CLINICAL RESEARCH PROTOCOL

DRUG:	Troriluzole
STUDY NUMBER(S):	BHV4157-206
PROTOCOL(S) TITLE:	A Phase III, Long-Term, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia
IND NUMBER:	129397
SPONSOR:	Biohaven Pharmaceuticals Inc.
ORIGINAL PROTOCOL DATE:	07AUG2018
VERSION NUMBER:	V09 Incorporates Administrative Letters Dated 09Oct18;18Mar19; 23Sep19; 28Oct19, 12Aug20,02Nov20, 09Apr21
VERSION DATE:	05DEC2022

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase III, Long-term, Randomized, Double-blind, Placebo-controlled trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia

Study No: BHV4157-206

Original Protocol Date: 07Aug2018

Protocol Version No: V09

Protocol Version Date: 05DEC2022

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

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

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

Name and Title	Signature Approval	Date
Author/Protocol Writer: [redacted]		
Clinical Operations: [redacted]		
Biostatistics: [redacted]		
Regulatory Affairs: [redacted]		

SUMMARY OF CHANGES[1]

Version Number	Brief Description of Changes	Page(s) Affected/Sections	Date
Original Protocol V01		NA	Aug2018
Protocol V02	1) Exploratory Objective added to compare the efficacy of troriluzole with placebo on the video-recorded administration of the SARA, as assessed via central rating 2) Falls diary removed from Exploratory Objectives 3) Administrative corrections made to the Schedule of Assessments to ensure footnotes are correct; Falls Diary removed from Schedule of Assessments, PIFAS removed from screening 4) Video equipment added in Study Materials section 5) Video recording added 6) Falls Diary Removed	P10, P41 P10, P11, P41 P45, P46, P47, P48, P49 P61 P66, P67 P68	21Aug2018

[1] If higher than v1.0

Protocol V03 Incorporates Administrative Letter dated 09Oct2018	1) Replaced BHV-4157 with Troriluzole	Throughout document	12FEB2019
	2) Changed primary outcome measure from the SARA to the Modified Functional SARA (f-SARA)	Throughout document	
	3) Revised Secondary and Exploratory Objectives and Exploratory Endpoints	Throughout document	
	4) Revisions made to Phase 2 Clinical Adverse Event Profile	Section 1.2.4.2	
	5) Added rationale for enriched SCA1 and SCA2 genotypes	Section 1.3.3	
	6) Modified Schedule of Assessments to reflect the changes to secondary and exploratory outcome assessments, update schedule of pregnancy testing, clarify Early Discontinuation Visit, add PK to Extension Phase for AEs due to study drug, and removed calculation of screening to baseline SARA scoring via the IWRS	Section 4.3	
	7) Changed Inclusion/Exclusion criteria to reflect f-SARA as opposed to Total SARA and also added	Section 5.2 and 5.3	
	8) Added items to study material	Section 6.1	
	9) Clarified who, at site, can administer the S-STS	Section 7.4.9	
	10) Rearranged order of Clinical Outcome Assessments	Section 7.5	
	11) Changed section 7.5.1 to reflect the change from the primary outcome from the mSARA to the f-SARA and deleted wording about use of central rating.	Section 7.5.1	
	12) Provided additional detail on Early Discontinuation Visit	Section 8	
	13) Clarified timing of dosing	Section 9.3.4	
	14) Added information about independent statistician to review randomization	Section 9.4	
	15) Clarifications added to Sample Size.	Section 11.2	

	16) Clarifications made to Population for Analysis	Section 11.3	
	17) Moved up and added clarification to Demographic and Baseline Characteristic section	Section 11.4.1	
	18) Changed analysis section to reflect change in primary outcome measure to the f-SARA	Section 11.4.2	
	19) Added section 11.4.3 to adjust statistical analysis for Multiplicity for secondary endpoints	Section 11.4.3	
	20) Updated Analysis of Safety section.	Section 11.4.5	
	21) Added central lab information to Appendix 19.1	Appendix 19.1	
	22) Deleted Declaration of Helsinki since protocol mentions we are operating under current version. Section 19.2 is now Appendix II.	Appendix 19.2	

V04	Incorporates Administrative Letters Dated 09Oct18;18Mar19; 23Sep19; 28Oct19. The number of randomized subjects has been revised from 230 to 210 throughout the protocol. The protocol was updated to reflect that SCA 1, 2, and 3 will comprise 80-90% of randomized subjects and SCA 6,7,8,and 10 will comprise the remainder of subjects. The primary and secondary objectives and study endpoints have been revised to include all SCAs as opposed to just SCA 1 and SCA 2. Study schematic footnote includes details about stratification. Section 1.2.2.3 updated to reflect that the BHV4157-201 Open Label Phase was extended to 144 weeks. Removed Section 1.3.3 titled Rationale for Enriched SCA 1 and SCA 2 Genotype. Section 1.4 updated research hypothesis. Section 4.1: Added clarification that, prior to down titration, these cases should be discussed with the Medical Monitor. Table 3. Modified language in Instruction Section for Baseline pregnancy testing. 4.3.1 Updated number of screened subjects from approximately 375 to 270. 4.3.2 Added details about randomization stratification and down titration. 7.4.2 Added clarification about determining clinical significance. 9.2 Updated with permitted temperature excursions. 9.3.1 and 9.3.2 Added additional details regarding down titration.		07NOV2019

	9.3.5 Two bullets added to clarify how to handle tolerability issues and dose titration. 11.2 Sample size section modified to account for changes in randomized subjects. 11.4.2 Primary endpoint section revised. 11.4.5 Added Missing Data section. 11.4.6 Analysis of Safety section revised.		
V05	Added additional window for Week 48 visit in order to proactively account for any subjects that may potentially be out of visit window due to concerns related to COVID-19 pandemic. [redacted] Included text throughout document to provide instruction in case participants are unable to come into the site due to concerns related to COVID-19. Minor typographical errors identified during review have been corrected.		17MAR2020

V06	Updated length of Open Label Extension Phase to 96 Weeks (from 48 Weeks) throughout the protocol and on study schematic. Section 1.2.1 Rational for Troriluzole in the Treatment of SCA has been updated. Section 1.2.2.2 Clinical Experience has been updated based on recent IB information. Section 1.2.3 Potential for Drug Drug Interactions has been updated based on recent clinical trials. Section 1.2.4 Special Populations is a new section added to protocol. Section 1.3.2 Dose Selection updated to increase the Extension Phase of the BHV4157-201 study. Table 4 Time and Events Schedule – Extension Phase is updated for 96 Weeks. 5.4 Prohibited Concomitant Medications updated to add information about strong to moderate CYP1A2 inhibitors. 7.5.1 Updated to note that video taping of the f-SARA is not required after Extension Week 48. 9.1.1 Investigational Product updated to add description of capsules. 9.4 Blinding and Unblinding section has been updated based on most recent Administrative Letter. 11.4.5 Missing Data section has been updated. 19.2 APPENDIX II has been updated based on recent findings. Clarifications made throughout document regarding down titration. General administrative changes made throughout document.		01MAR2021

V07	Incorporates revisions from Administrative Letter Dated 02Nov20 and 09Apr21.	Section 9.2; Section 10.2	03JAN2022
	Study Schematic updated to reflect 144 Weeks of Open Label Extension.	Study Summary and Section 4.2	
	[redacted]	Study Summary	
	Open Label Extension updated to 144 weeks from 96 Weeks.	Throughout Document	
	Pre-Clinical Section updated based on updated findings.	Section 1.2.2.1	
	Clinical Experience Section updated based on most recent Investigator Brochure.	Section 1.2.2.2	
	Phase 2 study information added based on most recent Investigator Brochure.	Sections 1.2.2.3 through 1.2.2.6	
	Potential Drug Drug interaction section updated.	Section 1.2.3	
	Clinical adverse event profile for troriluzole has been updated.	Section 1.2.5.1	
	Clinical adverse event profile for riluzole has been updated.	Section 1.2.5.3	
	Updated information regarding elevated liver function tests.	Section 1.2.5.4	
	Neutropenia section updated.	Section 1.2.5.5	
	Time and Events section updated and Extension Phase extended to 144 weeks.	Table 4	
	Laboratory Assessment section updated to clarify local lab results should be sent to Medical Monitor fir review.	Section 7.4.4	
	Pregnancy Section updated to specify WOCBP will be provided a urine pregnancy test to be used in between every three month visits.	Section 7.4.7	
	Lost to follow-up section added.	Section 9	
	Clarifications added regarding drug destruction.	Section 10.6	

	Added clarification about clinically significant labs being reported as adverse event. Primary endpoint section updated.	Section 11.3.1 Section 12.4.2	
V08	[redacted]	P14, 15 Sections 2.3, 3.3, 7.4.5, 7.4.6	03JUN2022
V09	Study schematic updated to reflect 192 weeks of Open Label Extension Open Label Extension updated to 192 weeks from 144 Weeks. Number of deaths in BHV4157-201 Adverse Event Profile updated from 2 to 3 as of July 28, 2022. Table 2 updated specific to falls reflecting 1% as noted in IBv8 instead of 2%. F-Sara recertification is only required until all subjects complete Open Label Extension Week 48. Appendix I updated to reflect change in Chief Medical Officer.	Study Summary and Section 4.2 Throughout document 1.2.5.2 1.2.5.2 7.5.1 20.1	05DEC2022

BHV4157-206

A PHASE III, LONG-TERM, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF TRORILUZOLE IN ADULT SUBJECTS WITH SPINOCEREBELLAR ATAXIA

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to troriluzole are the confidential and proprietary information of Biohaven Pharmaceuticals, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Biohaven.

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

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

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

STUDY SUMMARY

Title: A Phase III, Long-Term, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia

Rationale: Hereditary Spinocerebellar Ataxias (SCA) are disorders of spinocerebellar pathology that are characterized clinically by progressive ataxia and are attributed to various autosomal dominant genetic mutations. Ataxia, itself, is a symptom of loss of control of voluntary body movements and can involve unsteady gait, dysarthria, and clumsiness, potentially progressing to the stage of difficulty with swallowing and breathing. In patients with SCA, atrophy of the cerebellum and sometimes brainstem may be apparent on brain imaging. Lifespan is significantly shortened due to complications related to neurologic deficits. Currently, there are no FDA medications approved for this debilitating disorder and treatment remains supportive.

In this patient population, prior clinical studies have provided evidence for a potential therapeutic role for the glutamate modulating agent riluzole in the treatment of hereditary ataxias (1,2). Troriluzole is a glutamate modulating drug that is being developed for eventual commercial use in the treatment of patients with SCA. Troriluzole is a novel tripeptide prodrug of riluzole, optimized for improved bioavailability, pharmacokinetics and dosing. Troriluzole was designed to be readily cleaved into riluzole once it is in the plasma. In nonclinical species, the exposure of troriluzole was found to be less than 1% of riluzole exposure. The cleaved moiety of the prodrug is a three amino acid peptide that is anticipated to be safe and tolerable as the composite amino acids (glycine and sarcosine) are taken up into normal physiological roles in the body. Riluzole was first approved in 1995 and the demonstrated safety profile of riluzole from over 20 years of global clinical use combined with the nonclinical assessments of troriluzole suggests that there are no unwarranted clinical risks in advancing troriluzole into clinical trials.

As a prodrug of riluzole, troriluzole is being developed through the 505(b)(2) pathway, a regulatory mechanism that allows the FDA to rely on safety and/or efficacy data acquired for a previously approved agent. In the case of troriluzole, the 505(b)(2) regulatory pathway will rely on the well-characterized safety experience of riluzole. Relevant pharmacologic activities of riluzole, such as increasing glutamate transporters (3, 4) or potential activation of small-conductance calcium-activated potassium

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conductance calcium-activated potassium channels (5), prompted clinical testing in the treatment of ataxia. Two well-designed academic trials (1, 2) have demonstrated preliminary safety and robust efficacy of 50 mg twice per day in patients with SCA. Evidence from these studies suggests that riluzole may provide both symptomatic and disease-modifying effects in this patient population. Troriluzole was studied in a randomized, placebo-controlled trial in patients with SCA (BHV4157-201). Troriluzole at 140 md QD for eight weeks was well tolerated in adult subjects with SCA without any clinically significant safety signals or lab abnormalities. During the ongoing open-label extension phase, the safety profile of troriluzole 140 mg QD has been consistent with the troriluzole safety profile observed during the randomization phase.

Troriluzole 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 is also attributable to the high PK variability associated with riluzole (6-9). In addition, riluzole is associated with reduced exposure when taken with meals (i.e., a negative food effect), resulting in the guidance to take riluzole within a three hour fast (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.

Troriluzole was engineered to eliminate the negative food effect, optimize and enhance the bioavailability, pharmacokinetic profile and dosing schedule, and by-pass first-pass metabolism, resulting in lower drug burden on the liver and a better safety and tolerability profile. Based on the preclinical features of troriluzole and pharmacokinetics from three completed Phase 1 studies, we anticipate the clinical pharmacology to offer favorable properties as compared to available riluzole. To date, an ongoing Phase IIb/III study evaluating the safety of troriluzole in patients with SCA has shown troriluzole to be safe and well-tolerated in this patient population.

The overall objective of this study is to further evaluate the long-term efficacy and safety of troriluzole in adult patients with SCA.

Target Population: Male and female outpatient subjects between the ages of 18 – 75 years, inclusive, with a known or suspected diagnosis of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA10.

Number of Subjects: Approximately 210 randomized subjects. Subjects with SCA1, SCA2, and SCA 3 genotypes will comprise approximately 80%-90% of the randomized subjects. Subjects with SCA6, SCA7, SCA8, and SCA10 genotypes will comprise the remainder of the randomized subjects in total.

Objectives: **Primary Objectives**

- To compare the efficacy of troriluzole (200 mg once daily) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) at 48 weeks of double-blind treatment as measured by the total score on the Modified Functional Scale for the Assessment and Rating of Ataxia [f-SARA]

Secondary Objectives

- To compare the efficacy of troriluzole versus placebo on patient impression of benefit via use of the change from baseline in Patient Impression of Function and Activities of Daily Living Scale (PIFAS) at Randomization Phase Week 48

- To compare the efficacy of troriluzole versus placebo on activities of daily living as measured by the change from baseline in Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale (FARS-ADL) at Randomization Phase Week 48

- To compare the efficacy of troriluzole versus placebo on daily functioning as measured by the change from Baseline in Functional Staging for Ataxia Scale from the Friedreich's Ataxia Rating Scale (FARS-FUNC) at Randomization Week 48

- To assess of the safety and tolerability of troriluzole in subjects with SCA during the Randomization and Extension Phases

Exploratory Objectives

- To compare the efficacy of troriluzole versus placebo on lower extremity mobility and activities as measured by the change from baseline in Neurology Quality of Life (Neuro-QOL) Lower Extremity Mobility Scale at Randomization Phase Week 48

- To compare the efficacy of troriluzole versus placebo on upper extremity function and activities as measured by the change from baseline in Neurology Quality of Life (Neuro-QOL) Upper Extremity Scale at Randomization Phase Week 48

- To compare the efficacy of troriluzole versus placebo on daily fatigue and activities as measured by the change from baseline the Neurology Quality of Life (Neuro-QOL) Fatigue Scale at Randomization Phase Week 48

- To compare efficacy of troriluzole versus placebo on clinician impression of global functioning via use of the Clinical Global Impression-Global Improvement Scale (CGI-I) at Randomization Phase Week 48
- To compare the efficacy of troriluzole versus placebo on patient impression of global functioning as measured by the Patient Global Impression Scale (PGI) at Randomization Phase Week 48

[redacted]

Study Design:

BHV4157-206 is a Phase III, multicenter, randomized, double-blind, 2- arm placebo-controlled parallel-group study designed to assess safety, tolerability, and efficacy signals in a population of patients with Spinocerebellar Ataxia (SCA). Subjects will be randomized to receive placebo (QD) or troriluzole (200 mg QD) and will be stratified by diagnosis (genotype).

Dosing will continue for approximately 48 weeks. Subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit. In addition, subjects completing the Randomization Phase will be offered up to 192 weeks of open-label treatment as long as the Primary Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will not be required to wash-out of drug or complete the follow-up safety visit, but instead should continue dosing as specified in the extension phase. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug in the Extension Phase.

Primary Endpoint:

- Change from baseline in Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA) total score at Randomization Phase Week 48

Secondary Endpoints:

- Change from baseline in Patient Impression of Function and Activities of Daily Living Scale (PIFAS) score at Randomization Phase Week 48
- Change from baseline in Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale (FARS-ADL) at Randomization Week 48

- Change from baseline in Functional Staging for Ataxia (FARS-FUNC) at Randomization Phase Week 48
- Frequency of subjects with the following adverse events (AEs) identified from case report forms: AEs (by severity; by relationship to study drug; overall); SAEs; and AEs leading to treatment discontinuation

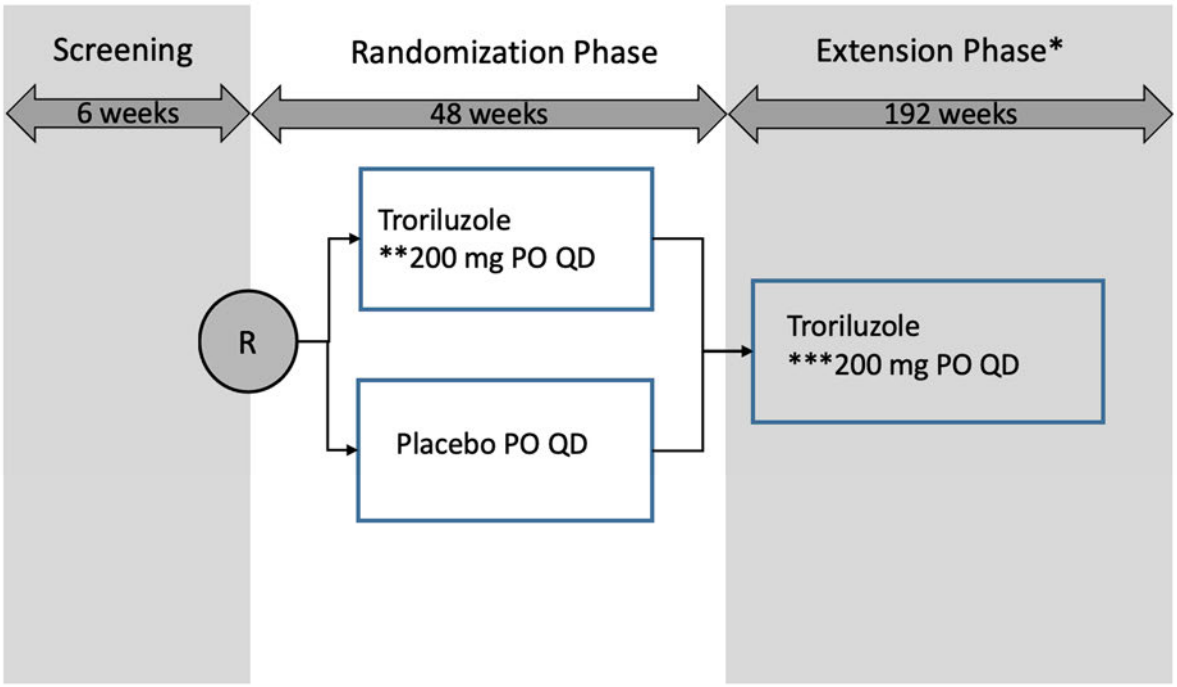
Exploratory Endpoints:

- Change from baseline in Neuro-QOL Lower Extremity score at Randomization Phase Week 48
- Change from baseline in Neuro-QOL Upper Extremity score at Randomization Phase Week 48
- Change from baseline in Neuro-QOL Fatigue at Randomization Phase Week 48
- Clinical Global Impression-Global Improvement Scale (CGI-I) at Randomization Phase Week 48
- Patient Global Impression Scale (PGI) at Randomization Phase Week 48
- [redacted]

[redacted]

[redacted]

STUDY SCHEMATIC



R, signifies randomization; randomization will be stratified by 3 SCA subgroups: SCA1 & 2; SCA3; and SCA 6, 7, 8, 10.
* Eligible subjects for the Extension Phase will include those for whom the PI believes extended treatment with troriluzole would offer an acceptable risk-benefit profile.
**Subjects will receive 140 mg for the first four (4) weeks and will then be increased to 200 mg for the duration of the study. Down titration will only be temporarily allowed to address tolerability issues.
***Subjects entering the Extension Phase will continue with the same dose taken at the end of the Randomization Phase. Subjects on placebo in the Randomization Phase will be switched in a blinded manner to 140 mg QD for the first four weeks and then will be increased to 200 mg QD for the duration of the study. Down titration after the first four weeks of the Extension Phase will only be allowed for tolerability purposes. All visits after Extension Phase Week 4 will be open-label.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
bid	Twice Daily
big-ET	Proendothelin-1
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C_{max}	Maximum Plasma Concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant Medication
CRF	Case Report Form
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
FEV_1	Forced Expiratory Volume
GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRB	Institutional Review Board

iv	Intravenous
kg	Kilogram
L	Liters
mg	Milligram
min	Minute
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
NO	Nitric Oxide
PK	Pharmacokinetic
po	By Mouth, Orally
qd	Once Daily
SAE	Serious Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Hereditary Spinocerebellar Ataxias (SCA) are disorders of spinocerebellar pathology that are characterized clinically by progressive ataxia and are attributed to various autosomal dominant genetic mutations. Ataxia, itself, is a symptom of loss of control of voluntary body movements and can involve unsteady gait, dysarthria, and clumsiness, potentially progressing to the stage of difficulty with swallowing and breathing. Atrophy of the cerebellum and sometimes brainstem may be apparent on brain imaging. The diagnosis of a spinocerebellar ataxia requires the exclusion of acquired, non-genetic causes of ataxia, including alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, and paraneoplastic disease. A definitive diagnosis requires genetic testing or occurrence within kindred. Lifespan is significantly shortened due to complications related to neurologic deficits. There are currently no FDA approved medications for the treatment of SCA.

Troriluzole is being developed for the treatment of SCA. Troriluzole is a novel pro-drug formulation of the generic drug riluzole. The FDA originally approved riluzole (RILUTEK®) 50 mg tablets, on December 12, 1995 (NDA #20-599) for "the treatment of patients with amyotrophic lateral sclerosis. Riluzole extends survival and/or time to tracheostomy." Based upon preclinical evidence and results from two academic health center randomized controlled trials examining the use of riluzole in hereditary cerebellar ataxias, troriluzole is being developed for SCA through the 505(b)(2) pathway, a regulatory mechanism that allows the FDA to rely on safety and/or efficacy data acquired for a previously approved agent. In the case of troriluzole, the 505(b)(2) regulatory pathway will rely on the well-characterized safety experience of riluzole, which has been marketed globally for over 20 years and is considered safe, well tolerated. Biohaven hypothesizes that the pleiotropic effects of riluzole (e.g., enhanced glutamate transporter activity and selective potassium channel activation) may target mechanisms underlying pathologic cerebellar function that is associated with SCA, and thus provide benefit in patients suffering from SCA - for whom there is no approved treatment.

1.1.1 Spinocerebellar Ataxia

Hereditary ataxias may transmit via multiple mechanisms such as autosomal dominant, autosomal recessive, X-linked and mitochondrial. Figure 1 provides an overview on the classification of genetic ataxias. Autosomal dominant hereditary ataxias include a group called the spinocerebellar ataxias (SCAs) (Figure 1). Most dominant mutations are associated with pathologic protein function due to expanded polyglutamine repeats. These aberrant proteins form toxic aggregates and damage neurons, leading to apoptosis.

The overlapping pathology leads to shared features among the SCAs. For example, they are associated with spinocerebellar degeneration, which is often observable on brain imaging.

In addition, symptom presentation among the SCA subtypes share many common, prominent features: slowly progressive, symmetrical, midline and appendicular ataxia with dysmetria (i.e., loss of accuracy); dysdiadochokinesis (loss of rhythm as in difficulty performing alternating

movements); decreased speed of eye movements that affect eye gaze (including nystagmus and diplopia); abnormalities of speech (dysarthria); difficulty swallowing; hand/foot incoordination (limb ataxia); abnormal station; and, abnormal gait. Notably, there can also be significant clinical variation in the order and/or extent of symptom expression between mutations, within a common mutation, and even within kindred that shares the same genotype. Non-cerebellar involvement may also occur in many SCA subtypes (e.g., cognition, pyramidal, extrapyramidal, motor neuron, peripheral nerve or macular involvement).

Signs and symptoms of SCA typically begin in early adulthood but can appear anytime from childhood to late adulthood; SCAs are degenerative and progress over a number of years. The severity of the disability and related mortality depends on type of ataxia, the age of onset of symptoms, and other factors that are poorly understood at this time. It is common for subsequent generations to experience earlier onset and more extensive disease, attributable to the phenomenon of "anticipation" whereby mutation length (e.g., polyglutamine triplet) expands over successive generations.

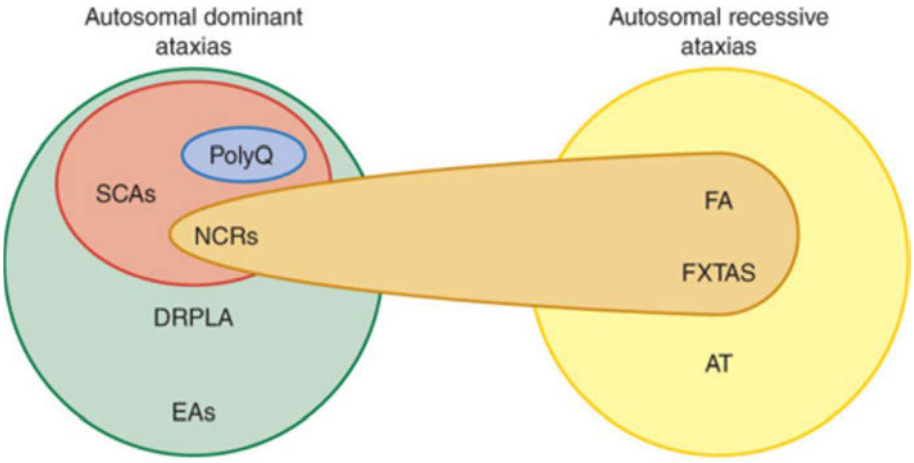
The typical clinical course of SCAs may be described, as follows. Balance and coordination are affected first. Incoordination of hands, arms, and legs, and slurring of speech are other common, early symptoms. Over time, individuals with SCA may develop numbness, tingling, or pain in the arms and legs (sensory neuropathy), uncontrolled muscle tensing (dystonia), muscle wasting (atrophy), and muscle twitches (fasciculations).

Walking becomes difficult and is characterized by walking with feet placed further apart to compensate for poor balance. Impaired coordination of the arms and hands affects the ability to perform tasks requiring fine motor control such as writing and eating. Rarely, rigidity, tremors, and involuntary jerking movements (chorea) have been reported in people who have been affected for many years.

Slow eye movements can be seen in some forms of ataxia, including weakness in the muscles that control eye movement (ophthalmoplegia). As time goes on, ataxia can affect speech and swallowing. Finally, individuals with SCA may also have difficulty processing, learning, and remembering information (cognitive impairment).

With the production of abnormal proteins, the affected nerve cells eventually begin to function poorly and ultimately degenerate. As SCA progresses, muscles become decreasingly coordinated, causing ataxia symptoms to become more pronounced.

Figure 1: Genetic mechanisms in hereditary ataxias



Source: M. J. Aminoff, D. A. Greenberg, R. P. Simon: Clinical Neurology, 9th Edition
www.accessmedicine.com

Genetic mechanisms in hereditary ataxias. Autosomal dominant ataxias include the spinocerebellar ataxias (SCAs), dentatorubral pallidoluysian atrophy (DRPLA), and the episodic ataxias (EAs). Autosomal recessive ataxias include Friedreich ataxia (FA), fragile X–associated tremor-ataxia syndrome (FXTAS), and ataxia-telangiectasia (AT). Two distinctive modes of autosomal dominant inheritance are observed in some, but not all, SCAs. In one of these (blue in figure), there is pathologic expansion of a CAG trinucleotide repeat in the coding region of an affected gene, which is translated into an abnormally long polyglutamine (PolyQ) tract within the protein (eg, SCA1, 2, 3, 6, 7, 8, 12, or 17). In the other (brown in figure), there is pathologic expansion of a tri- or pentanucleotide repeat in noncoding regions (NCRs) of the protein, which, although not translated, interferes with protein function (eg, SCA8, 10, or 31). Two autosomal recessive ataxias, FA and FXTAS, also involve trinucleotide repeats in noncoding regions [1].

The most common SCAs include type 1, 2, 3, 6, 7, 8 and 10. SCA1 produces gait ataxia, limb ataxia, and dysarthria, with brainstem involvement but little cognitive abnormality. SCA2 is notable for the association of ataxia and dysarthria with slow saccadic eye movements and polyneuropathy. SCA3 (Machado-Joseph disease) is accompanied by eyelid retraction, reduced blinking, external ophthalmoplegia, dysarthria, dysphagia, and sometimes parkinsonism or peripheral neuropathy. SCA6 is comparatively less severe, progresses more slowly, is more limited to cerebellar involvement than other SCAs, and has a later age of onset. SCA7 is distinguished by retinal degeneration leading to blindness, in addition to ataxia. Overall, there is significant symptom overlap among these SCAs. The shared symptomatic manifestations of the SCAs may reflect common pathology affecting cerebellar purkinje cell fibers.

Table 1: Genetic and Clinical Features of Common SCAs

Disease	Gene	Protein	Repeat	Features in addition to Ataxia
SCA1	ATXN1	Ataxin-1	CAG	10–25% of dominant ataxias; spasticity, polyneuropathy, ophthalmoparesis, dysarthria, pyramidal and extrapyramidal signs
SCA2	ATXN2	Ataxin-2	CAG	Neuropathy, ophthalmoparesis, extrapyramidal features, dysarthria, pyramidal signs, dementia
SCA3 (Machado- Joseph Disease)	ATXN3	Ataxin-3	CAG	25% of dominant ataxias, spasticity, neuropathy, extrapyramidal features, dysarthria, pyramidal signs, dementia
SCA6	CACNA1A	Alpha-1a Calcium Channel	CAG	20% of dominant ataxias; dysarthria, nystagmus, posterior column signs, dysarthria, and sometimes mild pyramidal signs
SCA7	ATXN7	Ataxin-7	CAG	Olivopontocerebellar atrophy and syndrome of retinal degeneration, hearing loss, ophthalmoplegia, spasticity, generational anticipation, dysarthria, and pigmentary maculopathy
SCA8	ATXN8	Ataxin-8	CTA/CTG	Slowly progressive sensory neuropathy, spasticity, known rapid infantile variant, dysarthria, pyramidal and extrapyramidal signs, dementia
SCA10	ATXN10	Ataxin-10	ATTCT	Seizures, personality change, ataxia, dysarthria, and sometimes mild pyramidal signs

[Adapted from Clinical Neurology 9th Edition and Adams and Victor's Principles Neurology 10th Edition] [1,2]

1.2 Study Rationale

1.2.1 Rationale for Troriluzole in the Treatment of SCA

Treatment for hereditary ataxias is supportive and no medications have been approved by the FDA for this condition. Recent evidence suggests that riluzole may provide both symptomatic and disease-modifying therapeutic effects. Troriluzole is a tripeptide prodrug of riluzole developed for improved bioavailability, pharmacokinetics and dosing. Since the active moiety of troriluzole is riluzole and circulating exposure of troriluzole is expected to be negligible (i.e., less than 1% the Cmax and AUC of riluzole as observed in Phase I), the safety of troriluzole is expected to be similar to riluzole. Currently, treatment for SCA focuses on targeting specific clinical features such as tremor, parkinsonism, dystonia, spasticity, urinary urgency, sleep pathology, fatigue and depression. Rehabilitative efforts (physical, occupational and speech

therapies) are employed to mitigate the impact of the core ataxia on mobility, speech and swallowing.

[redacted][7,8].

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Study BHV4157-201: BHV4157-201 is a Phase 2b/3 randomized, double-blind, placebo-controlled trial of troriluzole in adult subjects with SCA. The study was comprised of an 8-week randomization phase, followed by a 48-week open-label phase. An additional 96 weeks of open label was initiated, based on encouraging preliminary data at 1 year. Patients experienced a gap in troriluzole dosing for a range of up to 12 months prior to initiation of this additional open label extension during which they were off troriluzole.

In the primary analysis from the 8-week Randomization Phase of the trial, troriluzole did not differentiate from placebo on the primary outcome, change in the total score on the Scale for Assessment and Rating of Ataxia (SARA) at Week 8. Significant variability in the SARA scale was observed in the trial, as well as a higher than expected placebo response rate. Nonetheless, post-hoc analyses, chosen based on reducing rating variability, showed trends favoring troriluzole over placebo on the SARA.

The on-going, open-label, 192-week Extension Phase of BHV4157-201 has high participation rates and interim analysis of data from subjects who have completed up to 96 weeks of treatment demonstrate stability of SARA scores from baseline. After up to 96 weeks of open-label treatment with troriluzole, the mean change from baseline in total SARA score (mean change±SE) was 0.3 ± 0.30. Patients who had a gap in troriluzole treatment (3 weeks to 12 months) while awaiting approval of the protocol extension showed a greater than 1 point worsening during the off-treatment period. This worsening increased with longer duration off troriluzole. Improvements in total SARA score were observed after re-initiation of troriluzole therapy. The observed changes suggest an attenuation of disease progression in patients treated with troriluzole for up to 3 years, including up to a 1-year gap in dosing during which patients declined, versus the expected rate of decline in the SARA in untreated patients of approximately 1-2 points per year, based on cumulative natural history data[9]. These trends are consistent with the results from two prior studies (discussed above) using the active metabolite of troriluzole [7,8].

1.2.2 Pharmacokinetics

1.2.2.1 Pre-Clinical Studies

Data from preclinical studies support the following findings. Please refer to the IB for additional pre-clinical information.

- No activity at a broad screen of enzymes and receptors, including hERG;
- Preliminary toxicology studies in rats and monkeys reveal no novel findings relative to what has been reported for riluzole;
- Safety pharmacology studies indicate no clinically relevant changes in hERG, cardiovascular parameters or respiratory parameters. Minimal changes on neurobehavioral parameters at high dose levels are consistent with the known sedative effects of riluzole in rats;
- No signals for carcinogenicity (negative for Ames assay, in vitro chromosomal aberrations and in vivo micronucleus);
- More extended riluzole concentrations compared to oral doses of riluzole, as exemplified by the rat data. This is consistent with data suggesting the main route of prodrug cleavage is mediated by serum-based enzymes;
- Troriluzole is stable in saliva and crosses the buccal membrane (pig model), hence supporting testing for sublingual absorption in the clinic;
- [redacted]

1.2.2.2 Clinical Experience

Detailed information is available in the current version of the Investigator Brochure. Troriluzole has been observed to be well tolerated with no clinically relevant safety signals identified in the completed and ongoing clinical studies. The current troriluzole clinical program includes Phase 1 PK studies in normal healthy volunteers (BHV4157-101, BHV4157-102, BHV4157-103, BHV4157-104, BHV4157-105, BHV4157-106, BHV4157-107 and BHV4157-108), Phase 2 or 3 studies in subjects with SCA (BHV4157-201, BHV4157- 206), OCD (BHV4157-202), AD (BHV4157-203) and GAD (BHV4157-207). Overall, the PK and safety profile from the Phase 1 studies support the investigation of troriluzole at doses of 280 mg QD in Phase 2.

Several clinical studies, each with a double-blind phase with the potential for eligible subjects to enroll into an extension phase with open label troriluzole treatment, are ongoing or have been completed in the various indications noted above. A study is assessing efficacy in subjects with SCA randomized to 8 weeks of treatment with either troriluzole or placebo and up to 48 weeks of open label treatment with troriluzole. A study is assessing efficacy in subjects with OCD who were randomized to treatment with either troriluzole or placebo for 12 weeks with the option to enroll into an open label expanded extension phase through 96 weeks if eligible. A study is assessing subjects with AD randomized for 48 weeks to either troriluzole or placebo and up to 48

weeks of open label treatment with troriluzole. A study was completed of subjects with GAD randomized for 8 weeks to either troriluzole or placebo and up to 48 weeks of open label treatment with troriluzole. Please reference the current IB for further details.

The longer-term safety profile of troriluzole is expected to be similar to riluzole based on the following:

- Troriluzole is a tripeptide prodrug of riluzole. It readily metabolizes to riluzole and composite amino acids, sarcosine and glycine. These amino acids are generally non- toxic and will be taken up into their normal physiologic role in the body;

- Troriluzole was designed to be stable enough to bypass first-pass metabolism before being metabolized. Performance in healthy volunteers has been similar to what has been observed in preclinical species, insofar as the concentrations of troriluzole have been negligible compared to active metabolite and time to peak concentration of the active metabolite has been delayed relative to troriluzole. In addition, the time to peak concentration of the active metabolite (Tmax) is delayed compared to troriluzole. This Tmax is longer than that seen with rilutek tablets. This pharmacokinetic (PK) pattern of delayed time to peak riluzole concentration is consistent with diminished first pass liver metabolism.

- Troriluzole has no relevant intrinsic receptor activity as tested in 88 ion channels and receptors, including hERG;

- Toxicology assessments in two preclinical species reflect no novel safety signals as compared to riluzole;

Troriluzole, dosed between 140-280 mg, contains a comparable molar amount of riluzole as found in a 70-140 mg dose of riluzole, well below the 200 mg daily dose of riluzole that has been studied in frail subjects with Amyotrophic Lateral Sclerosis where it was found to be safely administered and generally well tolerated [10,11].

1.2.2.2.1 BHV4157 Phase I

Refer to the Investigators Brochure for detailed and updated information on Phase 1 studies.

1.2.2.2.1.1 Study BHV4157-101

Study BHV4157-101 was a Phase 1 randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of single and multiple ascending doses of troriluzole in normal healthy volunteers. Single doses of troriluzole were assessed (sequential cohorts 1 to 5 with 17.5, 35, 70, 140 and 200 mg) with cohort 5 (200 mg) undergoing a repeat single-dose administration under conditions of a high-fat meal (to determine food effects). Multiple dose cohorts were assessed for 5 days of dosing (sequential cohorts 6 to 10 with total daily doses of 35, 70, 140, and 200 mg).

With regards to Pharmacokinetics (PK), a single dose of 140 mg troriluzole yields exposures (e.g., AUCinf 1,059 ng*h/mL) that are expected to be similar to those achieved in prior academic clinical trials using twice daily riluzole in various indications (e.g., approximately 1254 ng*h/mL, based on Chandu [12], a dose which was previously studied in ataxia[7,8]. The multiple dose AUC for 200 mg troriluzole yielded AUC exposures of 1804 ng*h/mL riluzole.

Safety / Tolerability: Oral administration of troriluzole (17.5 mg to 200 mg) was well tolerated in healthy volunteers in this study at single doses up to 200 mg and multiple doses up to 200 mg daily. No evidence of new, clinically significant safety signals or lab abnormalities were evident, as compared to the Rilutek package label. There were no SAEs and the vast majority of AEs were mild in severity.

1.2.2.2.1.2 Study BHV4157-102

Study BHV4157-102 was a single-center, open-label, single-dose, randomized, 4-period, 2-sequence, fully replicated crossover study to compare the rate and extent of absorption of 2 formulations (i.e., Phase 2 formulation vs commercial-grade capsule formulation) and to evaluate the safety, tolerability, and PK of troriluzole in healthy subjects performed under fasting conditions. Subjects were randomized equally into 1 of the 4 treatment sequences to receive the 2 treatments twice (1 x 140 mg troriluzole as formulated capsule or 1 x 140 mg troriluzole as Phase 2-formulated capsule – without excipients) under fasting conditions in each period. Each period was separated by a washout period of at least 7 days. Subjects at the end of each period were crossed over to the next treatment in their sequence. Each subject was scheduled to receive a total of 4 treatments (each of the 2 treatments twice) by the end of the study.

Safety / Tolerability: Oral administration of 140 mg troriluzole formulated capsule (Commercial-ready formulation) or Phase 2 capsule was safe and well tolerated in healthy adult subjects, with no SAEs or deaths reported in the study.

Pharmacokinetics: Bioequivalence (BE) was demonstrated between the two formulations in accordance with both FDA and EMA guidance.

1.2.2.2.1.3 Study BHV4157-103

Study BHV4157-103 was a single-center, randomized, multiple-dose, placebo-controlled, double-blind,1-period, 1-cohort study to evaluate the safety, tolerability, and PK of troriluzole in healthy subjects under fasting conditions. Subjects were randomized to receive multiple doses of either troriluzole or placebo based on stratification factor of age group (< 65 years old vs. ≥ 65 years old). Six subjects were to be 65 to ≤ 85 years old and 4 subjects were to be < 65 years old. For subjects receiving matching placebo, 1 subject was to be < 65 years old and 1 subject was ≥65 years old. Eight (8) subjects were dosed with troriluzole, administered as a dose of 280 mg (2 x 140 mg capsules) once daily for 5 consecutive days.

Safety / Tolerability: Overall, the 280 mg dose of troriluzole was safe and well tolerated in healthy adult subjects. There were no deaths or other SAEs reported in this study.

Pharmacokinetics (preliminary data):

After administration of a single dose, 280 mg of troriluzole yielded geometric mean values for AUC_{0-24} of 4.46 ng*hr/mL and C_{max} of 5.40 ng/mL for BHV4157; and geometric mean values for AUC_{0-24} of 2797.0 ng*h/mL and C_{max} of 510.4 ng/mL, for riluzole. After administration of multiple doses (once daily for 5 days), 280 mg of troriluzole yielded geometric mean values for AUC_{0-inf} of 4.94 ng*hr/mL and C_{max} of 4.22 ng/mL for BHV4157; and an AUC_{0-inf} of 3439.6 ng*h/mL and C_{max} of 481.7 ng/mL, for riluzole.

These findings, taken together, provide reassurance that the riluzole exposure achieved in this study with troriluzole was well within the exposure range that has been safely administered previously. The 280 mg dose of troriluzole is the molar equivalent of 140 mg of riluzole.

Based on the visual inspection of the C_{trough} and repeated-measure analysis for riluzole, the steady-state could be considered as achieved after 5 days of oral administration of 280 mg troriluzole. The PK variability of riluzole AUC and C_{Max} (CVs of ~30%) was lower than what has been previously reported with riluzole tablets.

1.2.2.3 BHV4157 Phase 2: BHV4157-201

BHV4157-201 was a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled parallel-group study designed to assess the safety, tolerability, and efficacy of troriluzole in subjects with spinocerebellar ataxia (SCA). The study consisted of a double-blind 8 week randomization phase. Subjects completing the randomization phase were offered open-label troriluzole treatment based on investigator discretion. The randomization phase is complete. The expanded open-label extension phase through Week 192 is ongoing.

Overall, at greater than 2 years, the observed changes from randomization baseline in total SARA scores of +0.3 points in patients treated with troriluzole suggest an attenuation of disease progression versus the expected rate of decline of approximately +1 to +2 points per year in the SARA in untreated patients, based on cumulative natural history data. These results strongly suggest attenuation of disease progression in troriluzole treated subjects.

1.2.2.4 BHV4157Phase 2: BHV4157-202

BHV4157-202 is a 2b/3, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to assess safety, tolerability, and efficacy of troriluzole as adjunctive therapy when added to standard of care (SOC) treatment in subjects with OCD who failed to respond adequately to SOC pharmacotherapy. Inadequate response on the subjects' current SOC treatment was defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 19 or greater despite at least 10 weeks of treatment at Baseline with the maximum tolerated dose of a selective serotonin reuptake inhibitor (SSRI), clomipramine, venlafaxine or desvenlafaxine medication. The primary objective of the study is to evaluate the efficacy of troriluzole as adjunctive therapy in subjects with OCD who have had an inadequate response to a selective serotonin reuptake inhibitor (SSRI), clomipramine, venlafaxine or desvenlafaxine treatment.

Subjects were randomized to additionally receive placebo (QD) or troriuluzole (200 mg QD after 4 weeks at 140 mg QD). The total duration of the randomization phase was 12 weeks. Subjects who completed the randomization phase were to be offered approximately 96 weeks of open-label troriluzole in an extension phase, as per investigator discretion. The open-label extension phase is ongoing.

Efficacy findings indicate troriluzole 200 mg, administered once daily as adjunctive therapy in subjects with OCD who had an inadequate response to SOC treatment resulted in numerically greater improvement versus placebo in the total Y-BOCS score at Weeks, 4, 8, and 12 of the randomization phase. This difference was statistically significant at Week 8 ($p < 0.041$). At Week 12, the improvement in Y-BOCS score was numerically greater in the troriluzole group relative to placebo, but the treatment difference did not reach statistical significance ($p = 0.220$). In a post-hoc analysis, treatment with troriluzole resulted in improvement in OCD symptoms that was greater both at Week 8 and Week 12 in subjects who had more severe symptoms [redacted] versus less severe symptoms [redacted] at baseline. The treatment difference was statistically significant at Week 8 in the cohort with [redacted]

1.2.2.5 BHV4157 Phase 2: BHV4157-203

BHV4157-203 is an ongoing Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel group study in subjects with mild to moderate AD. Subjects were randomized (1:1) to receive either troriluzole or placebo for 48 weeks. There was a 2-week fixed titration period with a starting dose of troriluzole 140 mg QD or placebo QD. If there were no issues with tolerability of the study drug during the first 2 weeks of the study, the subjects received two 140 mg capsules (total daily dose of 280 mg) for the remaining duration of the study (46 weeks). Subjects who completed the randomization phase were offered approximately 48 weeks of open-label troriluzole in an extension phase, as per investigator discretion.[13] The randomization phase is complete. The open-label extension phase is ongoing. Results for the Week 48 co-primary endpoints indicated troriluzole 280 mg, administered once daily as adjunctive therapy on a background of AchEI and/or memantine medication for up to 48 weeks in participants with mild to moderated AD did not statistically differentiate from placebo on the study's co-primary endpoints, the Alzheimer's Disease Assessment Scale – 11-item cognitive subscale (ADAS-Cog 11) and the Clinical Dementia Rating Sum of Boxes (CDR-Sob).

1.2.2.6 BHV4157 Phase 2: BHV4157–207

BHV4157-207 was a Phase 3, multicenter, randomized, double blind, placebo controlled, 2 arm study designed to assess safety, tolerability and efficacy of troriluzole in subjects with GAD who have a HAM-A score of 18 or greater at screening and baseline. Additionally, GAD symptoms in subjects had to be present for ≥ 1 year and at least of moderate severity on the Clinical Global Impression Scale-Severity of Illness scale at study entry. Subjects were randomized to receive either troriluzole 200 mg (administered as 100 mg BID) or matching placebo for 8 weeks. Eligible subjects had the opportunity to continue in a 48 week extension phase. A total of 390 subjects were treated in the randomization phase.

The study has been completed. Results for the Week 8 primary and secondary endpoints, showed no improvement in GAD symptoms in subjects treated with troriluzole relative to placebo.

1.2.3 Potential for Drug-Drug Interactions

Troriluzole is rapidly converted to riluzole by aminopeptidases in plasma.

Preliminary results from a recently completed clinical drug-drug interaction study with fluvoxamine (CYP1A2 inhibitor) are available and described below.

The potential for troriluzole and riluzole to act as a victim and/or a perpetrator for drug-drug interactions has been evaluated in a number of in vitro assessments with the following conclusions:

Summary of CYP substrate and perpetrator potential assessment:

- Troriluzole is not a CYP substrate, while riluzole is a substrate for CYP1A2
- Neither troriluzole nor riluzole directly inhibits CYPs at >50x therapeutic concentrations (2 μM);
- Both troriluzole and riluzole have the potential to induce CYP2B6 and do not induce CYP3A4/5, whereas riluzole shows potential for inducing CYP1A2 at clinically relevant concentrations.

In transporter studies:

- [redacted]

[redacted]

[redacted]

[redacted]

In conclusion, CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when troriluzole is given concurrently with agents that affect CYP1A2 activity. Potent inhibitors of CYP1A2 (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, vemurafenib) could decrease the rate of

riluzole elimination, while inducers of CYP1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

Results from a drug-drug interaction clinical study of troriluzole with a strong CYP1A2 inhibitor, fluvoxamine, indicate that riluzole concentrations may be increased up to 3-fold, consistent with CYP1A2 inhibition of riluzole metabolism. These findings are consistent with in vitro results suggesting that riluzole is a sensitive CYP1A2 substrate.

Potential interactions may occur when troriluzole is given concurrently with other agents which are also metabolized primarily by CYP1A2 (e.g., theophylline, caffeine, and tacrine) and to a lesser extent, CYP2B6; these are however, less likely to be of clinical significance. Currently, it is not definitively known whether riluzole results in clinically significant CYP1A2 or CYP2B6 enzyme induction in humans, although lack of evidence of substantial autoinduction of riluzole metabolism after multiple dosing suggests only modest effects on CYP1A2. Additionally, although the BCRP and OAT3 transporters are inhibited by riluzole in vitro (IC_{50} > 5 μM for both), the magnitude of inhibition at the clinical dose of troriluzole is unlikely to be of clinical significance.

1.2.4 Specific Populations

As per the United States Product Insert (USPI), riluzole metabolism has been assessed in special populations, characterized by hepatic impairment (2 to 3 fold increase in AUC with Child-Pugh Scores of A and B), renal impairment (no effect), age (no effect), gender (no effect), smokers (20% faster elimination) and race (Japanese compared to Caucasians: no effect). Dedicated studies with troiluzole have not been conducted.

1.2.5 Clinical Adverse Event Profile

Troriluzole readily metabolizes to riluzole. Therefore, the 20 years' global clinical experience is important to summarize herein.

1.2.5.1 Troriluzole

As described in the current IB, clinical experience with troriluzole derives from Phase 1 studies in healthy volunteers and a Phase 2b/3 studies in subjects with SCA, OCD, GAD and AD. Single doses up to 200 mg and multiple doses up to 280 mg daily have been well tolerated without evidence of new, clinically significant safety signals or lab abnormalities compared to the Rilutek package label. As described in the current IB, clinical experience with troriluzole during the double-blind randomization phase of study BHV4157-201 at 140 mg QD for 8 weeks was well tolerated in adult subjects with SCA. The randomization phase is complete and the Week 192 extension phase is ongoing. Preliminary safety findings indicate that troriluzole up to 280 mg QD appear to be generally well tolerated.

1.2.5.2 BHV4157-201: Phase 2 Clinical Adverse Event Profile

Study BHV4157-201 is an ongoing study of adult subjects with spinocerebellar ataxia. In the initial part of the study subjects were either given BHV-4157 (140 mg once daily) or placebo. A

total of 141 subjects were enrolled. Of these subjects, 138 continued into a 48-week open label phase, where all subjects received troriluzole 140 mg daily. Troriluzole at 140 mg daily was well-tolerated without any meaningful events for safety or clinical lab values.

During the double-blind randomization phase, administration of troriluzole at 140 mg QD for 8 weeks was well tolerated in adult subjects with SCA. The safety profile of troriluzole 140 mg QD during long-term treatment (combined randomization and extension phases through the 07-Sep-2018 data cutoff date) was consistent with the troriluzole safety profile observed during the randomization phase.

There have been three deaths reported in this study as of July 28, 2022. The frequency of treatment-emergent serious AEs (SAE) was ≥ 5%.

During the randomization phase, no single SAE preferred term was reported by more than 1 subject. Pneumonia was the most frequently reported SAE for subjects who received at least 1 dose of troriluzole in either phase of the study (3 subjects). All other SAEs were reported for single subjects. As of 17-Sept-2018, in subjects who received at least one dose of troriluzole, there were 13 SAEs reported in 8 subjects: these events included syncope, fever, inflammation of the mesenteric tissue, pneumonia, dehydration, elevated CPK, weakness, severe back pain, suicidal ideation, cerebral infarction, atrial fibrillation, chest tightness and high blood pressure. All of these SAEs were considered not related to treatment with troriluzole, with the exception of 4 SAEs reported in 3 subjects. These treatment-related SAEs included atrial fibrillation and cerebral infarction (1 subject), pneumonia (1 subject) and syncope (1 subject).

Syncope was considered possibly related. Atrial fibrillation, cerebral infarction, and pneumonia were considered unlikely related to troriluzole.

The frequency of AEs leading to discontinuation was 4.2% in the troriluzole group and 0% in the placebo group during the randomization phase and 8.0% overall after at least 1 dose of troriluzole in either phase of the study.

During the randomization phase, no single AE preferred term led to discontinuation of more than 1 subject. Dizziness led to discontinuation of treatment for 3 (2.2%) subjects after at least 1 dose of troriluzole in either phase of the study. Fatigue, headache, and nausea each led to discontinuation of 2 (1.5%) troriluzole-treated subjects.

The majority of treatment-emergent AEs were mild in severity, not related to study therapy, and resolved spontaneously by the end of treatment. The most frequently (≥ 5%) reported treatment-emergent AEs during the randomization phase were dizziness (8/71 [11.3%] in the troriluzole group and 1/70 [1.4% in the placebo group), fatigue (6/71 [8.5%] in the troriluzole group and 3/70 [4.3% in the placebo group), fall (5/71 [7.0%] in the troriluzole group and 1/70 [1.4% in the placebo group), headache (4/71 [5.6%] in the troriluzole group and 4/70 [5.7% in the group placebo), nausea (4/71 [5.6%] in the troriluzole group and 4/70 [5.7% in the placebo group), and muscle spasm (4/71 [5.6%] in the troriluzole group and 2/70 [2.9% in the placebo group).

The most frequently (≥ 5%) reported treatment-emergent AEs after receiving at least 1 dose of troriluzole were similar to those reported during the randomization phase: fall (15.9%), dizziness

(12.3%), headache (10.1%), fatigue (9.4%), nausea (9.4%), balance disorder (8.0%), viral upper respiratory tract infection (7.3%), arthralgia (6.5%), back pain (6.5%), and muscle spasms (6.5%). The most frequently reported treatment-emergent AEs are presented in Table 2:

Table 2: Most Frequently Reported Treatment-emergent AEs in Study BHV4157-201

Treatment Emergent AE	Number of Participants (%)	Study Group
Dizziness	8 (11.27%) 1 (1.43%)	Troriluzole Placebo
Fatigue	6 (8.45%) 3 (4.29%)	Troriluzole Placebo
Fall	5 (7.04%) 1 (1.43%)	Troriluzole Placebo
Headache	4 (5.63%) 4 (5.71%)	Troriluzole Placebo
Nausea	4 (5.63%) 4 (5.71%)	Troriluzole Placebo
Muscle Spasms	4 (5.63%) 2 (2.86%)	Troriluzole Placebo

There were no clinically meaningful trends in laboratory values identified during the randomization phase and no subjects had AST or ALT laboratory values >3 X ULN. Refer to the most current IB for details.

1.2.5.3 Riluzole

The following key information regarding clinical safety of riluzole in ALS is presented from the current USPI. The adverse reactions of hepatic injury, neutropenia, and interstitial lung disease have been described under “Warnings and Precautions” in the riluzole USPI. See current IB for details.

The adverse reactions that occurred in at least 2% of Rilutek-treated patients (50 mg twice daily) in pooled placebo-controlled trials (Study 1 and 2), and at a higher rate than placebo are presented in the table below.

A recent systematic review and meta-analysis of riluzole clinical trial data from other neurological disease indications showed that treatment with riluzole was well tolerated at doses of up to 200 mg daily.[14] This study analyzed safety data from 9 studies encompassing 1528 randomized patients, with Huntington’s disease, Parkinson’s disease, multiple systems atrophy, progressive supranuclear palsy, and several forms of ataxia.

Riluzole-Adverse Reactions in Pooled Placebo-Controlled Trials in Patients with ALS

Rilutek 50 mg Twice Daily (N=313)		**Placebo (N=320)**	
Asthenia	19%		12%
Nausea	16%		11%
Decreased lung function	10%		9%
Hypertension	5%		4%
Abdominal Pain	5%		4%
Vomiting	4%		2%
Arthralgia	4%		3%
Dizziness	4%		3%
Dry Mouth	4%		3%
Insomnia	4%		3%
Pruritus	4%		3%
Tachycardia	3%		1%
Flatulence	3%		2%
Increased Cough	3%		2%
Peripheral Edema	3%		2%
Urinary Tract Infection	3%		2%
Circumoral Paresthesia	2%		0%
Somnolence	2%		1%
Vertigo	2%		1%
Eczema	2%		1%

Source: COVIS USPI, 2020

1.2.5.4 Elevations in Liver Function Tests

In the Phase I studies BHV4157-101, BHV4157-102, BHV4157-103, BHV4157-104, BHV4157-105, BHV4157-106 or BHV4157-107 no clinically significant LFT changes (values >3x ULN) were observed in subjects on study drug.

In the 8 week placebo controlled phase of BHV4157-201 study, there were no subjects who received at least one dose of troriluzole either during the randomization phase or the open-label extension phase (through 48 weeks) that experienced treatment emergent AST or ALT laboratory abnormalities > 3x ULN, or total bilirubin elevations > 2x ULN.

In the 12 week placebo controlled phase of BHV4157-202 study, most subjects in both treatment groups had normal ALT, AST, and total bilirubin both at baseline and on treatment. Assessment of maximum observed LFT abnormalities on treatment in the troriluzole group identified 2/118 (1.7%) subjects with on-treatment ALT > 3x and <5x ULN (both with normal ALT at baseline), and 2/118 (1.7%) subjects with AST > 5x ULN (both with normal AST at baseline). No subjects in the troriluzole group had on-treatment abnormalities of total bilirubin > 2x ULN during the randomization phase; one subject had total bilirubin 1.9x ULN. None of subjects had both ALT and total bilirubin elevations that met criteria for Hy's Law.

In the BHV4157-203 study, overall, the liver profile of troriluzole was comparable to that of placebo. For most subjects in both treatment groups, the maximum observed LFT measurements were normal at baseline and on treatment. Assessment of maximum observed abnormalities on treatment identified 4 subjects in the troriluzole group with ALT > 3x ULN on treatment (1 with ALT > 5x ULN, and all 4 with normal ALT at baseline) and 1 subject with AST > 3x ULN on treatment (and normal AST at baseline). None of the placebo-treated subjects had ALT or AST > 3x ULN. One subject in the troriluzole group had total bilirubin > 2x ULN on treatment (with > ULN to ≤ 1.5x ULN at baseline), and 2 subjects in the placebo group had total bilirubin > 2x ULN on treatment, both with elevated total bilirubin at baseline.

In the BHV4157-206 study which is ongoing in the randomization phase and remains blinded to treatment assignment, 216 subjects have been randomized and received at least 1 dose of blinded study drug (either troriluzole or placebo, with a 1:1 randomization assignment) as of 28-Jun-2021. SAEs have been reported in 18 subjects; 1 SAE (liver function test increased) was considered related to study drug.

In the BHV4157-207 study, most subjects in both treatment groups had normal ALT, AST and total bilirubin both at baseline and on-treatment during the double-blind randomization phase. Assessment of maximum observed LFT abnormalities on treatment in the troriluzole group identified 7 (3.6%) on-treatment ALT > 3x ULN, and 2 (1%) on-treatment AST > 3x ULN in the troriluzole group. One (0.5%) on-treatment ALT > 3x ULN and 1 (1.1%) on-treatment AST > 3x ULN was observed in the placebo group. On-treatment abnormalities of total bilirubin were infrequent (none in the troriluzole group and 1 in the placebo group).

Cases of drug-induced liver injury, some of which were fatal, have been reported in patients taking Rilutek. Asymptomatic elevations of hepatic transaminases have also been reported, and in some patients have recurred upon re-challenge with Rilutek. In clinical studies, the incidence of elevations in hepatic transaminases was greater in Rilutek-treated patients than placebo-treated patients. The incidence of elevations of ALT above 5x ULN was 2% in Rilutek-treated patients. Maximum increases in ALT occurred within 3 months after starting Rilutek. About 50% and 8% of Rilutek-treated patients in pooled Studies 1 and 2, had at least one elevated ALT level above ULN and above 3x ULN, respectively. Monitor patients for signs and symptoms of hepatic injury, every month for the first 3 months of treatment, and periodically thereafter. The use of Rilutek is not recommended if patients develop hepatic transaminases levels greater than 5x ULN. Discontinue Rilutek if there is evidence of liver dysfunction (e.g., elevated bilirubin).

1.2.5.5 Neutropenia

Troriluzole has not been associated with hematologic findings in nonclinical toxicology studies to date. In Study BHV4157-101, one subject in the 17.5 mg BID cohort experienced transient and mildly decreased white blood cell count after three days of treatment; however, this subject evidenced moderate decline during the screening period prior to medication administration. The subject's count increased while on continued study drug and normalized within 6 days after onset. Cases of severe neutropenia (absolute neutrophil count less than 500 per mm^3) within the first 2 months of Rilutek treatment have been reported. Advise patients to report febrile illnesses.

1.2.5.6 Interstitial Lung Disease

Troriluzole has not been associated with pulmonary findings in nonclinical toxicology studies to date.

For riluzole according to the USPI, rare cases of interstitial lung disease have been reported, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis. If respiratory symptoms develop such as dry cough and/or dyspnea, chest radiography should be performed, and in case of findings suggestive of interstitial lung disease or hypersensitivity pneumonitis (e.g., bilateral diffuse lung opacities), riluzole should be discontinued immediately. In the majority of the reported cases, symptoms resolved after drug discontinuation and symptomatic treatment.

1.2.6 Potential Risk to Fetal Development

Troriluzole has not yet been assessed in fertility and fetal development studies.

As described in the USPI, oral administration of riluzole to pregnant animals during the period of organogenesis caused embryotoxicity in rats and rabbits at doses of 27 mg/kg and 60 mg/kg, respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m^2 basis. Evidence of maternal toxicity was also observed at these doses. When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

1.3 Study Rationale

1.3.1 Study Design Rationale

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

1.3.2 Dose Selection

[redacted]

[redacted]

1.3.3 Preclinical Pharmacology

Troriluzole is a new chemical entity prodrug that upon being cleaved in the plasma releases riluzole. Troriluzole is stable in saliva and gastric fluids, and was designed to avoid first pass metabolism in the liver before being cleaved to riluzole. Preclinical studies in rodents with troriluzole show extended riluzole concentrations as compared to oral doses of riluzole itself. Both oral gavage and IV administration of troriluzole to cynomolgus monkeys results in cleavage to riluzole. This is consistent with data suggesting that the main route of prodrug cleavage is mediated by serum-based enzymes.

Because of its unique glutamate-modulating properties that have been elucidated over the last decade, riluzole has gained considerable attention. Riluzole appears to modulate glutamate neurotransmission by several pharmacological mechanisms. The drug was originally developed as an anticonvulsant, and early studies showed it to oppose several actions of glutamate *in vitro* and *in vivo* [23,24] . More recent studies demonstrate that the drug may act by several distinct mechanisms effecting amino acid neurotransmitter (AANt) function. Riluzole has also been shown to inhibit the release of glutamate *in vivo* [25] and *in vitro* [26-28]. Riluzole interacts with a large number of ion channels (voltage-activated sodium channels [29-32,] voltage-gated calcium channels [33,34], and voltage-gated potassium channels [31,35-38]) that may contribute to a reduction in glutamate release.

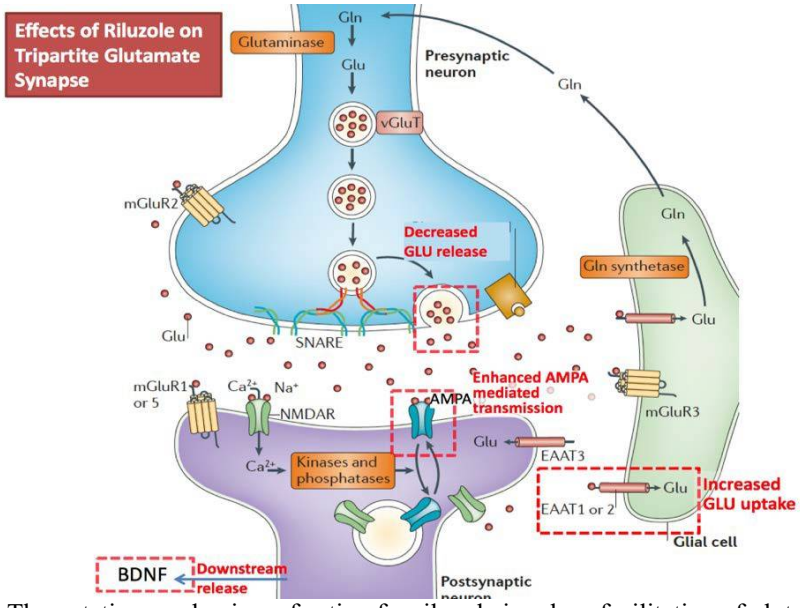
Recently another action of riluzole has been described which may prove to be of substantial importance for its clinical actions: enhancement of glial reuptake of glutamate occurring in animal models at free concentrations achieved with clinical doses. In rat synaptosomes, acute riluzole treatment was shown to increase glutamate uptake [39,40.] More recently, the drug was found to specifically enhance glutamate uptake by astrocytes in culture [41], and in HEK cells expressing excitatory amino acid transporters [42.] The same effect has been documented *in vivo* in rat spinal cord, where riluzole reverses the decrease in glutamate transport seen after nerve injury[43.] While the molecular mechanisms underlying this effect remain unclear, it is likely that riluzole interacts with and/or upregulates one or more of the excitatory amino acid transporters (EAAT).

Recent evidence, supports this mechanism by demonstrating that chronic administration of riluzole increases EAAT2 (also called GLT-1) expression and increases both glial and neuron amino acid neurotransmitter cycling in rats [44,45.] This finding is consistent with the observation in humans that riluzole increases glutamate-glutamine cycling [46.]

Synaptic and extrasynaptic glutamate can have dramatically different effects on a neuron. Synaptic glutamate, and specifically the activation of synaptic NMDA and AMPA receptors [47-50], activates trophic downstream effectors, including CREB and BDNF, and preserves neuronal viability. Conversely, extrasynaptic glutamate and activation of extrasynaptic NMDA receptors reduces CREB activity and BDNF expression, opposes trophic effects on neurons, and can lead to atrophy and cell death [51-54.] It is therefore postulated that the upregulation of glial glutamate reuptake results in decreased extrasynaptic glutamate concentrations and a release from the tonic inhibition of the presynaptic neurons by activation of the presynaptic mGluR 2/3 receptors. This may provide a mechanism for the finding that riluzole can induce trophic factors, including BDNF, and lead to neuroprotection and resiliency [55-57.] As an additional potential mechanism of neuroplasticity action, riluzole has also been recently shown to enhance the surface expression of GluR1 and GluR2 and increase membrane potential depolarization in a time- and dose-dependent manner in cultured hippocampal neurons [58].

While the prominence of riluzole effects on glutamatergic neurotransmission has been amply documented, riluzole apparently alters signaling of other neurotransmitter systems, as well. While these effects occur at higher concentrations, it cannot be excluded that some of the biological effects of riluzole are attributable to non-glutamatergic effects.

Figure 2: Schematic representation on the mechanism of action of riluzole



The putative mechanism of action for riluzole involves facilitation of glutamate update at Excitatory Amino Acid Transporters located on glia (60).

In summary, riluzole has been documented to have a wealth of pharmacological actions, including interactions with several types of ion channels, cellular signaling mechanisms, and facilitation of glutamate reuptake. Several of these actions of riluzole could be viewed as

neuroprotective, and potentially confer therapeutic effects in SCA. Specifically, the Sponsor considers several mechanisms as relevant to SCA (illustrated in Figure 2):

- Activating effects at small-conductance (KCa2.1-2.3) and intermediate-conductance (KCa3.1) calcium-activated potassium channels;
- Altering GABAergic neurotransmission;
- Facilitation of glutamate uptake via EAATs located on glial cells;
- Reducing presynaptic glutamate release through actions at the voltage-gated ion channels;
- Enhanced transmission through synaptic AMPA receptors;
- Effects on neurotrophic agents such as BDNF.

1.4 Research Hypothesis

Troriluzole monotherapy for 48 weeks is superior to placebo in the treatment of Spinocerebellar Ataxia.

2 STUDY OBJECTIVES

2.1 Primary

- To compare the efficacy of troriluzole (200 mg once daily) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) after 48 weeks of treatment as measured by the total score on the Modified Functional Scale for the Assessment and Rating of Ataxia [f-SARA]

2.2 Secondary

- To compare the efficacy of troriluzole versus placebo on patient impression of benefit via use of the Patient Impression of Function and Activities of Daily Living Scale (PIFAS), an internally developed twelve-item instrument modeled after the FACIT-Fatigue Scale
- To compare the efficacy of troriluzole versus placebo on activities of daily living as measured by the Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale (FARS-ADL)
- To compare the efficacy of troriluzole versus placebo on daily functioning as measured by the Functional Staging for Ataxia Scale from the Friedreich's Ataxia Rating Scale (FARS-FUNC)
- To assess of the safety and tolerability of troriluzole in subjects with SCA

2.3 Exploratory

- To compare the efficacy of troriluzole versus placebo on lower extremity mobility and activities as measured by the Neuro-QOL Lower extremity mobility scale
- To compare the efficacy of troriluzole versus placebo on upper extremity function and activities as measured by the Neuro-QOL Upper Extremity Scale
- To compare the efficacy of troriluzole versus placebo on daily fatigue and activities as measured by the Neuro-QOL Fatigue Scale
- To compare efficacy of troriluzole versus placebo on clinician impression of global functioning via use of the Clinical Global Impression-Global Improvement Scale (CGI-I)
- To compare the efficacy of troriluzole versus placebo on patient impression of global functioning as measured by the Patient Global Impression Scale (PGI)
- [redacted]

[redacted]

[redacted]

3 STUDY ENDPOINTS

3.1 Primary

- The total score on the Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA) at Week 48

3.2 Secondary

- Patient Impression of Function and Activities of Daily Living Scale (PIFAS)
- Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale (FARS-ADL)
- Functional Staging for Ataxia (FARS-FUNC)
- Safety and tolerability of troriluzole will be measured by the frequency and severity of adverse events and discontinuations due to adverse events.

3.3 Exploratory Outcome Measures

- Neuro-QOL Lower Extremity
- Neuro-QOL Upper Extremity
- Neuro-QOL Fatigue
- Clinical Global Impression-Global Improvement Scale (CGI-I)
- Patient Global Impression Scale (PGI)
- [redacted]

[redacted]

[redacted]

3.4 Clinical Lab Test

- Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count;
- Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin (if ≥ 2 mg/dl bilirubin will be fractionated for reporting of direct and indirect values), glucose, eGFR, creatinine, BUN, uric acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase, Lipase, TSH, and T4
- Urinalysis: pH, specific gravity, protein, ketones, glucose, blood, and microscopic exam (completed only if any part of the urinalysis is not negative);
- Additional tests: HIV, HBsAg and HCV antibody at screening

4 STUDY PLAN

4.1 Study Design and Duration

BHV4157-206 is a Phase III, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to assess safety, tolerability, and efficacy in a population of patients with Spinocerebellar Ataxia (SCA). Subjects will be randomized to receive placebo (QD) or troriluzole (200 mg QD) and will be stratified by diagnosis (genotype). The 200 mg dosage was selected for evaluation in the current study based on evidence summarized in Section 1.3.2.

Subjects with SCA1, SCA2, and SCA3 genotypes will comprise approximately 80%-90% of the randomized subjects. Patients with SCA6, SCA7, SCA8, and SCA10 genotypes will comprise approximately 10% of the randomized subjects in total. Eligible subjects will be randomized to receive once daily dosing of troriluzole or placebo. Randomization will be stratified by 3 SCA subgroups: SCA1 & 2; SCA3; and SCA 6, 7, 8, 10. Subjects will receive either troriluzole (140mg) or matching placebo for the first 4 weeks and then will be increased to 200 mg (or matching placebo) for the duration of the study. Down titration in the Randomization Phase will only be temporarily allowed for tolerability purposes. **Prior to down titration, these cases should be discussed with the Biohaven Medical Monitor. For patients who experience fatigue or dizziness after dosing, dosing should be given every night at bedtime (QHS).**

Dosing will continue for approximately 48 weeks. If absolutely necessary, treatment duration may be longer due to the COVID-19 pandemic as detailed in the time and events table. Under these circumstances, the sponsor medical monitor should be consulted and must approve the request to change the treatment duration (may be extended if necessitated by the COVID-19 pandemic from 48 weeks up to maximum of 60 weeks (12 week extension)).

Subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit. In addition, subjects completing the Randomization Phase will be offered up to 192 weeks of open-label treatment provided the Primary Investigator (PI) believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will not be required to wash-out of drug or complete the follow-up safety visit, but instead should continue dosing as specified in the extension phase.

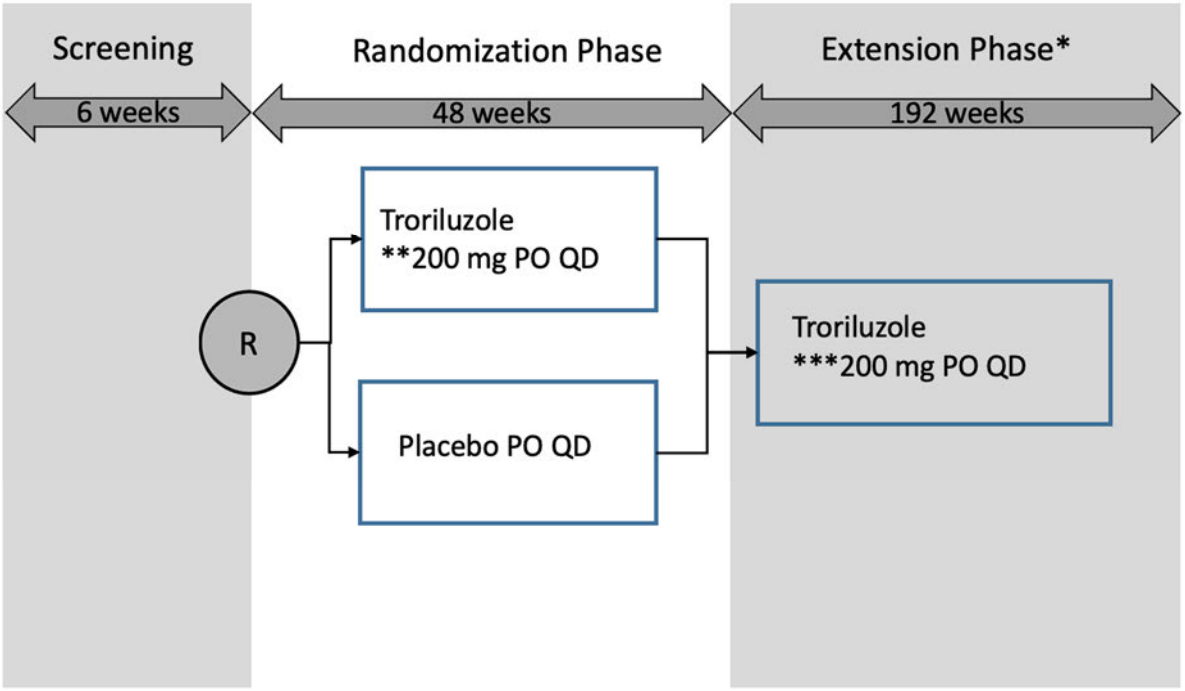
Subjects entering the Extension Phase will have their first Extension Visit four weeks after the Week 48 Randomization Phase visit. Thereafter, subjects will undergo visits every four weeks up through week 12 of the Extension Phase as outlined in Table 4 (Schedule of Assessments/Time & Events- Extension Phase). Subjects will then undergo visits every 12 weeks up to Week 192 of the Extension phase. All subjects will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Extension Phase will continue with the same dose taken at the end of the Randomization Phase. Subjects on placebo in the Randomization Phase will be switched in a blinded manner to troriluzole 140 mg for the first four weeks and then will be increased to 200 mg for the duration of the study. Temporary down titration while on the 200 mg dosing will only be allowed for tolerability purposes and must be discussed with the medical monitor. All Visits after Extension week 4 will be open-label. Subjects who enter the Extension Phase on 140mg due to intolerability issues can be rechallenged to increase to 200mg after Extension Week 4 at PI discretion.

Subjects will be assessed at clinic visits per the Schedule of Assessments/Time & Events.

4.2 Study Schematic

Figure 3: Study Schematic



R, signifies randomization; randomization will be stratified by 3 SCA subgroups: SCA1 & 2; SCA3; and SCA 6, 7, 8, 10.

* Eligible subjects for the Extension Phase will include those for whom the PI believes extended treatment with troriluzole would offer an acceptable risk-benefit profile.
**Subjects will receive 140 mg for the first four (4) weeks and will then be increased to 200 mg for the duration of the study. Down titration to 140 mg will only be temporarily allowed to address tolerability issues.

***Subjects entering the Extension Phase will continue with the same dose taken at the end of the Randomization Phase. Subjects on placebo in the Randomization Phase will be switched in a blinded manner to 140 mg QD for the first four weeks and then will be increased to 200 mg QD for the duration of the study. Down titration after the first four weeks of the Extension Phase will only be allowed for tolerability purposes. All visits after Extension Phase Week 4 will be open-label.

4.3 Schedule of Assessments

Table 3: Schedule of Assessments and Events – Randomization Phase

	Screen	Baseline	Week 4 (+/-5)	Week 8 (+/-5)	Week 12 (+/-5)	Week 16[2] (+/-5)	Week 24 (+/-7)	Week 36 (+/-7)	Week 48[3, 5] Or Early DC (+/-14)	Follow-up Week 2 (ONLY for subjects NOT entering extension phase or who discontinued early)[4]	Additional Instruction
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
Eligibility Assessments											
Informed Consent	X										
Inclusion/Exclusion	X										Should be re-reviewed at Baseline
Medical History	X										
Demographic Assessment	X										
Disease History	X										
Neurological Exam	X			X							
Mini Mental State Exam (MMSE)	X										
Pregnancy Test for WOCBP (serum)	X								X		
Pregnancy Test for WOCBP (urine)[1]		X	X		X		X	X			The site may test a patient at any time if they suspect the patient may be pregnant.

	Screen	Baseline	Week 4 (+/-5)	Week 8 (+/-5)	Week 12 (+/-5)	Week 16[2] (+/-5)	Week 24 (+/-7)	Week 36 (+/-7)	Week 48[3, 5] Or Early DC (+/-14)	Follow-up Week 2 (ONLY for subjects NOT entering extension phase or who discontinued early)[4]	Additional Instruction
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
Safety Assessments											
Laboratory Assessments including chemistry, hematology & urinalysis	X	X	X	X	X	X	X	X	X	X	No fasting required
Pharmacokinetics Sample			X	X	X		X	X	X		PK samples should also be drawn when there are any SAEs or severe AEs that are possibly drug related
Pharmacogenetics Sample	X										
Physical Exam	X	X			X		X		X		PE will be done at W4 if warranted by emergence of new AE's
Physical Measurements	X	X	X	X	X		X	X	X		
Vital Signs	X	X	X	X	X		X	X	X		
12-Lead ECG	X			X	X		X		X		
Concomitant Medication Review	X	X	X	X	X		X	X	X	X	
Adverse Event Assessments		X	X	X	X		X	X	X	X	

	Screen	Baseline	Week 4 (+/-5)	Week 8 (+/-5)	Week 12 (+/-5)	Week 16[2] (+/-5)	Week 24 (+/-7)	Week 36 (+/-7)	Week 48[3, 5] Or Early DC (+/-14)	Follow-up Week 2 (ONLY for subjects NOT entering extension phase or who discontinued early)[4]	Additional Instruction
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X		X	X	X	X	
Clinical Outcome Assessments											
f-SARA	X	X	X	X	X		X	X	X	X	This should be the first clinical outcome assessment done at each visit. Subjects with a 2-point change or greater on the Modified Functional SARA between Screening and Baseline will not be eligible for randomization.
PIFAS		X	X	X	X		X	X	X		
FARS-ADL		X	X	X	X		X	X	X		
FARS-FUNC		X	X	X	X		X	X	X		
Neuro-QOL Lower Extremity		X		X	X		X	X	X		
Neuro-QOL Upper Extremity		X		X	X		X	X	X		

	Screen	Baseline	Week 4 (+/-5)	Week 8 (+/-5)	Week 12 (+/-5)	Week 16[2] (+/-5)	Week 24 (+/-7)	Week 36 (+/-7)	Week 48[3, 5] Or Early DC (+/-14)	Follow-up Week 2 (ONLY for subjects NOT entering extension phase or who discontinued early)[4]	Additional Instruction
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	
Neuro-QOL Fatigue		X		X	X		X	X	X		
CGI-I				X			X		X		
PGI				X			X		X		
Clinical Drug Supply											
Randomization		X									
Dispense Study Drug[6]		X	X	X	X		X	X	X		Dispense at Wk 48 only if entering Extension Phase
Drug Accountability			X	X	X		X	X	X		

[1] WOCBP will be provided with an at home pregnancy test to take in between the every 3 month visits (12 – 48). Subjects should be instructed to contact the study doctor if they become pregnant at any time during the study. Site should report pregnancies to PPD. Site should also contact the subject in between the 3-month office visits to remind them of the pregnancy testing requirement, as applicable. Site may test a patient at any time if pregnancy is suspected.
[2]The week 16 Visit is only for routine labs, which may be done locally
[3]The week 48 Visit is +/- 2 Weeks to ensure the primary f-SARA rater is present at the 48 Week Visit
Visit Window during the Randomization Phase is +/- 5 Days for Weeks 4, 8, 12, and 16; and +/- 7 days for Weeks 24 and 36
[4]All subjects who discontinue study treatment early should complete an early discontinuation visit as well as the 2-Week Post Dose Visit. The 2-Week Post Dose Visit would not need to occur if the subject discontinued dosing more than 2 weeks prior to the early discontinuation visit
[5] If absolutely necessary, treatment duration may be extended due to the COVID-19 pandemic. Under these circumstances, the sponsor medical monitor should be consulted and must approve the request to change the treatment duration (may be extended if necessitated by the COVID-19 pandemic from 48 weeks up to maximum of 60 weeks).
[6] If the study site needs to send drug overnight via certified and tracked courier and this is acceptable to the institution because a visit is absolutely not possible because of the COVID-19 pandemic, this is permissible per study. The sponsor should be consulted prior to shipping drug.

Table 4: BHV4157-206 SCA Time & Events Schedule - Extension Phase

	Extension Week 4	Extension Week 8	Extension Week 12	Extension Week 16[2]	Extension Week 24	Extension Week 36	Extension Week 48	Extension Week 60	Extension Week 72	Extension Week 84	Extension Week 96 or Early DC (If DC prior to Ext Week 96)	2-Wk Post Last Dose Only complete if the subject DCs prior to Week 96 or is not continuing in extension
Eligibility Assessments												
Neurological Exam					X		X		X		X	
Pregnancy Test for WOCBP (serum)					X		X	X	X	X	X	X
Pregnancy Test for WOCBP (urine)[1]	X	X	X			X						
Safety Assessments												
Laboratory Assessments including urinalysis	X				X		X		X		X	
Pharmacokinetic Sample[3]												
Lab: LFT tests only (ALT, AST, BILI, GGT)		X	X	X		X		X		X		X
Physical Exam					X		X		X		X	
Physical Measurements	X	X	X		X	X	X	X	X	X	X	
Vital Signs	X	X	X		X	X	X	X	X	X	X	
12-Lead ECG					X		X		X		X	

	Extension Week 4	Extension Week 8	Extension Week 12	Extension Week 16[2]	Extension Week 24	Extension Week 36	Extension Week 48	Extension Week 60	Extension Week 72	Extension Week 84	Extension Week 96 or Early DC (If DC prior to Ext Week 96)	2-Wk Post Last Dose Only complete if the subject DCs prior to Week 96 or is not continuing in extension
Concomitant Medication Review	X	X	X		X	X	X	X	X	X	X	X
Adverse Event Assessments	X	X	X		X	X	X	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X		X	X	X	X	X	X	X	X
Clinical Outcome Assessments												
f-SARA	X	X	X		X	X	X	X	X	X	X	X
PIFAS	X	X	X		X		X		X		X	
FARS-ADL	X	X	X		X		X				X	
FARS-FUNC	X	X	X		X		X				X	
Neuro-QOL Lower Extremity		X			X		X				X	
Neuro-QOL Upper Extremity		X			X		X				X	
Neuro-QOL Fatigue					X		X				X	
CGI-I					X		X				X	
PGI					X		X				X	

	Extension Week 4	Extension Week 8	Extension Week 12	Extension Week 16[2]	Extension Week 24	Extension Week 36	Extension Week 48	Extension Week 60	Extension Week 72	Extension Week 84	Extension Week 96 or Early DC (If DC prior to Ext Week 96)	2-Wk Post Last Dose Only complete if the subject DCs prior to Week 96 or is not continuing in extension
Clinical Drug Supply												
Dispense Study Drug	X	X	X		X	X	X	X	X	X	X if continuing in extension	
Drug Accountability	X	X	X		X	X	X	X	X	X	X	

	Extension Week 108	**Extension Week 120**	**Extension Week 132**	**Extension Week 144 or Early DC (if DC is after Ext. Week 96)**	**2-Week Post Last Dose[4] (ONLY complete if subject discontinues after EW 96 or at EW 144)**
Eligibility Assessments					
Neurological Exam		X		X	
Pregnancy Test for WOCBP (serum)	X	X	X	X	X
Pregnancy Test for WOCBP (urine)[1]					
Safety Assessments					
Laboratory Assessments including urinalysis		X		X	
Pharmacokinetic Sample[3]					
Lab: LFT tests only (ALT, AST, BILI, GGT)	X		X		X
Physical Exam		X		X	
Physical Measurements	X	X	X	X	
Vital Signs	X	X	X	X	
12-Lead ECG		X		X	
Concomitant Medication Review	X	X	X	X	X
Adverse Event Assessments	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X

	Extension Week 108	Extension Week 120	Extension Week 132	Extension Week 144 or Early DC (if DC is after Ext. Week 96)	2-Week Post Last Dose[4] (ONLY complete if subject discontinues after EW 96 or at EW 144)
Clinical Outcome Assessments					
f-SARA	X	X	X	X	X
PIFAS		X		X	
FARS-ADL				X	
FARS-FUNC				X	
Neuro-QOL Lower Extremity				X	
Neuro-QOL Upper Extremity				X	
Neuro-QOL Fatigue				X	
CGI-I				X	
PGI				X	
Clinical Drug Supply					
Dispense Study Drug	X	X	X	X (if continuing in extension)	
Drug Accountability	X	X	X	X	

[1] WOCBP will be provided with an at home pregnancy test to take in between the every 3 month visits (12 – 192). Subjects should be instructed to contact the study doctor if they become pregnant at any time during the study. Site should report pregnancies to PPD. Site should also contact the subject in between the 3-month office visits to remind them of the pregnancy testing requirement, as applicable. Site may test a patient at any time if pregnancy is suspected.

[2]The Extension Week 16 Visit is only for routine labs, which may be done locally.
[3] PK samples to be drawn only if there is an AE determined to be related to study drug.
[4]All subjects who discontinue study treatment early should complete an early discontinuation visit as well as the 2-Week Post Dose Visit. The 2-Week Post Dose Visit would not need to occur if the subject discontinued dosing more than 2 weeks prior to the early discontinuation visit.
Visit window is +/- 7 days during the extension phase.

	Extension Week 156	**Extension Week 168**	**Extension Week 180**	**Extension Week 192 or Early DC (if DC is after Ext. Week 144)**	**2-Week Post Last Dose[4]**
Eligibility Assessments					
Neurological Exam		X		X	
Pregnancy Test for WOCBP (serum)	X	X	X	X	X
Pregnancy Test for WOCBP (urine)[1]					
Safety Assessments					
Laboratory Assessments including urinalysis		X		X	
Pharmacokinetic Sample[3]					
Lab: LFT tests only (ALT, AST, BILI, GGT)	X		X		X
Physical Exam		X		X	
Physical Measurements	X	X	X	X	
Vital Signs	X	X	X	X	
12-Lead ECG		X		X	
Concomitant Medication Review	X	X	X	X	X
Adverse Event Assessments	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X

	Extension Week 156	Extension Week 168	Extension Week 180	Extension Week 192 or Early DC (if DC is after Ext. Week 144)	2-Week Post Last Dose[4]
Clinical Outcome Assessments					
f-SARA	X	X	X	X	X
PIFAS		X		X	
FARS-ADL				X	
FARS-FUNC				X	
Neuro-QOL Lower Extremity				X	
Neuro-QOL Upper Extremity				X	
Neuro-QOL Fatigue				X	
CGI-I				X	
PGI				X	
Clinical Drug Supply					
Dispense Study Drug	X	X	X		
Drug Accountability	X	X	X	X	

[1] WOCBP will be provided with an at home pregnancy test to take in between the every 3 month visits (12 – 192). Subjects should be instructed to contact the study doctor if they become pregnant at any time during the study. Site should report pregnancies to PPD. Site should also contact the subject in between the 3-month office visits to remind them of the pregnancy testing requirement, as applicable. Site may test a patient at any time if pregnancy is suspected.
[2]The Extension Week 16 Visit is only for routine labs, which may be done locally.
[3] PK samples to be drawn only if there is an AE determined to be related to study drug.

[4]All subjects who discontinue study treatment early should complete an early discontinuation visit as well as the 2-Week Post Dose Visit. The 2-Week Post Dose Visit would not need to occur if the subject discontinued dosing more than 2 weeks prior to the early discontinuation visit.

Visit window is +/- 7 days during the extension phase.

4.3.1 Screening Phase

The Screening Phase will range from a minimum of 3 days to a maximum of 42. The purpose of the Screening Visit is to ensure that the appropriate patients are entered into the trial. The investigator will determine that the patient meets eligibility criteria and will collect demographic and medical data presenting a full characterization of the patient. It is estimated approximately 270 subjects will enter this phase of the trial.

Please refer to the Schedule of Assessments/Time & Events for details on Screening Procedures.

4.3.2 Randomization Phase

Subjects who are determined to be eligible for the study will enter the Randomization Phase. It is estimated that approximately 210 subjects will enter this phase of the trial. Randomization will be stratified by 3 SCA subgroups: SCA1 & 2; SCA3; and SCA 6, 7, 8, 10. Subjects will receive either troriluzole (140 mg) or matching placebo (in a 1:1 ratio) for the first 4 weeks and then will be increased to 200 mg (or matching placebo) for the duration of the study.

Dosing will continue for approximately 48 weeks. Subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit. Subjects completing the Randomization Phase will be offered approximately 192 weeks of open-label treatment as long as the PI believes open-label treatment offers an acceptable risk-benefit profile.

- Subjects should take their medication daily. If tolerability issues, such as fatigue or dizziness arise, patients should be instructed to take their medication at bedtime (QHS).

- Subjects who continue to experience issues with tolerability after switching to nighttime dosing may temporarily down titrate to 140mg. However, **prior to down titrating their dose**, these patients should be discussed with the Biohaven Medical Monitor.

Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Randomization Phase. There is a visit window of +/- 5 days for Week 4, Week 8, Week 12, and Week 16 Visits; and +/- 7 days for Week 24 and Week 36 Visits during the Randomization Phase of the study. The Week 48 Visit is +/- 2 weeks to ensure the primary f-SARA rater is present at the 48 Week Visit. If absolutely necessary, treatment duration may be longer due to the COVID-19 pandemic. Under these circumstances, the sponsor medical monitor should be consulted and must approve the request to change the treatment duration (may be extended if necessitated by the COVID-19 pandemic from 48 weeks up to maximum of 60 weeks (12 week extension)).

[redacted]

[redacted]

Sponsor Medical Monitor

[redacted]

4.3.3 Extension Phase

Subjects will have visits in the Extension Phase every four weeks through Week 12 and then every 12 weeks thereafter up to Week 192. All subjects will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase. Subjects receiving placebo in the randomization phase will be switched in a blinded manner to 140mg for the first 4 weeks and will then be increased to 200 mg (at the Week 4 visit). Temporary down titration will only be allowed to address tolerability issues and must be discussed with the medical monitor. All visits starting at Week 4 of the Extension Phase will be open-label. Subjects who enter the Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension Week 4 at PI discretion.

Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Extension Phase. There is a visit window of +/- 7 days during the Extension Phase of the study.

4.3.4 Post Study Access to Therapy (if applicable)

There is an open-label extension phase of this trial for up to 192 weeks as described in Section 4.3.3. No other study drug access is available after the extension.

5 POPULATION

5.1 Number of Subjects

Approximately 210 subjects are expected to be randomized into this study.

5.2 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 Population

    a. Subjects with a known or suspected diagnosis of the following specific hereditary ataxias: SCA1, SCA2, SCA3, SCA6, SCA7, SCA8 and SCA10;

        i. A subject should have a confirmed genotypic diagnosis from a CLIA certified lab (can produce test results); or,

        ii. A subject has a family member that has a confirmed genotypic diagnosis from a CLIA certified lab (can produce test results) and must be willing to undergo genetic testing to confirm underlying SCA diagnosis; or,

        iii. A subject has a confirmed genotypic diagnosis from a lab that is not CLIA certified and must be willing to undergo genetic testing to confirm underlying SCA diagnosis; or,

        iv. A subject has clinical evidence that supports diagnosis of one of the aforementioned SCA genotypes but does not have producible test results from a CLIA certified lab from either a family member or for his or herself and the subject must be willing to undergo such testing to confirm the SCA diagnosis (in this case, site must wait for results of genotypic testing prior to randomization)

4. Ability to ambulate 8 meters without human assistance (canes and other devices allowed);

5. Screening f-SARA total score ≥3;

6. Score of ≥1 on gait subsection of the f-SARA;

7. 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;

8. [redacted]

[redacted]

5.3 Exclusion Criteria

12. Target Disease Exceptions

Subjects will be excluded if they have:

a. A ≥ 2-point difference on the Modified Functional SARA score between screening and baseline;

b. MMSE score <24;

c. 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);

d. A prominent spasticity or dystonia that, in the opinion of the investigator, will compromise the ability of the f-SARA instrument to assess underlying ataxia severity

e. A score of 4 on any individual item (Items 1-4) of the f-SARA;

f. 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.

g. Subjects should be excluded at screening or baseline if medical conditions have arisen or there is a change in disease status that could confound the ability of the f- SARA to accurately reflect changes in ataxia severity.

13. 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. [redacted]

c. Active liver disease or a history of hepatic intolerance to medications that in the investigator's judgment, is medically significant;

[redacted]

[redacted]

[redacted]

[redacted]

5.4 Prohibited Concomitant Medications

The Biohaven Medical Monitor should be contacted to discuss any subjects who have been previously treated with riluzole. Treatment with riluzole in the 60 days prior to randomization and during the study is prohibited. Subjects with prior use of riluzole who discontinued due to tolerability or lack of clinical benefit (in the opinion of the Investigator) are not eligible for this

study. Reasons for discontinuation of riluzole should be documented in the subjects' medical chart.

[redacted]

[redacted]

5.5 Women of Childbearing Potential

Women of childbearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post-menopausal is defined as:

- Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL or;
- Woman with irregular menstrual periods and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL or;
- NOTE: FSH level testing is not required for women greater than or equal to 62 years old with amenorrhea of greater than or equal to one year;
- Woman on hormone replacement therapy (HRT).

The requisite drug interaction studies to determine the interaction of troriluzole with oral contraceptives have not been completed to date. It is therefore not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP who are participating in 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 30 days prior to baseline) through 30 days **after** the last dose of study drug. The two methods should include one barrier method (e.g. diaphragm with spermicidal gel, condom with spermicidal gel, intrauterine devices, cervical cap)

and one other method. The other method could include oral contraceptives (e.g. oral contraceptives, injectable contraceptives or contraceptive implant) or another barrier method.

Any male who has a female partner of WOCBP has to avoid becoming pregnant while participating in this study. If male subjects are sexually active and not vasectomized for at least 6 months, and if the subject's female partner is not surgically sterile or is not post- menopausal, then one of the following accepted methods of contraception should be used throughout the study and for 90 days after the last study drug administration:

- Simultaneous use of male condom, and for the female partner, hormonal contraceptives (e.g., birth control pills, implants, patch, depot injection, used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks) before sexual intercourse;

- Simultaneous use of male condom, and for the female partner, diaphragm with intravaginally applied spermicide.

5.6 Deviation from Inclusion/Exclusion Criteria

Any significant event that does not comply with the inclusion exclusion criteria, study conduct, or study procedures will be documented as a deviation. Deviations will be documented and reported through the clinical monitoring of the trial. Deviations will be reported to the IRB/EC at the frequency required by your IRB/EC. There will be no protocol exceptions granted by the Sponsor for Inclusion/Exclusion criteria.

6 STUDY CONDUCT

6.1 Study Materials

The sponsor will provide investigational product which will include troriluzole (140 mg and 60 mg) capsules and matching placebo.

Sites will also be provided with a Regulatory binder, IWRS Manual and any unique source documents and rating scales. Instructions on specimens collected will be provided by a central laboratory.

All sites will use an Electronic Data Capture (EDC) tool to submit study data. Electronic Case Report Forms (eCRFs) will be prepared for all data collections.

Sites will be provided with a Biohaven approved protocol and any amendments.

The investigator will be required to have a centrifuge, a secure locked cabinet or similar (for drug storage) as well as appropriate containers and dry ice for shipment and storage of blood and plasma samples. Enough dry ice, when indicated, should be utilized to allow samples to arrive at their designated laboratory in a frozen state.

Additionally, sites will be provided with the necessary equipment for videotaping administration of the f-SARA. This will include a high-definition video recording device, aluminum tripod, a countdown timer, and gaffers tape.

7 ELIGIBILITY ASSESSMENTS

7.1 Mini Mental State Examination (MMSE)

The MMSE is a 30-point (11-question) measure commonly used to measure cognitive impairment. It tests five areas of cognitive function including orientation, registration, attention and calculation, recall and language.

7.2 Neurologic Exam

A neurological examination will be performed by a trained examining neurologist, which will involve mental status/cognition, cranial nerves, motor system, sensory system, reflexes and coordination/gait. The examination should be carefully documented in the subject's medical and/or study chart.

7.3 Medical History

A full medical history will need to be obtained at the screening visit. This will include but is not limited to: smoking history, cardiovascular disease, and family history of ataxia, if available.

7.4 Safety Assessments

Safety and tolerability will be evaluated by report of adverse events (AE) and by evaluation of abnormalities and clinically significant changes in physical examinations, ECGs, vital signs, and laboratory tests.

7.4.1 Vital Signs and Physical Measurements (Height and Weight)

Sitting vital sign measurements (temperature, blood pressure, and heart rate) will be recorded during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary.

Body weight and height will be recorded at scheduled visits. The following guidelines will aid in the standardization of these measurements.

- The same scale should be used to weigh a given subject throughout the study.
- Scales should be calibrated and zeroed just prior to each subject's weigh-in session.
- A subject should void just prior to being weighed.
- Weight should be recorded before a meal (if applicable) and at approximately the same time each day.

- A subject should be minimally clothed (i.e., no shoes or heavy garments).

7.4.2 Electrocardiogram (ECG)

A 12-Lead ECG will be recorded during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary. Any abnormal ECGs should be reviewed by a cardiologist if the PI is unsure of the clinical significance. If a site is unable to identify a cardiologist for this task, the Medical Lead at Cognitive Research Corporation can review the ECG to determine clinical significance.

7.4.3 Physical Exam

Subjects will undergo a complete physical exam in both the Randomization and Extension Phase of the study. The Physical Exam should include at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, chest (breast) and lungs, cardiovascular, abdomen, skin, and musculoskeletal evaluation by the Principal Investigator or a medically qualified delegate.

7.4.4 Laboratory Assessments

Laboratory testing will include the following:

a. Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count

b. Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, eGFR, creatinine, BUN, uric acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase, Lipase, TSH, and T4;

c. Urinalysis: macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, glucose, and occult blood will be performed during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary. If blood, protein, or leukocytes, are positive microscopic examination will be performed on abnormal findings;

d. Urine pregnancy tests will be performed 72 hours prior to dosing at Baseline, at study visits where lab assessments are not performed, or at the discretion of the Investigator;

e. 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. In addition, if warranted repeat labs can be drawn.

If a participant is unable to come in to the study site and needs to have safety labs conducted locally this is acceptable. The study site should provide the participant or local laboratory with a requisition and should collect the results. All local labs should be sent to the medical monitor for review. Any clinically significant local lab abnormalities should be brought to the Biohaven Medical Monitor's attention immediately.

7.4.5 Pharmacogenetic Blood Sample Collection

A pharmacogenetic sample will be collected at screening in all subjects, who consent to collection of banked sample, for possible exploratory genotype. A pharmacogenetic sample will also be collected at screening for diagnostic genotyping in subjects if testing has not been previously done on the study subject and a copy of results is not available for verification. [redacted]

7.4.6 Pharmacokinetics

[redacted] Subjects should take their dose at their routine time on the days of these visits. Subjects should record the time of their last dose and time of last meal prior to PK assessment to provide to the study staff for entry into the eDC system.

Additionally, PK samples should be drawn if there are any SAEs that could possibly be drug related or severe AEs that could be drug related.

[redacted]

7.4.7 Pregnancy Testing

Pregnancy testing should be performed on all women of childbearing potential (WOCBP) during both the Randomization Phase and Extension Phase of the study. Refer to the Schedule of Assessments/Time & Events for detailed time points in which serum pregnancy tests and urine pregnancy tests are required.

WOCBP will be provided with an at home pregnancy test to take in between the every 3 month visits. Subjects should be instructed to contact the study doctor if they become pregnant at any time during the study. Site should also contact the subject in between the 3-month office visits to remind them of the pregnancy testing requirement, as applicable.

Urine pregnancy testing may also be done at the discretion of the Investigator at any time during the study. Subjects should not continue in the study if the pregnancy test is positive at any time.

7.4.8 Evaluation of Laboratory Assessments

The management of abnormal LFTs are described herein. Scheduled LFTs (ALT, AST, bilirubin, alkaline phosphatase) at Week 4 and through Week 48 visits (see Schedule of Assessments for details) will be evaluated by a physician or other qualified medical personnel.

If AST or ALT values are between 3x ULN and <5x ULN, the Investigator will medically evaluate the subject. Medical assessment of the subject can include the following:

- Must include repeat LFT assessments (ALT, AST, total and direct bilirubin, alkaline phosphatase, PT, aPTT, INR) within 1 week and follow until resolution. The frequency of the repeat tests will be clinically based on trajectory of change (e.g., improving, stable vs increasing). These tests can be performed either at a local, or preferably, central lab

- Assessment of AEs, usage of concomitant medications, exposure to potential hepatic toxins, risk factors for hepatitis or alcoholic liver disease

- Based on overall clinical presentation (severity and extent of lab abnormalities; rate of change of lab values), additional evaluations (as outlined under the scenario of ALT/AST > 5xULN) may be considered.

If any visit shows ALT or AST>5x ULN, the Investigator will assess this as an SAE. The subject will be managed as appropriate, including:

- Study medication must be discontinued immediately

- Bring subject in for physical exam and evaluation.

    - Assess for right heart failure, hypotension, and signs/symptoms of alcohol abuse

    - assess for exposure to toxic dietary/herbal supplements and/or prescriptions drugs that are associated with hepatic effects, such as acetaminophen;

    - assess for potential exposure to environmental toxins

    - Evaluate for abdominal pain, splenomegaly, hepatomegaly

- Repeat LFTs (AST, ALT, total and direct bilirubin, alkaline phosphatase) as soon as possible, with either a local lab or preferably central lab; and, follow to resolution;

- Order other labs tests to rule-out other causes of lab abnormalities and to assess extent of hepatic effects

    - coagulation factors (PT, aPTT, INR)

    - Hepatitis A, B and C serologies

- Epstein-Barr virus serology

- Assess AEs

- Consider gall bladder or ductal imaging studies if presentation suggests potential for gall stones.

Entry into the Extension Phase requires continued impression that open-label treatment offers an acceptable risk-benefit profile. If lab abnormalities in the Randomization Phase are potentially clinically significant then treatment with study drug in the Extension Phase should not begin until such labs near normal limits or in the case of elevated transaminases (ALT or AST) are within 3x ULN. If results from the scheduled Week 48 assessment show emergence of potentially clinically significant lab abnormalities and the subject has already started open-label troriluzole, then labs must be repeated and the LM, based on clinical impression concerning the nature and severity of results, may decide to continue troriluzole. In the case of AST or ALT > 5 x ULN, re-challenge with study drug will not be allowed.

7.4.9 Sheehan Suicidality Tracking Scale (Sheehan-STS)

The Sheehan-STS (S-STS) is a prospective, patient self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors. The S-STS will be completed on a paper form by the clinician, or Sponsor approved designee, at the site. At the screening visit, the recall period for completing the S-STS is 12 months prior; at all other visits, the recall period for completing the S-STS is since the last visit. Subjects who have a S-STS score > 0 should be evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor.

7.5 Clinical Outcomes Assessments

The clinical outcome assessments and other interviews/scales should be performed at a similar time of day at each visit.

- If subjects are traveling a significant distance consideration should be given to minimizing the effects of travel fatigue.

- The order of the tests should include the administration of the f-SARA prior to other clinical / safety outcome assessments

7.5.1 The Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA)

The Modified Functional Scale for the Assessment and Rating of Ataxia (f-SARA) is a modified version of the standard SARA, designed to create new response categories that reflect clinically meaningful changes in patient function. Additionally, the f-SARA includes only the axial items

of the SARA, or items 1 though 4. The appendicular items (items 5-8) are not included in the f-SARA, as they are not sensitive to change over a period of time during which there is a clear decline on other measures. This was assessed in a population of SCA patients administered the SARA approximately every six months for up to two years. This analysis was done on the population described by Ashizawa in 2013.[59]

The f-SARA is administered in the same way the SARA is administered, but the response categories have been modified. Response categories for teach item of the f-SARA range from "0" to "4." In general, these response categories are modified to reflect the following:

0. Normal (no impairment)
1. Mildly impaired function, but no assistance required
2. Moderately impaired function, but needs assistance for certain parts of the task
3. Severely impaired function to the degree that assistance is needed for all parts of the task
4. Unable to perform function

Raters must be pre-approved by sponsor or sponsor representative (i.e. CRO) to rate subjects on the f-SARA. The primary f-SARA rater at each site MUST be present to rate the f-SARA at all visits. A secondary, pre-approved rater may rate visits, with the exception of screening, baseline, and Week 48 in the event the primary rater is unavailable. A secondary rater should only be used for extenuating circumstances.

All f-SARA raters will participate in training on both administration of the f-SARA and rating of the f-SARA. Additionally, raters will be required to be certified in both administration and rating prior to beginning the study, at 3 months, and every 6 months thereafter until completion of the study. **Recertification will not be required after all subjects complete the Open Label Extension Visit Week 48.**

Video recording: Each administration of the f-SARA should be video recorded and up-loaded to a central repository. Approved video-recording equipment will be provided to each site and standardized instructions for videotaping will be provided. Each video recording will be identified by subject number and date (with no personal identifying information allowed). These recordings may be shown for educational purposes, in which case any identifying features (e.g., face) will be blurred so as to protect the identity of any participant. **Subjects who do not wish to be video recorded will be allowed to participate in the study. Video-recording is not required after Open Label Extension Visit Week 48.**

7.5.2 The Patient Impression of Function and Activities of Daily Living Scale (PIFAS)

The Patient Impression of Function and Activities of Daily Living Scale (PIFAS) is a multi-item instrument designed to assess level of functional disability. The scale is rater administered and the items were selected to encompass domains of relevance to SCA (ie mobility, speech/swallowing, fatigue), and to capture primarily function and activities of daily living within these domains. Statements are rated on a 5-point Likert scale ranging from "0" reflecting "not at all" to "4" reflecting "very much."

7.5.3 The Activities of Daily Living Scale from the Friedreich's Ataxia Rating Scale (FARS-ADL)

The FARS is a multicomponent scale designed to assess neurological domains affected in Friedreich's Ataxia, another hereditary cerebellar ataxia disorder. The FARS-Activities of daily Living Sub-scale has been validated in Friedreich's Ataxia, is a measure of functional disability, and correlates with SARA total scores [60.] It assesses 9 areas of activities of daily living with response categories rated on a 5-point scale with "0" reflecting "normal" and "4" reflecting and inability to perform the specific function.

7.5.4 The Functional Staging for Ataxia Scale from the Friedreich's Ataxia Rating Scale (FARS-FUNC)

The FARS-FUNC is a subscale of the FARS designed to provide functional staging for ataxia in which clinicians are asked to assess function on a 6-stage staging system, with "0" reflecting "normal" and "6" reflecting a stage in which the patient is "total disabled." Severity of neurologic disabilities as expressed by both the FARS-ADL and FARS-FUNC have been shown to correlate with disease progression and duration in Friedreich's Ataxia [61].

7.5.5 The Neurology Quality of Life (Neuro-QOL) Lower Extremity Scale (long form)

The Neuro-QOL-Lower Extremity Scale is designed to assess fine motor skills of the lower extremities by asking specific questions about activities of daily living[62.] This is a 19-item scale with questions rated on a 5-point Likert Scale, with "5" reflecting "no difficulty" and "1" reflecting "unable to do" said activity.

7.5.6 The Neurology Quality of Life (Neuro-QOL) Upper Extremity Scale (long form)

The Neuro-QOL-Upper Extremity Scale is designed to assess fine motor skills of the upper extremities by asking specific questions about activities of daily living[62.] This is a 20-item scale with questions rated on a 5-point Likert Scale, with "5" reflecting "no difficulty" and "1" reflecting "unable to do" said activity.

7.5.7 The Neurology Quality of Life (Neuro-QOL) Fatigue Scale (long form)

The Neuro-QOL Fatigue Scale is designed to assess level of fatigue in patients with neurologic disorders [62]. This is a 19-item, patient-rated scale designed to rate a patient's fatigue over the past 7 days. Patients are asked to rate answers to these items on a 5-point Likert scale, with "1" reflecting "never" and "5" reflecting "always."

7.5.8 The Clinical Global Impression-Global Improvement Scale (CGI-I)

The CGI-I is a 7-point scale that requires the clinician to assess how much the subject's illness has improved or worsened relative to the baseline visit and it is rated on a 7 point scale, with "1" reflecting "very much improved" and "7" reflecting "very much worse."

7.5.9 The Patient Global Impression Scale (PGI)

The PGI is a patient self-reported, Likert-based scale used to assess the response of a condition to a therapy. The response categories of the scale range from "no change" to "a great deal better."

8 EARLY DISCONTINUATION OF STUDY

All subjects who discontinue the study early should complete an early discontinuation visit as well as the 2-Week Post Dose Visit. The 2-Week Post Dose Visit would not need to occur if the subject discontinued dosing more than 2 weeks prior to the early discontinuation visit. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

9 LOST TO FOLLOW-UP

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

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

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

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. The reason for withdrawal should be noted as lost to follow-up.

10 STUDY DRUG MANAGEMENT

10.1 Description

10.1.1 Investigational Product

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

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

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

In this protocol, the investigational products are: Troriluzole capsules 140 mg and 60 mg (and matching placebo). Troriluzole will be provided as formulated capsules. Troriluzole 140mg active and placebo capsules may be white capsules or the capsule may have two black lines printed on them. The different capsules will be used equally across the active and placebo capsule strengths to maintain the integrity of the blind.

10.2 Packaging and Shipment

Clinical Trial Materials should be stored at controlled temperature between 20^0C and 25^0 C (68^0F -77^0F) with excursions permitted between 15^0C and 30^0 C (59^0F -86^0F). Clinical Trial Material should 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 storage conditions.

10.3 Dose and Administration

10.3.1 Randomization Phase

During the randomization phase, all subjects will be randomized to receive 140 mg or placebo, QD, for the first four (4) weeks of the Randomization Phase. Subjects will then be increased to 200 mg (provided as one bottle of 140 mg and one bottle of 60 mg) or matching placebo for the duration of the Randomization Phase.

It is recommended that all patients ingest study drug once every day (approximately at the same time each day), without regard to meals.

- If subjects have difficulty tolerating the medication (such as experiencing sedation or dizziness) then the investigator should advise the subject to switch to night time dosing (and document this change in the subject's records).

- Subjects who continue to experience issues with tolerability after switching to night time dosing may temporarily down titrate to 140mg. However, **prior to down titrating their dose**, these patients should be discussed with the Biohaven Medical Monitor.

10.3.2 Extension Phase

Subjects completing the Randomization Phase will be offered approximately 192 weeks of troriluzole treatment as long as the PI believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will receive troriluzole.

In order to maintain the blind of the Randomization Phase and to safely increase all subjects to 200mg after Extension Phase Week 4, the first 4 weeks of the Extension Phase will remain blinded. If a subject has to delay the Randomization Phase Week 48 visit due to concerns about COVID-19, the site should contact the Sponsor immediately upon learning about the cancelation so that the Sponsor can provide instruction on providing study drug. Subjects will not be allowed to transition to the Extension Phase until they have an in-person Week 48 visit.

If a subject was on active treatment in the Randomization Phase, they will start the Extension Phase on the same dose that they were taking at Week 48 of the Randomization Phase.

If a subject received placebo in the Randomization Phase, they will be switched in a blinded manner to 140mg for the first 4 weeks of the Extension Phase.

After Extension Phase Week 4 all subjects will be on open label troriluzole 200 mg. Down titration to 140mg will only be allowed to address tolerability issues. Subjects who enter the Extension Phase on 140mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension Week 4 at PI discretion.

Due to the change of dose throughout the study it is imperative that subjects are educated and reminded to take one capsule from each bottle for each dose.

10.3.3 Method of Assigning Patient Identification

The investigator or designee will need to access an Interactive Web-based Response System (IWRS) in order to register each subject in each study phase. Initially the investigator or designee will enter the subject into the study at the Screening Visit after informed consent is obtained and a subject number is assigned via the IWRS. After completion of all screening evaluations, all eligible subjects will be randomized, in a 1:1 ratio to receive either placebo (QD) or troriluzole. Treatment assignments will be obtained by the investigator (or designee) via the IWRS system.

Investigational sites will access the IWRS at each scheduled study visit throughout the Randomization Phase. The IWRS system will assign specific bottle numbers for all blinded study drug to be dispensed to the subject. Once a bottle has been assigned it cannot be dispensed to another study subject.

Once a subject completes the Randomization Phase or if a subject is discontinued early from the study, the investigator or designee must access the IWRS to discontinue the patient from participation in the study.

Subjects who complete 48 weeks of treatment in the Randomization Phase may be eligible for an Extension Phase of the study. The investigator or designee must access the IWRS to enter the subject in the Extension Phase. Investigational sites will access the IWRS at each scheduled study visit throughout the Extension Phase. If a subject has to delay the Randomization Phase Week 48 visit due to concerns about COVID-19, the subject should remain on current blinded drug until the subject is in the office. Subjects will not transition to extension phase until completing the Week 48 visit in person. If study site needs to send drug via certified and tracked courier (and this is acceptable to the institution) because an in person visit is not possible due to COVID-19 concerns, this is permissible per study. Site should contact Sponsor for IWRS instructions to dispense blinded drug that may be needed for subjects who are unable to come into the office for Week 48 visit and require drug to be shipped.

Study medication will be assigned via the IWRS system in the Extension Phase. The first 4 weeks of treatment in the Extension Phase will be blinded in order to maintain the blind in the randomization phase. From Extension Phase Week 4 on, the study will be open-label. Sites will be responsible for recording the bottle numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record. Once a subject completes the Extension Phase or if a subject is discontinued early from the Extension Phase of the study, the investigator or designee must access the IWRS to document the discontinuation of the subject from participation in the study.

10.3.4 Selection and Timing of Dose Administration

During the randomization phase of the study, subjects will be randomized to receive placebo (QD) or troriluzole (QD). Study Drug will be dispensed at the Baseline visit. Subjects should take the first dose the day after the baseline visit. Study medication should be administered in the morning without regard to meals. Open label BHV-4157 will be provided during the extension phase at Week 4.

10.3.5 Dose Modifications

Randomization Phase: Subjects will receive 140 mg or Placebo for the first four (4) weeks and will then be increased to 200 mg or placebo for the duration of the study.

- If subjects have difficulty tolerating the medication (such as experiencing sedation or dizziness) then the investigator should advise the subject to switch to night time dosing (and document this change in the subject's records).

- Subjects who continue to experience issues with tolerability after switching to night time dosing may temporarily down titrate to 140mg. However, **prior to down titrating their dose**, these patients should be discussed with the Biohaven Medical Monitor.

Extension Phase: Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase. Subjects receiving placebo in the randomization phase will be switched in a blinded manner to 140 mg for the first 4 weeks and will then be increased to 200 mg (at the Week 4 visits). Down titration to 140 mg will only be temporarily allowed to address tolerability issues. Subjects who enter the Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension Week 4 at PI discretion.

For subjects who do not tolerate their study treatment (200 mg), the investigator may permit them to switch to night time dosing if there is reason to believe that may help tolerability. Any such changes must be documented by the investigator. Every other day dosing is NOT permitted.

10.4 Blinding and Unblinding

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

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

A pharmacokineticist, bioanalytical scientists, IWRS randomization manager, and pharmacovigilance role may be unblinded during the course of the study in order to perform specific study related activities (i.e. PK assessment, randomization coordination, and unblinded safety assessments) before data are unblinded for the primary end point and all subjects complete the study. In order to minimize unnecessary analysis of placebo blood PK samples, the bioanalytical scientist will be unblinded to treatment prior to unblinding for the primary end point. Results of the blood concentration assay will be kept secure until database lock unblinding for the primary endpoint. Additionally, an independent statistician will review the unblinded randomization assignments when 5% and 10% of the subjects have been randomized to ensure the IWRS system is assigning as specified. If enrollment is evenly distributed across the SCA strata, 10% will show approximately 2 blocks filled per strata. If at least 1 block per strata is not filled, then a review will occur when 15% of the subjects are randomized. Except as noted above, other members of the sponsor and CRO research team will remain blinded until the database is locked for the primary analysis.

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

10.5 Treatment Compliance

Responsible study personnel will dispense the study drug. Accountability and compliance verification should be documented in the subject's study records.

Subjects will be counseled on the importance of taking the study drug as directed at all study visits. If poor compliance continues, (i.e., multiple missed doses resulting in less than 80% overall compliance during the Randomization Phase), discontinuation of the subject from the trial should be considered.

10.6 Destruction and Return of Study Drug

All unused and/or partially used study drug can be destroyed, per site Standard Operating Procedure (SOP), only after being inspected and reconciled by the responsible Biohaven Study Monitor or the sponsor's designee. If a site does not have drug destruction SOPs in place, they should contact Biohaven to arrange for study drug to be sent back to the drug depot for destruction.

If it is site policy to destroy study drug on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be destroyed after being inspected and reconciled by the responsible Biohaven Study Monitor or the sponsor's designee.

11 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding for example) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Adverse events can be spontaneously reported or elicited during an open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs. The collection of non-serious AE information should begin at the initiation of study drug.

11.1 Serious Adverse Events

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

11.1.1 Definition of Serious Adverse Event (SAE)

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

- Death;
- Life-threatening;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject who received troriluzole;
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm;
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization;
    - Development of drug dependency or drug abuse;
    - Potential drug induced liver injury.

11.1.2 Definition of Terms

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

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

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

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

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If

anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

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

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

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

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

11.2 Collection and Reporting of Serious Adverse Events

Following the patient’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specific procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuation of dosing. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specific procedures.

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

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

SAEs, whether related or not related to study drug, overdose (see section 11.2.1 Overdose), potential drug induced liver injury (see section 11.2.3 Potential Drug Induced Liver Injury (DILI)) and pregnancies (see section 11.2.2 Pregnancy) must be reported within 24 hours of the

Investigator becoming aware of the event. For this study we will be capturing SAEs through electronic data capture (EDC) and on the SAE form.

The Investigator is responsible for reporting all SAEs and all Other Important Medical Events to PPD immediately via telephone, upon observing or learning of the event. PPD will then immediately notify the Biohaven Medical Monitor of the event. The SAE form must then be submitted to PPD within one working day. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering in the SAE information in the Electronic Data Capture (eDC) system (i.e.: event term, start stop dates, causality, severity).

Additionally, any serious adverse experience must be **reported immediately or no later than 24 hours** after awareness of the event to the PPD Pharmacovigilance (PVG) department.

The Serious Adverse Event Report Form (SAERF) should be submitted to PPD PVG by facsimile (FAX).

North America: **1-888-488-9697**

Reports can be made by telephone via the Safety Hotline Number below if a SAERF cannot be immediately submitted.

North America: **1-800-201-8725**

For any questions relating to SAEs, please contact the Medical Monitor via telephone:

SAE Telephone Contact: [redacted]

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

All SAEs should be followed to resolution or stabilization.

11.2.1 Overdose

An overdose is defined as the accidental or intentional administration of any dose of the product that is considered both excessive and medically important. All occurrences of overdose (suspected or confirmed and irrespective of whether or not it involved BHV- 4157) must be communicated to Biohaven or a specified designee within 24 hours of the Investigator becoming aware of the updated information and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

11.2.2 Pregnancy

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

Sites should instruct patients to contact the investigator if they become pregnant during the course of the study. The investigator must immediately notify PPD of the event within 24 hours of the Investigator becoming aware of the information. The site must complete a Pregnancy Report Form. Follow up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable offspring information must also be reported on a Pregnancy Report Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to PPD.

11.2.3 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 11.2 Collection and Reporting of Serious Adverse Events.

Potential drug induced liver injury is defined as:

- Aminotransferases (AT) (ALT or AST) elevation > 3 times the upper limit of normal (ULN);
  AND
- Total bilirubin (TBL) > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase);
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

If any potential DILI is identified and meets the criteria above, the Biohaven Medical Monitor should immediately be contacted for further instruction on dosing adjustments and whether the patient must discontinue from the trial and appropriate follow up requirements.

11.3 Non-Serious Adverse Events

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

11.3.1 Collecting and Reporting of Non-Serious Adverse Events

The collection of non-serious AE information should begin at the initiation of study drug.

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

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

- Any laboratory test result that is deemed clinically significant by the PI or meets the definition of an SAE;
- Any laboratory abnormality that required the patient to have the study drug discontinued or interrupted;
- Any laboratory abnormality that required the patient to receive specific corrective therapy.

12 STATISTICS

Detailed plans for analysis will be summarized in a separate Statistical Analysis Plan document, to be written and approved prior to database unblinding. A summary of statistical aspects of the design and intended analysis is provided here.

12.1 General Procedures

Categorical variables are tabulated with counts and percentages. Continuous variables are summarized with univariate statistics (e.g., n, mean, standard error, median, minimum and maximum).

For the calculation of descriptive statistics of observed data, subjects must have a baseline value to be evaluable for endpoints based on values and changes from baseline over time.

Tabulations of the following endpoints present the number of unique subjects with an event: protocol deviations; non-study medications; adverse events; and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

Unless otherwise specified, the randomization phase and the extension phase will be analyzed separately.

12.2 Sample Size

The sample size for this study will be approximately 210 randomized subjects to accommodate for dropouts and based on the rationale that follows.

As the f-SARA is a new scale with no data to estimate changes and variance in this patient population a modified SARA from study BHV4157-201 is used as a proxy. Both scales essentially have the same structure, consisting of 4 items with 5 points/item. The mean changes from randomized baseline using a modified SARA were -0.3 (SD=1.35) and 0.0 (SD=1.44) at Open-Label Weeks 24 and 48, respectively, for all genotypes. Because this study expects an increase on the f-SARA for the non-treated patients, the Week 48 difference in the change from baseline in f-SARA between treatment groups (troriluzole – placebo) is estimated to be -0.75. For the primary endpoint, 210 mITT subjects will provide 90% power, based on a two-sample t—test, assuming a two-sided alpha of 0.05, a SD of 1.44, a delta of 0.75 and 25% dropout.

12.3 Populations for Analysis

The following analysis sets are defined for this protocol:

- Enrolled subjects: Patients who signed an informed consent form and were assigned a Patient Identification number (PID)
- Randomized subjects: Enrolled subjects who received a treatment assignment from the Interactive Web Response System (IWRS) (troriluzole or placebo).
- Treated subjects/Safety: Enrolled subjects who received at least one dose of study therapy (blinded or open-label troriluzole, or blinded placebo).
- Troriluzole Safety: Enrolled subjects who received at least one dose of blinded or open-label troriluzole.
- Modified Intent to Treat (mITT) subjects: Randomized subjects who received at least one dose of blinded study therapy and provided at least one post-baseline efficacy assessment

12.4 Statistical Methods

12.4.1 Demographic and Baseline Characteristics

Tabulations of demographic and baseline characteristics will be made for all treated subjects. A separate set of tabulations will be made for subjects enrolled but not randomized.

Demographic information will be summarized (n, mean, SD, minimum, maximum for continuous endpoints; n and % for categorical endpoints) by treatment group and for all treatment groups combined for select analysis populations in Section 11.3.

12.4.2 Primary Endpoint(s)

As the primary objective of this study is based on the symptoms of ataxia in subjects with SCA, the estimand for the primary endpoint will be the effect due to the initially randomized treatments if taken as directed, a de jure efficacy estimand. The target population will be the mITT population. The primary endpoint will be the change from baseline in f-SARA total score, troriluzole relative to placebo at Week 48 in the randomization phase. The treatment effects will be summarized as the difference in change from baseline between placebo and troriluzole-treated subjects.

Since the primary intent of this trial is to evaluate the effect of the drug when taken as intended in the protocol, a hypothetical strategy will be employed for the intercurrent event of treatment/study discontinuation (due to any reason). Specifically, the assumption will be that had the subjects not discontinued, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did not discontinue. For other intercurrent events that do not cause treatment/study discontinuation such as modest treatment non-compliance, protocol allowed dose adjustments, or initiation or adjustment of concomitant medications related to other symptoms all observed values will be used.

The treatment comparison of troriluzole versus placebo will use a two-sided alpha level of 0.05 and a Mixed Model for Repeated Measures (MMRM) that will include fixed effect factors for treatment group, SCA randomization strata, visit week, treatment group-by-visit week interation, country, and baseline f-SARA score as a covariate. MMRM-based estimates (i.e., least-squares mean [LSM] with corresponding SE and 95% CI) of values and changes from baseline will be presented by treatment group and visit week. In addition, the LSM difference in change from baseline between treatment groups (troriluzole – placebo) at Week 48 with corresponding SE, 95% CI, and p-value from MMRM will also be presented.

Observed values and changes from baseline in f-SARA total score will also be summarized using descriptive statistics over time by treatment group during the Randomization and Extension Phases.

12.4.3 Secondary Endpoint(s)

Continuous secondary, change-from-baseline endpoints (i.e., PIFAS, FARS-ADL, FARS-FUNC) will be analyzed for mITT subjects using the same methodology described in Section 11.4.2.

12.4.4 Adjustment for Multiplicity

Type 1 error will be controlled for the primary and secondary efficacy endpoints by testing them with a gate-keeping procedure. The primary endpoint will be tested at a two-sided alpha level of 0.05. If this test is significant (i.e., p-value < 0.05), then the secondary efficacy endpoints will be tested using Hochberg's procedure. If the test of the primary endpoint is not significant, then the unadjusted p-values for the secondary endpoints will be presented only for descriptive purposes, and no conclusions will be drawn from these results.

No attempt will be made to adjust for multiplicity when testing the exploratory endpoints. Any exploratory endpoint subjected to significance testing will be evaluated at an unadjusted two-sided alpha level of 0.05.

12.4.5 Missing Data

As a sensitivity analysis to assess missing data assumptions of the MMRM model, the missing data will be multiply imputed for the primary endpoint using “jump to reference”, “copy reference” and "tipping point" methods. Further details on the handling of missing data are provided in the statistical analysis plan.

12.4.6 Analysis of Safety

The investigators will determine the severity of AEs and the relationship of AEs to study therapy. The investigators’ terms will be coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available to the analyst. AEs will be presented by system organ class and preferred term for each treatment group. If a subject had an AE with different severities over time in a study phase, then only the worst severity will be reported for that phase.

The frequency (i.e., number and percentage) of the following safety events are summarized by treatment group and overall for treated subjects: AEs (by severity, by relationship to study drug, and overall); deaths; SAEs; AEs leading to treatment discontinuation; and clinically relevant laboratory abnormalities. Observed values and changes from baseline in continuous safety parameters (laboratory tests, ECGs, vital signs) over time will also be presented.

Safety endpoints will be assessed by treatment group separately for the following phases and populations:

- Double-blind treatment (i.e., Randomization Phase) for the safety set;
- Troriluzole treatment (i.e., double-blind or open-label troriluzole during the Randomization and Extension Phases combined) for the troriluzole safety set.

13 ETHICS AND RESPONSIBILITIES

13.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

This study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All serious breaches must be reported to Biohaven (or designee) immediately. A Serious breach is a breach of the conditions and principles of GCP in connection with the study or protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the patients of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment).

13.2 Data and Safety Monitoring Board

This study will not make use of a Data Safety Monitoring Committee (DMC). The study medication troriluzole has been tested and found to be well-tolerated. Safety will be closely monitored via the sites and procedures for unblinding in case of emergency will be followed.

13.3 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC 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 Investigator 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 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, prior to subsequently obtaining each subject's consent.

The Principal investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

13.4 Informed Consent

Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives, are clearly and fully informed about the

purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Biohaven (or designee) will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by

ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Before the potential subject has undergone any study-related screening procedures, the nature of the study and the potential risks associated with it will be explained to the subject, and the subject will be given an opportunity to ask questions to his or her satisfaction. After the questions are answered, but before proceeding further, the subject must read and sign a written informed consent form. This signed informed consent form will be reviewed and approved by an IRB/IEC, revisions to the protocol and informed consent form will be reviewed and approved by the IRB/IEC, a copy retained in the Study Master File, and the date and time the subject signed the form will be entered in his or her CRF. The subject will be provided with a copy of his or her signed and dated informed consent form.

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

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

The rights, safety, and well-being of study patients are the most important considerations and should prevail over interests of science and society.

13.5 Case Report Forms

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

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

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

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

14 RECORDS MANAGEMENT

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

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

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

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

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

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

14.1 Source Documentation

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

If source documents are created to support the collection of study information, this must be retained with the other pertinent medical record for each patient for verification of data points, unless otherwise instructed by the Sponsor or designee to enter data directly on the CRF.

14.2 Study Files and Record Retention

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

15 AMENDMENTS

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

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

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

16 STUDY REPORT AND PUBLICATIONS

Biohaven is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements. The publication policy of Biohaven is discussed in the investigator's Clinical Research Agreement.

17 STUDY DISCONTINUATION

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

18 CONFIDENTIALITY

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

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

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

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20 APPENDICES

20.1 APPENDIX I – Names of Study Personnel

Sponsor:	Biohaven Pharmaceutical Holding Company Limited c/o Biohaven Pharmaceuticals, Inc. 215 Church Street New Haven, CT 06510
Medical Monitor:	[redacted] Biohaven Pharmaceuticals, Inc 215 Church Street New Haven, CT 06510 [redacted] [redacted] Biohaven Pharmaceuticals, Inc 215 Church Street New Haven, CT 06510 [redacted]
Clinical Research Organizations:	[redacted] Cognitive Research Corporation 200 Central Ave., Suite 1230 Saint Petersburg, FL 33701 [redacted]
Central Laboratory:	LabConnect, LLC 2304 Silverdale Dr. Johnson City, TN. 37601

20.2 APPENDIX II – Potent and Moderate Inhibitors and Inducers of the CYP1A2 Enzyme System

CYP1A2 Potent and Moderate Inhibitors

Amiodarone

Ciprofloxacin

Efavirenz

Enoxacin

Furafylline

Fluvoxamine

Genistein

Idrocilamide

Interferon

Methoxsalen

Mexiletine

Osilodrostat

Phenylpropanolamine

Pipemidic Acid

Propranolol

Rofecoxib

Rucaparib

Ticlopidine

Troleandomycin

Vemurafenib

Zafirlukast

CYP1A2 Potent and Moderate Inducers

Beta-napththoflavone

Carbamazepine

Insulin

Methylcholanthrene

Modafinil

Nafcillin

Phenytoin

Primidone

Rifampin

Ritonavir

Teriflunomide

*This list is not exhaustive.