 mg QD). Dosing will continue for 12 weeks, with subjects being seen every 4 weeks. Subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit. Subjects will be offered an additional 36 weeks of extension treatment (as allowed by the FDA) as long as the PI believes the extension treatment offers an acceptable risk-benefit profile. Subjects entering the Compassionate Extension Phase will undergo visits every 12 weeks up to Week 48. All subjects will undergo a termination visit two weeks after the last dose of study drug.
Subjects:	Up to 24 male and female outpatient subjects between the ages of 18 – 75, inclusive, with a known or suspected diagnosis of the following specific ataxias: SCA3/dizziness predominant (up to 4 subjects); SCA1, SCA2, SCA3, or SCA6 already taking Riluzole for more than 8 weeks (up to 4 subjects, who will directly switch to BHV4157 at Baseline visit); non-genetic pure cerebellar ataxia (up to 4 subjects); MSA-C (up to 12 subjects).

Inclusion criteria:	**1. Informed Consent** a. Subjects (or legally acceptable representative as required by the IRB/IEC) must provide a written signed informed consent form/forms (IRB/EC specific) prior to the initiation of any protocol required procedures. **2. Age and Sex** a. Male and female outpatient subjects between the ages of 18 - 75, inclusive **3. Target Populations** a. **Subjects with (1) a known or suspected diagnosis of a specific hereditary ataxia: SCA3/dizziness-predominant or SCA1, SCA2, SCA3, SCA6, already taking Riluzole for more than 8 weeks; (2) other genetic or non-genetic pure cerebellar ataxia; (3) MSA-C:** i. SCA subjects should have confirmed genotypic diagnosis from a CLIA-certified lab or a family member that has had such testing. ii. Alternatively, subjects must be willing to undergo genetic testing from a CLIA-certified lab if testing

	has not been previously done on the study subject and a copy of results is not available for verification. b. Ability to ambulate 8 meters without assistance (canes and other devices allowed); c. Determined by the investigator to be medically stable at Baseline/randomization as assessed by medical history, physical examination, laboratory test results, and electrocardiogram testing. Subjects must be physically able and expected to complete the trial as designed; d. Minimum of 6 years of education; e. Subjects must have adequate hearing, vision, and language skills to perform interviews as specified in the protocol; f. Subjects must be able to understand and agree to comply with the prescribed dosage regimens and procedures; report for regularly scheduled office visits; and reliably communicate with study personnel about adverse events and concomitant medications; g. Women of childbearing potential (WOCBP) and men must be using an acceptable method of contraception to avoid pregnancy throughout the study and for up to 30 day after the last dose of investigational product in such a manner that risk of pregnancy is minimized. The requisite drug interaction studies to determine the interaction of BHV-4157 with oral contraceptives have not been performed to date. It is therefore not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP who participation this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited. It is required that all WOCBP use two methods of contraception for the duration of the study (i.e. beginning at first treatment to 30 days **after** the last dose of study drug).The two methods should include one barrier method (ex. condom with spermicidal gel, intrauterine devices, cervical cap etc.) and one other method. The other method could include oral contraceptives or another barrier method. h. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test within 72 hours prior to first dosing. **i. SCA subjects (SCA3/dizziness predominant; SCA1, 2, 3, 6 on Riluzole for more than 8 weeks) will not be limited to Inclusion Criteria of Screening SARA score ≥8 or Score of ≥ 2 on gait subsection of the SARA.**
Exclusion criteria:	**1. Target Disease Exceptions** a. Any medical condition other than one of the hereditary ataxias specified in the inclusion criteria that could predominantly explain or contribute significantly to the subjects' symptoms of ataxia (for example, alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, paraneoplastic disease, head injury, idiopathic late onset ataxia, multisystem atrophy) or that can confound assessment of ataxia symptoms (for example, stroke, arthritis); b. MMSE score < 24; c. Subjects with prominent spasticity or dystonia that meet

	either of the following criteria: i. In the opinion of the investigator will compromise the ability of the SARA instrument to assess underlying ataxia severity; or, ii. Are associated on the INAS instrument at screening with moderate or severe scores on dystonia (at least 3 of 5 items) or spasticity (at least 2 of 3 items) or rigidity (at least 2 of 3 items) d. SARA total score of > 30 points at screening; e. Subjects may not have started physical or occupational therapy within one month of screening and are not expected to start such therapy during the randomization phase. Subjects with ongoing occupational or physical therapy may be allowed to continue as long as the intensity remains unchanged from two months prior to screening throughout the randomization period. **2. Medical History Exclusions** a. Clinical history of stroke. Note: Subjects with a history of transient ischemic attack (TIA) may be enrolled, if it occurred at least 3 months prior to screening and the subject is prescribed appropriate treatment [e.g., platelet aggregation inhibitors]; b. Immunocompromised subjects. Note: Subjects taking a systemic immunosuppressive agent may be randomized only if they are on a stable dose, have no clinically relevant immunosuppression, and have a white blood count (WBC) within normal limits; c. Active liver disease or a history of hepatic intolerance to medications that in the investigator's judgment, is medically significant; d. History of medically significant gastrointestinal (GI) illnesses including: i. A current diagnosis of active, peptic ulceration or gastrointestinal bleeding within the last 6 months and/or chronic inflammatory bowel disease at screening; ii. A history of any gastrointestinal surgery that impacts the absorption of study drug; iii. Chronic or frequent episodes of loose stools; bowel movements; e. Vitamin B12 or folate deficiency Note: Subjects with a B12 deficiency can participate in the study if they are on stable Vitamin B12 replacement for at least 3 months prior to randomization and their B12 levels are within normal limits prior to randomization; f. Hematologic or solid malignancy diagnosis within 5 years prior to screening. (Note: Subjects with a history of localized skin cancer, basal cell or squamous cell carcinoma, may be enrolled in the study as long as they are cancer free prior to randomization. Subjects with other localized cancers (without metastatic spread) who have previously completed their course of treatment more than 2 years prior to baseline, are not currently receiving treatment and have been in remission may be enrolled only if, in the opinion of the investigator, there is no expectation for recurrence or further cancer

	treatment during the study period. Antihormonal therapy (e.g., tamoxifen) is allowed if the subject's cancer is in remission and the subject is on maintenance therapy to reduce their risk of recurrence; g. Any unstable cardiovascular (includes uncontrolled hypertension), pulmonary, gastrointestinal, or hepatic disease 30 days prior to screening; h. End-stage cardiovascular disease (e.g., Congestive Heart Failure New York Heart Association/CHF NYHA Class III or IV or unstable angina); i. Treated for, or have had a lifetime diagnosis of, schizophrenia or bipolar disorder; j. Active major depressive episode within the past 6 months. Note: Subjects on a stable maintenance dose of a non-tricyclic, non-monoamine oxidase inhibitor (MAOI) antidepressant medication (e.g., serotonin reuptake inhibitor, bupropion) with symptoms in remission may be eligible; k. History of neurosyphilis (as indicated by a positive rapid plasma reagin [RPR] test and a positive confirmatory test); l. History of drug or alcohol abuse within 12 months as defined by DSM-IV-TR-TR criteria; m. History or evidence of any medical, neurological or psychological condition that would expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety and efficacy during the course of the trial as determined by the clinical judgment of the investigator; n. History of chronic pulmonary disease or chronic pulmonary symptoms. **3. Physical and Laboratory Test Findings** a. Uncontrolled hypertension at screening (e.g., repeated diastolic measurements ≥ 96 mmHg); b. Diagnosis of hypothyroidism by a screening thyroid stimulating hormone (TSH) value > the upper limit of normal (ULN) and free thyroxine (T4) index < the lower limit of normal (Note: Subjects with history of hypothyroidism may participate in the study, provided they are euthyroid on stable thyroid replacement therapy for at least 3 months prior to screening, and therapy is expected to remain stable during the course of the study; c. Hepatic test abnormalities at screening: i. Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or GGT > 2 times the upper limit of normal; or ii. Total bilirubin > 2 times the upper limit of normal (ULN); d. P-Amylase or Lipase values greater than 2 times the upper limit of normal at screening (ULN); e. HbA1C > 7.5% at screening; f. Pathologic renal findings at screening as defined by the presence of either of the following criteria: i. Estimated glomerular filtration rate (eGFR) according to the re-expressed abbreviated (four-variable) Modification of Diet in Renal Disease

	(MDRD) Study equation < 30 ml/min/ 1.73m^2; The MDRD estimation is calculated as follows: eGFR (mL/min/1.73m^2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black). [Scr: Standardized serum creatinine] g. Hematologic abnormalities at screening: i. Hemoglobin < 10 g/dL; or ii. WBC < 3.0 x 10^3/mm^3; or iii. Platelet count < 100,000/mm^3; h. Human Immunodeficiency Virus (HIV) positive at screening (indicated by positive confirmatory Western Blot); i. HBsAg or HCV positive at screening; j. QTc (Bazett's) and QTc (Fridericia) interval > 480 msec at screening and confirmed by repeat measurement or uncontrolled arrhythmia or frequent premature ventricular contraction (PVCs) (> 5/minute) or Mobitz Type II second or third degree atrioventricular (AV) block or evidence of acute or sub-acute myocardial infarction or ischemia. *[Note: Subjects with MRI compatible pacemakers or bundle branch block (BBB) and a paced QTc (Fridericia) < 480 msec and a stable cardiac status may be enrolled after obtaining a cardiology consult. It must be determined by the consulting cardiologist that the subject's cardiac status is stable and does not pose a risk for participation in the trial.]* k. Screening laboratory testing can be done at patient's primary care physician's office up to 6 weeks prior to Screening visit, provided that results are available at time of Screening visit. **4. Prohibited Treatments and/or Therapies** a. History of not tolerating treatment with riluzole for any reason b. Treatment with riluzole in the 30 days prior to screening and/or during the study; **[with the exception of the switch group of SCA subjects].** c. Prior trial of riluzole treatment of at least 8 weeks duration ; **[with the exception of the switch group of SCA subjects].** d. Use of chlorzoxazone is prohibited 30 days prior to screening and during the study; e. Use of aminopyridine is prohibited 30 days prior to screening and during the study; f. Use of tricyclic antidepressants and mono-amine-oxidase (MAO) inhibitors are prohibited 30 days prior to screening and during the study; g. Use of any approved treatments for Alzheimer's Disease (AD). Subjects should be free of such medications (donepezil, galantamine, rivastigmine and memantine) for at least 3 months prior to Baseline with no plans to start such medications during the study; or, subjects should be on stable doses of these medications for at least 3 months prior to the baseline visit; h. Use of memantine is prohibited 30 days prior to screening and during the study; i. A new anxiolytic or sleep medication not taken at a stable dose within 30 days prior to screening. Note: Low dose anxiolytic pre-medications prior to diagnostic testing (e.g., MRI) as well as sleep medications taken prn (as needed) are

	allowed; j. Chronic NSAID use (e.g., naproxen, acetylsalicylic acid, ibuprofen) should be treated with proton pump inhibitors unless otherwise clinically prohibited; k. Medical marijuana use within 30 days of baseline visit (and subjects will be expected to refrain from use during the period of the study).
Concomitant Medications:	1. Antidepressant Use: The use of tricyclic antidepressants and mono-amine-oxidase (MAO) inhibitors are prohibited 30 days prior to screening and during the study. Other antidepressants (e.g., bupropion, citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine, and duloxetine) are permitted if the subject has been treated with a stable dose for 3 months prior to randomization and no dose changes are expected throughout the randomization phase of the study. 2. Hypnotic Use: New use of hypnotics should be avoided. For the management of persistent sleeping difficulties or insomnia, subjects may receive the following medications at the indicated doses (or equivalent doses in countries outside of the US) such as: • zolpidem tartrate (Ambien): up to 10 mg at bedtime (HS) as needed (prn) • zolpidem tartrate extended-release (Ambien CR®): 12.5 mg at HS prn • zaleplon (Sonata): 20 mg at HS prn eszopiclone (Lunesta): 3 mg at HS prn
Screening Procedures:	• **Eligibility assessments include**: Inclusion/exclusion, medical history, demographics, disease history, neurological exam, Mini Mental State Exam, and pregnancy testing for WOCBP at screening and 72 hours prior to first dose. • **Safety assessments include**: Laboratory assessments, physical exam, physical measurements, vital signs, 12-lead ECG, concomitant medication review, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Sheehan Suicidality Tracking Scale Sheehan (STS). • **Clinical outcome assessments include**: The Scale for the Assessment and Rating of Ataxia (SARA), Inventory of Non-Ataxia Symptoms (INAS), 9 Hole Peg Test, 8 Meter Walk, Clinical Global Impression of Change (CGIC), Patient Global Impression of Change Scale (PGIC); and dizziness assessments (SCA3/dizziness predominant subjects only).
Randomization Phase:	N/A All subjects will receive open drug during the initial 12 weeks of the study.
Extension Phase:	Subjects completing the initial 12 week open-label administration will be offered and additional 36 weeks of open-label extension treatment (as allowed by the FDA) as long as the PI believes continued open-label treatment offers an acceptable risk-benefit profile.
Drug Administrations:	Subjects will receive oral BHV-4157 (140 mg QD).

Laboratory Assessments and Sample Collection:	• **Laboratory Assessments**: All laboratory testing should be done fasting and testing will include the following. Laboratory testing designated as Screening can be done up to 12 weeks prior to the Baseline visit: a) Hematology: hemoglobin, hematocrit, red blood cells, white blood cells, differential count and absolute platelet count [Screening, Week 12, Week 24, Week 36, and Week 48]. b) Serum Chemistry: albumin, sodium, potassium, chloride, calcium, AST, ALT, LDH, alkaline phosphatase, GGT, CPK, total protein, total bilirubin, glucose, creatinine, blood urea nitrogen (BUN), uric acid, triglycerides, total cholesterol, HbA1C, P- Amylase or Lipase, TSH, T4, and urine pregnancy testing will be performed at Screening. Urine pregnancy testing will be repeated at Baseline (up to 72 hours prior) and Week 12. AST, ALT, LDH, alkaline phosphatase, GGT, and total bilirubin will be repeated at Week 12, Week 24, Week 36, and Week 48. c) Urinalysis: macroscopic examination, pH, specific gravity, ketones, nitrites, bilirubin, urobilinogen, leukocyte esterase, protein, glucose, and occult blood will be performed at Screening. d) HBsAg, HCV and HIV antibody detection will be performed at Screening Any lab value outside of the normal range must be brought to the attention of a physician (Investigator or Sub-Investigator) at the site. The Investigator will indicate whether or not a flagged value is of clinical significance. • **BDNF Blood Sample Collection**: N/A • **Pharmacogenetic Blood Sample Collection:** N/A • **Pharmacokinetic Sample Collection: N/A**

Subject Safety:	**Initial 12 week open-drug administration** • Review of subject eligibility before dosing; • Concomitant medication review: At Screening, Baseline, and through the 2-week Post Last Dose; • Physical examination at Screening, Baseline, and Week 12 • Physical measurements and vital signs will be done assessed at Screening, Baseline, and Week 12; • The Beck Depression Inventory (BDI) and The Beck Anxiety Inventory (BAI) will be assessed at Screening, Baseline, and Week 12. The Sheehan Suicidality Tracking Scale (Sheehan STS) will be assessed at Screening and all visits through the 2-Weeks Post Last Dose Visit; • 12-Lead ECG will be done at Screening and Week 12; • Hematology, serum chemistries, and urinalysis at screening. • CBC and Liver Function Tests will be done at Screening and Week 12; • Urine pregnancy testing will be performed on WOCBP at screening, baseline, and Week 12. Urine pregnancy testing may also be done at the discretion of the Investigator. • Subjects will be monitored throughout the study for adverse events. **Extension Phase [Week 12 through Week 48]** • Physical examination will be assessed at Baseline/Week 12, Week 24, Week 48, and 2-Weeks Post Dose; • Physical measurements and vital signs will be assessed at Baseline/Week 12 visit through 2-Weeks Post Last Dose; • The Beck Depression Inventory (BDI) and The Beck Anxiety Inventory (BAI) will be assessed at Baseline, Weeks 24, 48 and 2-Weeks Post Dose. The Sheehan Suicidality Tracking Scale (Sheehan STS) will be assessed at Baseline/Week 12 visit through 2-Weeks Post Last Dose; • 12-Lead ECG will be done at Baseline/Week 12. • Hematology, serum chemistry, and urinalysis at Baseline/Week 12.

	• CBC and Liver Function Tests will be done at Baseline/Week 12, Weeks 24, 36, 48 and 2-Weeks Post Last Dose; • Urine pregnancy testing will be performed on WOCBP at Baseline/Week 12 and at the discretion of the Investigator. • Subjects will be monitored throughout the study for adverse events.
Study Endpoints:	• **Primary** The total score on the Scale for the Assessment and Rating of Ataxia (SARA) • **Secondary / Exploratory** a) Clinical outcomes: o The Inventory of Non-Ataxia Symptoms (INAS) o UHDRS-IV o 8 Meter Walk o 9-hole peg test • EQ-5D • Dizziness scales (for SCA3/dizziness-predominant) • **Safety assessments** a) Liver function tests b) CBC with differential c) ECG assessments d) Vital Sign Measurements e) Adverse Events will be assessed throughout the study
Statistical Analyses:	TBD

Proposed Recruitment Groups

SCA3/dizziness predominant; no SARA limitations	**Up to 4 subjects**
SCA1, 2, 3, 6 on Riluzole for >8weeks; no SARA limitations	**Up to 4subjects**
Non-genetic pure cerebellar ataxia	**Up to 4 subjects**
MSA-C	**Up to 12 subjects**