DRUG:	Troriluzole
STUDY NUMBER(S):	BHV4157-201
PROTOCOL(S) TITLE:	A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of Troriluzole in Adult Subjects with Spinocerebellar Ataxia
IND NUMBER:	129397
SPONSOR:	Biohaven Pharmaceuticals, Inc.
ORIGINAL PROTOCOL DATE:	16 June 2016
VERSION NUMBER:	V08 (Incorporates Amendments 02, 03, 04, and 05, 06 and 07; Administrative Letters 1, 2, 3, and 4,)
VERSION DATE:	17April2020

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase IIb/III, Randomized, Double-blind, Placebo-controlled Trial of **Troriluzole** in Adult Subjects with Spinocerebellar Ataxia

Study No: BHV4157-201

Original Protocol Date: 16 June 2016
Protocol Version No: V08
Protocol Version Date: 17 April 2020

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**
[redacted]		
Other: _____ _____ [Name] [Title]		

SUMMARY OF CHANGES

Version Number	**Brief description summary of changes**	**Date**
Version 01 Original Protocol	NA	16 Jun16
Version 02 Amendment 01	Protocol revisions made based on site feedback. Minor administrative corrections made as well. See below for a description of changes.	27 Sept 2016
Version 03 Amendment 02	Protocol revisions incorporate changes based on Administrative Letters 1 and 2; Addition of Exclusion Criteria (Section 5.3) 1.f; Updates to Statistical Sections; Correction of typographical errors.	16 May 2017
Version 04 Amendment 03	The Patient Global Impression of Change (PGI-C) was promoted from an exploratory endpoint to a secondary endpoint. [redacted]	27 July 2017
Version 05 Amendment 04	An additional 48 weeks is added to the extension phase. Language was added to allow a dose increase to 280mg/d for subjects who experience clinical decline as evidenced on the SARA scale. [redacted] Exclusion criteria were modified to accommodate subjects who are re-entering the expanded extension phase [redacted] Protocol version 05 also incorporates Administrative Letter 3, which provided updates to the Investigational Product and Study Drug Management sections. Safety Reporting section was updated to reflect the addition of [redacted] as the Pharmacovigilance vendor.	19 Jun 18

Version 06 Amendment 05	Table 4 Schedule of Assessments updated Expanded Extension Visit 10 (for continuing subjects) and Expanded Extension Visit 8 (for returning subjects) as also being an Early Discontinuation Visit. [redacted] Section 6.5 Early Discontinuation of Study: Clarified that Early Discontinuation Visit is required in addition to 2-Week Post Last Dose Visit unless the last dose occurred 2 weeks prior to Early Discontinuation Visit. Section 7.3 Blinding and Unblinding: Clarified Sponsor remains blinded until primary analysis is complete. 16.1 Appendix 1: Updated Medical Monitor and Medical Monitor Back-up information. [redacted] Incorporates changes based on Administrative Letter 4.	11 Dec 2018

Version 07 Amendment 06	BHV-4157 has been replaced with troriluzole throughout protocol. Time and Events schedule has been modified to include and additional 48 weeks of Expanded Extension. Some procedures have been removed at EE Week 60 for continuing subjects (or Week 108 for returning subjects). The length of the expanded extension phase has been updated in the time and events and throughout the document. Sheehan Suicidality Tracking Scale (S-STS): Additional language was added to the S-STS description specifying that any score above zero should be evaluated by Investigator and recorded as AE or SAE as determined by investigator and reported within 24 hours to Sponsor. Section 6.2.2 updated to note any abnormal ECGs should be reviewed by a cardiologist or [redacted] 6.2.4 updated to note that any local lab that is out of range should be brought to the attention of the Biohaven Medical Monitor. Declaration of Helsinki Appendix II deleted as this is covered in Ethics and Responsibility Section.	08 July 2019

Version 08 Amendment 07	Time and Events schedule has been modified to extend the Expanded Extension for another 48 weeks. Length of Expanded Extension has been revised throughout document to 192 weeks (continuing subjects) or 144 weeks (returning subjects). Section 4.3.3: Language has been added to confirm sites may do remote safety visits, if sponsor medical monitor approved, due to subjects inability to come to the office for regular study visits due to COVID-19. Updated Medical Monitor contact information.	17 April 2020

Changes included in Amendment 04:

STUDY SUMMARY (SYNOPSIS) Objectives

The exploratory objectives:

[redacted]

[redacted]

LIST OF ABBREVIATIONS

[redacted]

Section 1.1 Background

[redacted]

- New section added (Section 1.1.6.2) to provide preliminary BHV4157-201 AE profile data.

Section 2 Study Objectives

The exploratory objectives:

[redacted]

Section 3 Study Endpoints

The secondary endpoint:

[redacted]

Section 4.1 Study Design and Duration

- Updated Section 4.1 to include 48-week Expanded Extension Phase as well as the rationale and criteria for dose increase to 280mg.
- Updated Study Schematic to include dose increase language as well as the addition of the 48-week expanded extension phase.

Section 4.3 Schedule of Assessments

- Section 4.3 Tables 3-5 updated to include 48-week Expanded Extension Phase, additional Laboratory Tests required for subjects re-entering study, and requirement for additional Laboratory Testing for subjects who's dose has been increased.
- [redacted]
- Miscellaneous updates to footnotes to support the above referenced changes.

Section 4.3.3 Extension Phase

- Updated to include Expanded Extension Phase description and requirements.

Section 5.3 Exclusion Criteria

[redacted]

Section 6 Study Conduct and Description of Study Procedures

[redacted]

Section 7.1.1 Investigational Product

Currently written:

In this protocol, the investigational products are: BHV-4157 capsules 140 mg (and matching placebo). BHV-4157 will be provided as a loose filled capsule.
Should read:

In this protocol, the investigational products are: BHV-4157 capsules 140 mg (and matching placebo). BHV-4157 will be provided as a loose filled capsule in the Randomization Phase and as loose filled or formulated capsules (dependent on lot) in the Extension Phase. Formulated capsules have black markings on the capsule which differentiates them from the loose filled capsules. Study BHV4157-102 demonstrated bioequivalence of the two formulations

Section 7.2 Dose and Administration

Currently written: Subjects will receive placebo (QD) or BHV-4157 (140 mg QD) loose filled capsule.

Should read: Subjects will receive placebo (QD) or BHV-4157 (140 mg QD) loose filled capsules in the Randomization Phase and loose filled or formulated capsules (dependent on lot) in the Extension Phase. Formulated capsules have black markings on the capsule which differentiates them from the loose filled capsules.

Section 7.2 Study Drug Management

- Section 7.2 was updated to include criteria for dose increase as well as inclusion of the 48-week Expanded Extension Phase
- Section 7.2.1 was updated to provide method of assigning IP to subjects re-entering the study for the 48-week Expanded Extension Phase

Section 8.1.3 Collection and Reporting Serious Adverse Events

- Section 8.1.3 and 8.1.5 were updated to replace [redacted] as the pharmacovigilance vendor.

Changes included in Amendment 05:

Table 4 Schedule of Assessments updated Expanded Extension Visit 10 (for continuing subjects) and Expanded Extension Visit 8 (for returning subjects) as also being an Early Discontinuation Visit.

[redacted]

Section 6.5 Early Discontinuation of Study: Clarified that Early Discontinuation Visit is required in addition to 2-Week Post Last Dose Visit unless the last dose occurred 2 weeks prior to Early Discontinuation Visit.

Section 7.3 Blinding and Unblinding: Clarified Sponsor remains blinded until primary analysis is complete.

16.1 Appendix 1: Updated Medical Monitor and Medical Monitor Back-up information.

[redacted]

Changes in Amendment 06 include:

BHV-4157 replaced with troriluzole throughout document

Time and Events schedule has been modified to include and additional 48 weeks of Expanded Extension. Some procedures have been removed at EE Week 60 for continuing subjects (or Week 108 for returning subjects). The length of the expanded extension phase has been updated in the time and events and throughout the document.

Sheehan Suicidality Tracking Scale (S-STS): Additional language was added to the S-STS description specifying that any score above zero should be evaluated by Investigator and recorded as AE or SAE as determined by investigator and reported within 24 hours to Sponsor.

Section 6.2.2 updated to note any abnormal ECGs should be reviewed by a cardiologist or [redacted] Medical Lead.

6.2.4 updated to note that any local lab that is out of range should be brought to the attention of the Biohaven Medical Monitor.

Declaration of Helsinki Appendix II deleted as this is covered in Ethics and Responsibility Section.

Changes in Amendment 07 include:

Time and Events schedule has been modified to extend the Expanded Extension for another 48 weeks.

Length of Expanded Extension has been revised throughout document to 192 weeks (continuing subjects) or 144 weeks (returning subjects).

Section 4.3.3: Language has been added to confirm sites may do remote safety visits, if sponsor medical monitor approved, due to subjects inability to come to the office for regular study visits due to COVID-19.

Updated Medical Monitor contact information.

BHV4157-201

A Randomized, Phase IIb/III, 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 Pharmaceutical Holding Company Limited, 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 Pharmaceutical Holding Company Limited.

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 Pharmaceutical Holding Company Limited. or specified designees. I will discuss the material with them to ensure that they are fully informed about Biohaven and the study.

Principal Investigator Name (printed) Signature

_____ _____

_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

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

Rationale: Troriluzole is a glutamate modulating drug that is being developed for eventual commercial use in the treatment of spinocerebellar ataxia (SCA). There are currently no FDA approved medications indicated for SCA.

[redacted]

[redacted]

Troriluzole was developed to advance upon the limitations of riluzole that have restricted its broader clinical application. [redacted]

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 120 randomized subjects (limit of approximately 10% of subjects with SCA3)

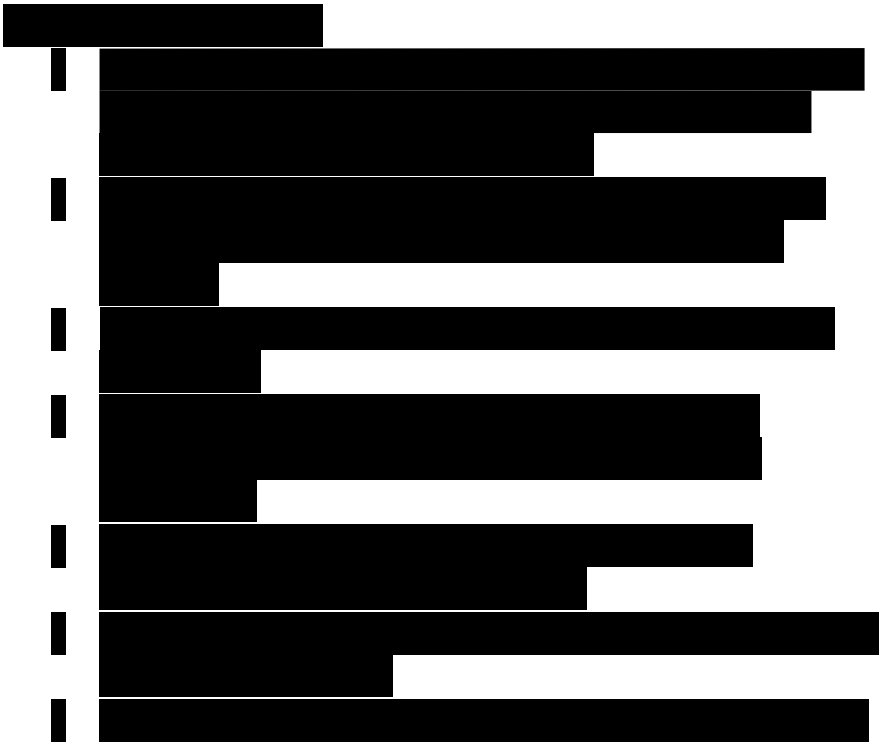
Objectives:

Primary Objectives

- To compare the efficacy of troriluzole (140 mg once daily) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) after 8 weeks of treatment as measured by the total score on the Scale for the Assessment and Rating of Ataxia [SARA]

Secondary Objectives

- To assess of the safety and tolerability of troriluzole in subjects with SCA
- To compare efficacy of troriluzole with placebo on patient impression of benefit via use of the PGI-C



[redacted]

Study Design:

BHV4157-201 is a Phase IIb/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 (140 mg QD), [redacted]

Subjects with SCA3 genotype will be limited to comprise up to approximately 10% of the total population so that this most common type of SCA is not over-represented.

Dosing will continue for 8 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 approximately 192 weeks of open-label 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 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 would have their first Extension Visit four weeks after the Week 8 Randomization Phase visit. If there is a delay of two weeks or more in dosing between the Randomization Phase and the Extension Phase, subjects will be required to complete an Extension Baseline Visit. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug in the Extension Phase.

Subjects who previously completed the extension phase will be allowed to participate in the expanded extension phase for a total of 144 weeks of open-label administration of troriluzole, provided the PI deems this treatment to present an acceptable risk-benefit profile. Such subjects who have been off of medication for at least 2 weeks, will need additional Baseline Visits followed by visits scheduled approximately every 12 weeks, as well as laboratory assessments at approximately 4 and 8 weeks after re-starting medication. In addition, these subjects will be required to have clinical laboratory assessment results that are not deemed clinically significant, available prior to the Baseline Visit and drawn within 6 weeks prior to that visit. These subjects should have not taken riluzole for at least 12 hours prior to re-starting troriluzole.

For subjects who experienced decline (as defined below) over at least 9 months of treatment with 140 mg troriluzole in the first Extension Phase, the PI may offer an increased dose of 280 mg daily based on anticipated tolerability (e.g., the patient was tolerating the 140 mg dose well). Decline will be defined as demonstration of a 2 point or greater decline from Randomization Phase baseline on the SARA scale on each of two most recent consecutive visits (at least one month apart) accompanied by PI impression of clinical worsening. Patients who do not tolerate 280 mg daily or demonstrate clinically significant lab abnormalities may have their dose adjusted to 140 mg daily. Subjects who increase to 280 mg daily will have lab tests at approximately 4, 8 and 12 weeks after the dose increase, then no less often that approximately every 12 weeks. Subjects who are given a trial of 280 mg daily troriluzole will require additional clinical lab assessments (LFTs) at approximately 4 and 8 weeks after starting the increased dosing. For subjects who were tolerating 140 mg

without adverse effects, the dose increase may occur at the usual dosing time. Some subjects may better tolerate dosing at bedtime to minimize any impact of sedation. In addition, the PI may split doses (twice daily) if adverse events suggest that this could enhance tolerability.

Primary Endpoint: The total score on the Scale for the Assessment and Rating of Ataxia (SARA)

Secondary Endpoints: PGI-C

Tolerability and safety of troriluzole will be measured by the frequency and severity of adverse events and discontinuations secondary to adverse events.

[redacted]

[redacted]

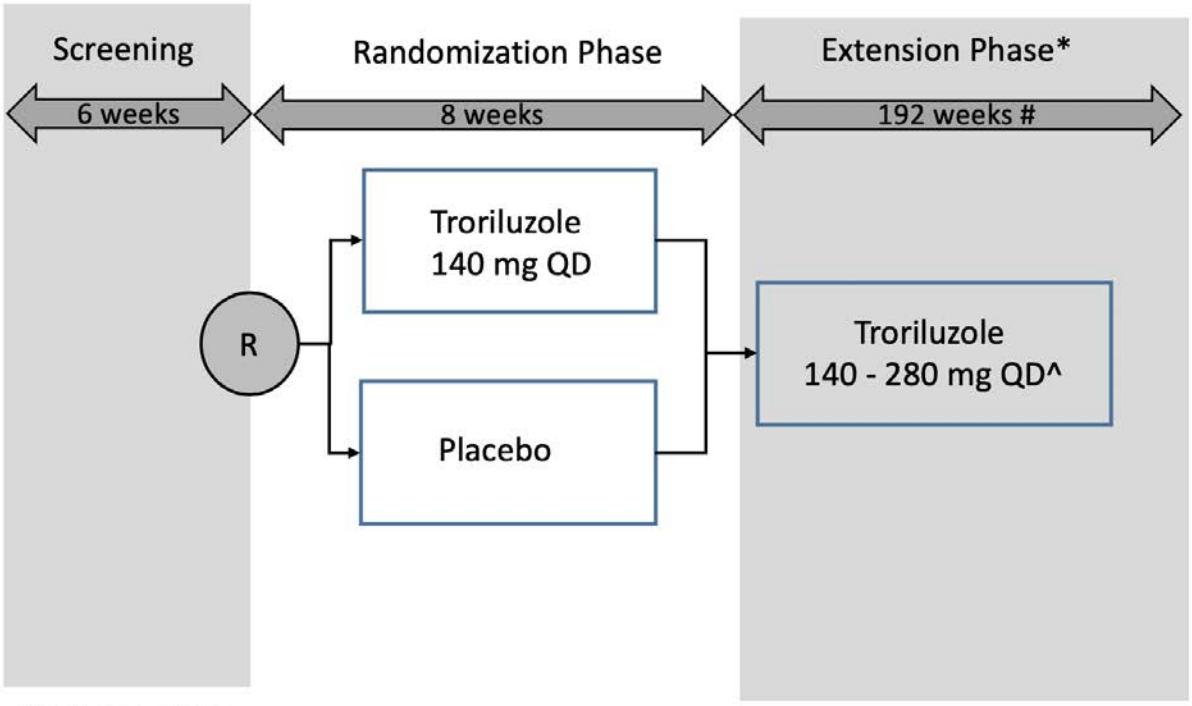
Measures of Interest:

Safety and Other assessments:

- Sheehan Suicidality Tracking Scale (STS)
- ECG assessments
- Vital Sign and Physical Measurements

[redacted]

STUDY SCHEMATIC



R, Signifies randomization
*, Eligible subjects will include those who perceived benefit in earlier phases or for whom the PI believes extended treatment with troriluzole would offer an acceptable risk-benefit profile.
#, Maximum duration of troriluzole treatment of 192 weeks (not required to be continuous dosing weeks if subjects already completed 48 Week Extension Phase).
^, As per Protocol, subjects demonstrating decline on at least 9 months of 140 mg troriluzole may be offered a higher dose of 280mg daily.

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

[redacted] [redacted]

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
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 a kindred. Lifespan is significantly shortened due to complications related to neurologic deficits. There are currently no FDA approved medications for the treatment of SCA.

Biohaven Pharmaceutical Holding Company Limited [Biohaven] is developing a new drug, troriluzole, for treatment of SCA. Troriluzole is a novel pro-drug formulation of the generic drug riluzole. [redacted]

1.1.1 Spinocerebellar Ataxia (SCA)

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 a 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.

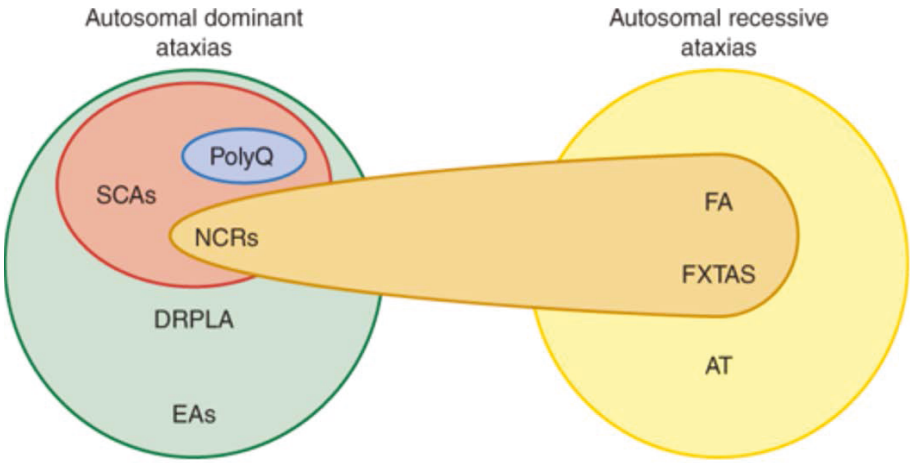
The typical clinical course of SCAs may be described, as follows. Balance and coordination are affected first. Incoordination of hands, arms, and legs, and slurring of speech are other common, early symptoms. Over time, individuals with SCA may develop numbness, tingling, or pain in the arms and legs (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 (10).

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] **(10, 11)**

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.6.2 BHV4157-201: Phase 2 Clinical Adverse Event Profile

During the double-blind randomization phase of the current study (BHV4157-201), administration of 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.

A total of 141 participants were enrolled into the randomization phase of this study. Overall, troriluzole 140 mg once daily for 8 weeks was well tolerated in adult participants with SCA. The majority of adverse events were mild or moderate in severity. To date, there have been no deaths reported in the study and no SAE has been judged by the investigator to be treatment related. During the randomization phase, treatment-emergent SAEs were reported for five (3.55%) subjects, including four troriluzole -treated subjects (SAEs by subject: dehydration, elevated CPK, and weakness; suicidal ideation; cerebral infarction; and, back pain) and one placebo-treated subject (SAE: chest discomfort, high blood pressure). The frequency of

treatment emergent AEs that led to withdrawal from the study drug was 4.2% (3/71 subjects) in the troriluzole group and no subjects in the placebo group. AEs that led to withdrawal from study drug occurred in one subject each and included asthenia, gait disturbance, anhedonia, suicidal ideation, increase in blood creatine phosphokinase, dehydration, dizziness, somnolemnce, and hospitalization. The majority of treatment-emergent AEs were mild or moderate in severity, not related to study drug, and resolved spontaneously by the end of treatment. The most frequently reported treatment-emergent AEs were dizziness, fatigue, fall, headache, nausea, and muscle spasms.

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.

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. 131 subjects entered this phase. During this phase, there were no deaths SAEs were reported in 5 subjects (syncope considered as possibly related by the PI; pneumonia in three subjects considered as not related in two subjects [one of whom also had inflammation of mesenteric tissue] and unlikely related in one subject; and, an additional subject with a pre-study history of breathing difficulties and pneumonia was hospitalized for worsened breathing difficulties, with the investigator considering this event as possibly related).

1.1.6.3 Riluzole

Clinical information on riluzole, as reflected in the USPI, is predominantly based on experience from approximately 4000 patients given riluzole for ALS. Refer to the US Prescribing Information (15) where greater details on the adverse event profile of riluzole can be found. [redacted]

Overall, riluzole tablets have been well tolerated in populations with ALS and diverse neuropsychiatric conditions that include MDD and GAD. In randomized controlled trials comparing a 100 mg daily dose of riluzole with placebo, no AEs occurred at rates greater than 5% and twice that of placebo. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.6.3.1 Elevations in Liver Function Tests

Troriluzole has not been associated with significant changes in liver function or pathology in nonclinical toxicology studies to date, as reflected in the IB.

[redacted]

[redacted]

1.1.6.3.2 Neutropenia

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

[redacted]

1.1.6.3.3 Interstitial Lung Disease

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

[redacted]

1.1.7 Potential Risk to Fetal Development

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

[redacted]

1.2 Study Rationale

[redacted]

Figure 3. Schematic representation on the mechanism of action of riluzole

1.3 Research Hypothesis

Troriluzole monotherapy for 8 weeks is superior to placebo in the treatment of Spinocerebellar Ataxia.

2 STUDY OBJECTIVES

2.1 Primary

- To compare the efficacy of troriluzole (140 mg once daily) versus placebo on ataxia symptoms in subjects with spinocerebellar ataxia (SCA) after 8 weeks of treatment as measured by the total score on the Scale for the Assessment and Rating of Ataxia [SARA]

2.2 Secondary

- To assess the safety and tolerability of troriluzole in subjects with SCA
- To compare efficacy of troriluzole with placebo on patient impression of benefit via use of the PGI-C

[redacted]

3 STUDY ENDPOINTS

3.1 Primary

- The total score on the Scale for the Assessment and Rating of Ataxia (SARA).

3.2 Secondary

- Tolerability and safety of troriluzole will be measured by the frequency and severity of adverse events and discontinuations of adverse events.

- Patient Global Impression of Change (PGI-C);

[redacted]

[redacted]

3.4 Measures of Interest

- Safety and Other assessments:
  - Sheehan Suicidality Tracking Scale (STS)
  - ECG assessments;
  - Vital Sign and Physical Measurements;

[redacted]

4 STUDY PLAN

4.1 Study Design and Duration

BHV4157-201 is a Phase IIb/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. Subjects will be randomized to receive placebo (QD) or troriluzole (140 mg QD), [redacted]

Subjects with SCA3 genotype will be limited to comprise up to approximately 10% so that this most common type of SCA is not over-represented.

Dosing will continue for 8 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 approximately 192 weeks of open- label 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 not complete the follow-up safety visit and should continue dosing as specified.

Subjects entering the Extension Phase would have their first Extension Visit four weeks after the Week 8 Randomization Phase visit. If there is a delay of two weeks or more in dosing between the Randomization Phase and the Extension Phase, subjects would be required to complete an Extension Baseline Visit. Thereafter, subjects will undergo visits every fourth week through Week 12 of this phase. Then subjects will undergo visits every 12 weeks up to Week 192 of this phase. All subjects will undergo a termination visit two weeks after the last dose of study drug.

Subjects who previously completed the extension phase will be allowed to participate in the expanded extension phase for a total of 144 weeks of open-label administration of troriluzole, provided the PI deems this treatment to present an acceptable risk-benefit profile. Such subjects who have been off of medication for at least 2 weeks, will need additional Baseline Visits followed by visits scheduled approximately every 12 weeks, as well as laboratory assessments at approximately 4 and 8 weeks after re-starting medication. In addition, these subjects will be required to have clinical laboratory assessment results that are not deemed clinically significant, available prior to the Baseline Visit and drawn within 6 weeks prior to that visit. These subjects should not have taken riluzole for at least 12 hours prior to re-starting troriluzole.

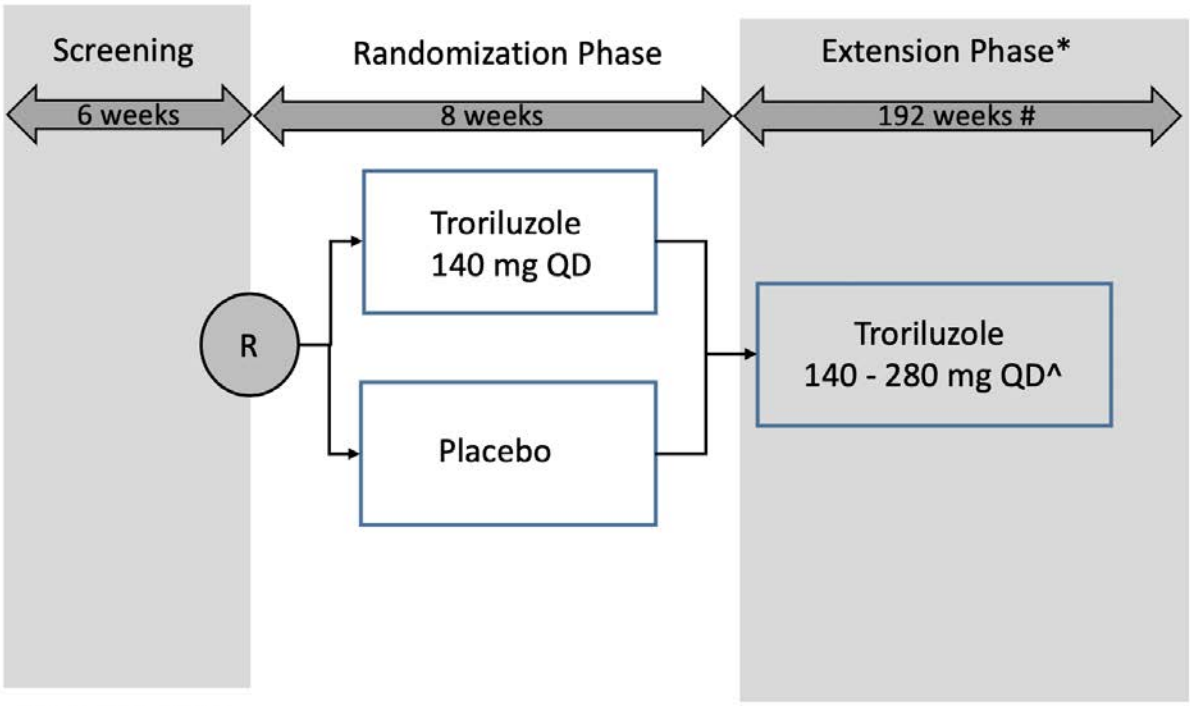
For subjects who experienced decline (as defined below) over at least 9 months of treatment with 140 mg troriluzole, the PI may offer an increased dose of 280 mg daily based on anticipated tolerability (e.g., the patient was tolerating the 140 mg dose well). Decline will be defined as demonstration of a 2 point or greater decline from baseline on the SARA scale on two most recent consecutive visits (at least one month apart) accompanied by PI opinion clinical worsening. Patients who do not tolerate 280 mg daily or demonstrate clinically significant lab abnormalities may have their dose adjusted to 140 mg daily. Subjects who increase to 280 mg daily will have lab tests at approximately 4, 8 and 12 weeks after the dose increase, then no less often that approximately every 12 weeks. Subjects who are given a trial

of 280 mg daily troriluzole will require additional clinical lab assessments (LFTs) at approximately 4 and 8 weeks after starting the increased dosing. For subjects who were tolerating 140 mg without adverse effects, the dose increase may occur at the usual dosing time. Some subjects may better tolerate dosing at bedtime to minimize any impact of sedation. In addition, the PI may split doses (twice daily) if adverse events suggest that this could enhance tolerability. Dosing regimen should be recorded in the CRF.

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

4.2 Study Schematic

Figure 4. Study Schematic



R, Signifies randomization
*, Eligible subjects will include those who perceived benefit in earlier phases or for whom the PI believes extended treatment with troriluzole would offer an acceptable risk-benefit profile.
#, Maximum duration of troriluzole treatment of 192 weeks (not required to be continuous dosing weeks if subjects already completed 48 Week Extension Phase).
^, As per Protocol, subjects demonstrating decline on at least 9 months of 140 mg troriluzole may be offered a higher dose of 280mg daily.

4.3 Schedule of Assessments

Table 2. Schedule of Assessments and Events - Randomization Phase

	SCR	Baseline	Wk 4	Wk 8	2-Wk Post Last Dose (ONLY for subjects NOT entering extension phase or who discontinue early)	Additional Instruction
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
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		X		
Pregnancy Test for WOCBP (urine)		X	X			To be done within 72 hours prior to dosing at visit 2 (Baseline Visit). The site may test a patient at any time if they suspect the patient may be pregnant.
Safety Assessments						
Laboratory Assessments including urinalysis	X	X		X	X	No fasting required
Serum Chemistry			X			A physician who is not the SARA rater must be available to review lab tests and manage any potential medical evaluation throughout the randomization phase
[redacted]						
Physical Exam	X			X		PE will be done at W4 if warranted by emergence of new AE's
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	
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X	
Clinical Outcome Assessments						
SARA	X	X	X	X	X	This should be the first clinical outcome assessment done at each visit.
[redacted]						
[redacted]						
Randomization		X				
Dispense Study Drug		X	X	X		Dispense at Wk 8 only if entering Extension Phase
Drug Accountability			X	X		

Visit Window is +/- 2 days during the Randomization Phase

Table 3. Schedule of Assessments and Events - Extension Phase

	[1]Baseline Visit	Ext. Wk 4	Ext. Wk 8	Ext. Wk 12	Ext. Wk 24	Ext. Wk 36	Ext. Wk 48
Visit		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Eligibility Assessments							
[4]Informed Consent	X						
Neurological Exam					X		X
Pregnancy Test for WOCBP (serum)	X				X		X
[2]Pregnancy Test for WOCBP (urine)	X	X	X	X		X	
Safety Assessments							
Laboratory Assessments including urinalysis	X				X		X
[3]Lab: LFT tests only (ALT, AST, BILI, GGT)		X	X	X		X	
Physical Exam	X				X		X
[redacted]							
Physical Measurements	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
12-Lead ECG	X				X		X
Concomitant Medication Review	X	X	X	X	X	X	X
Adverse Event Assessments	X	X	X	X	X	X	X
Sheehan Suicidality Tracking Scale (Sheehan STS)	X	X	X	X	X	X	X
*** Clinical Outcome Assessment**							
SARA	X		X		X	X	X
[redacted]							
Clinical Drug Supply							
Dispense Study Drug	X	X	X	X	X	X	X
Drug Accountability		X	X	X	X	X	X

[1] Baseline visit for the Extension Phase is ***only required*** if there is an extended break (≥2 weeks) in dosing between the Randomization and Extension Phases.

[2] Subjects will be provided with pregnancy tests to take in between every 3-month office visit. Subjects should be instructed to contact [redacted] if they become pregnant at any time during the study.

[3], Subjects whose dose is increased to 280 mg daily will require LFT tests approximately 4 and 8 weeks after the increase and then approximately every 12 weeks thereafter

[4] Informed Consent for continuing subjects entering the expanded extension phase will be obtained at next scheduled visit. Visit window is +/- 7 days during the extension phase.

Table 4. Schedule of Assessments and Events - 144-Week Expanded Extension Phase (continuing subjects)

	Exp.Ext. Wk 60	Exp. Ext. Wk 72	Exp. Ext. Wk 84	Exp. Ext. Wk 96 or early discontinuation visit (less than or equal to EE Wk 96)
Visit	Visit 7	Visit 8	Visit 9	Visit 10
Eligibility Assessments				
Neurological Exam		X		X
Pregnancy Test for WOCBP (serum)		X		X
[1]Pregnancy Test for WOCBP (urine)	X		X	
Safety Assessments				
Laboratory Assessments including urinalysis		X		X
[2]Lab: LFT tests only (ALT, AST, BILI, GGT)	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
Adverse Event Assessments	X	X	X	X
Sheehan Suicidality Tracking Scale (Sheehan STS)	X	X	X	X
*** Clinical Outcome Assessment**				
SARA	X	X	X	X
[redacted]				
Clinical Drug Supply				
Dispense Study Drug	X	X	X	
Drug Accountability	X	X	X	X

	EE Wk108	EE Wk 120	EE Wk 132	EE Wk 144
Visit	Visit 11	Visit 12	Visit 13	Visit 14
Eligibility Assessments				
Neurological Exam		X		X
[3]Pregnancy Test for WOCBP (serum)	X	X	X	X
Safety Assessments				
[2, 3]Lab: LFT tests only (ALT, AST, BILI)	X	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
Adverse Event Assessments	X	X	X	X
Sheehan Suicidality Tracking Scale (Sheehan STS)	X	X	X	X
Clinical Outcome Assessments				
SARA	X	X	X	X
Clinical Drug Supply				
Dispense Study Drug[4]	X	X	X	
Drug Accountability	X	X	X	X

	EE Wk 156	EE Wk 168	EE Wk 180	EE Wk 192 or Early Discontinuation	EE 2-Wk Post Last Dose
Visit	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19
Eligibility Assessments					
Neurological Exam		X		X	
[3]Pregnancy Test for WOCBP (serum)	X	X	X	X	
Safety Assessments					
[2, 3]Lab: LFT tests only (ALT, AST, BILI)	X	X	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 (Sheehan STS)	X	X	X	X	X
Clinical Outcome Assessments					
SARA	X	X	X	X	X
[redacted]					
Clinical Drug Supply					
Dispense Study Drug[4]	X	X	X		
Drug Accountability	X	X	X	X	

[1] Subjects will be provided with pregnancy tests to take in between every 3-month office visit. Subjects should be instructed to contact [redacted] if they become pregnant at any time during the study. Pregnancy testing in between visits is not required EE Week 108 through EE 2-Week Post Dose.

[2] Subjects whose dose is increased to 280 mg daily will require LFT tests approximately 4 and 8 weeks after the increase and then approximately every 12 weeks thereafter

[3] Lab will not be done by a Central Lab and must be done at local lab.

[4] 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.

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

Table 5. Schedule of Assessments and Events – 144 -Week Expanded Extension Phase (returning subjects)

	[1]Baseline Visit 1	[2]Baseline Visit 2	Exp.Ext. Wk 4	Exp. Ext. Wk 8	Exp. Ext. Wk 12	Exp. Ext. Wk 24	Exp. Ext. Wk 36	Exp. Ext. Wk 48 or early discontinuation (less than or equal to EE Wk 48)
Visit	Visit EE1	Visit EE2	Visit EE3	Visit EE4	Visit EE5	Visit EE6	Visit EE7	Visit EE8
Eligibility Assessments								
Informed Consent	X							
[5]Neurological Exam	X					X		X
Pregnancy Test for WOCBP (serum)						X		X
[3]Pregnancy Test for WOCBP (urine)	X				X		X	
Safety Assessments								
[6]Laboratory Assessments including	X	X				X		X
[4]Lab: LFT tests only (ALT, AST, BILI, GGT)			X	X	X		X	
Physical Exam	X					X		X
Physical Measurements	X				X	X	X	X
Vital Signs	X				X	X	X	X
12-Lead ECG						X		X
Concomitant Medication Review	X				X	X	X	X
Adverse Event Assessments					X	X	X	X
Sheehan Suicidality Tracking Scale (Sheehan STS)	X				X	X	X	X
*** Clinical Outcome Assessment**								
SARA		X			X	X	X	X
[redacted]								
Clinical Drug Supply								
Dispense Study Drug		X			X	X	X	
Drug Accountability					X	X	X	X

	Exp. Ext. Wk 60	Exp. Ext. Wk 72	Exp. Ext. Wk 84	Exp. Ext. Wk 96	Exp. Ext. 2-Wk Post Last Dose
Visit	Visit EE 9	Visit EE 10	Visit EE 11	Visit EE 12	Visit EE 13
Eligibility Assessments					
Neurological Exam		X		X	
[7]Pregnancy Test for WOCBP (serum)	X	X	X	X	
Safety Assessments					
[4,7]Lab: LFT tests only (ALT, AST, BILI)	X	X	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 (Sheehan STS)	X	X	X	X	X
Clinical Outcome Assessments					
SARA	X	X	X	X	X
Clinical Drug Supply					
Dispense Study Drug[8]	X	X	X		
Drug Accountability	X	X	X	X	

	Exp. Ext. Wk 108	Exp. Ext. Wk 120	Exp. Ext. Wk 132	Exp. Ext. Wk 144 or Early Discontinuation	Exp. Ext. 2-Wk Post Last Dose
Visit	Visit EE 9	Visit EE 10	Visit EE 11	Visit EE 12	Visit EE 13
Eligibility Assessments					
Neurological Exam		X		X	
[7]Pregnancy Test for WOCBP (serum)	X	X	X	X	
Safety Assessments					
[4,7]Lab: LFT tests only (ALT, AST, BILI)	X	X	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 (Sheehan STS)	X	X	X	X	X
Clinical Outcome Assessments					
SARA	X	X	X	X	X
[redacted]					
Clinical Drug Supply					
Dispense Study Drug[8]	X	X	X		
Drug Accountability	X	X	X	X	

[1] Baseline 1 and Baseline 2 visits for the 48-Week Expanded Extension Phase are ***only required*** for subjects re-entering the study**.**

[2]Baseline 2 visit for the Extension Phase is ***only required*** if results of Baseline 1 visit meet study eligibility criteria.

[3] Subjects will be provided with pregnancy tests to take in between every 3-month office visit. Subjects should be instructed to contact [redacted] if they become pregnant at any time during the study. Pregnancy testing in between visits is not required EE Week 60 through EE 2-Week Post Dose.

[4] Subjects whose dose is increased to 280 mg daily will require LFT tests approximately 4 and 8 weeks after the increase and then approximately every 12 weeks thereafter. Subjects re-entering the extension phase will require LFT tests approximately 4 and 8 weeks after dosing is re-started.

[5] Neurological exam is required for subjects whose Baseline 2 visit is greater than 7 days after Baseline 1.

[6] Safety Laboratory Assessments are required for subjects whose Baseline 2 visit is greater than 7 days after Baseline 1. Repeat of BL visit 1 labs can be done with permission from Sponsor.

[7] Lab will not be done by a Central Lab and must be done by local lab.

[8] 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.

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 138 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. Subjects will receive placebo (QD) or troriluzole (140 mg QD). Dosing will continue for 8 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 48 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 in the mornings. If tolerability issues arise please refer to section 7.2.3

Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Randomization Phase. There is a visit window of +/- 2 day visit window during the Randomization Phase of the study. It is estimated that approximately 120 subjects will enter this phase of the trial.

4.3.3 Extension Phase (if applicable)

The Extension Phase includes a Baseline Visit; however, that visit is only required if there is a break in dosing two weeks or greater between the Week 8 Visit in the Randomization Phase and the Week 4 visit in the Extension Phase. The Extension Phase also includes a Baseline Visit 1 and Baseline Visit 2; however those visits are only required for subjects who have previously completed the 2 week post-dose visit in the Extension Phase, and who will be re-entering the extension phase of open-label treatment beginning at Week 60 through Week 144. Subjects re-entering the extension phase will complete the Baseline 1 visit to confirm that they meet safety eligibility requirements, then return for the Baseline 2 visit, followed by visits scheduled approximately every 12 weeks, as well as laboratory assessments at approximately 4 and 8 weeks after re-starting medication. Thereafter, subjects will undergo visits every 12 weeks up to Week 144 of the Extension Phase (or 192 weeks for continuing subjects). All subjects will undergo a termination visit two weeks after the last dose of study drug.

[redacted]

Sponsor Medical Monitor

[redacted]

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.

4.4 Post Study Access to Therapy (if applicable)

There is an extension phase of this trial for up to 192 weeks (144 weeks for returning subjects) 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 120 subjects are expected to be randomized in 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;

[redacted]

b. Ability to ambulate 8 meters without assistance (canes and other devices allowed);
c. Screening total SARA total score ≥8;
d. Score of ≥ 2 on gait subsection of the SARA;
e. 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;

5.3 Exclusion Criteria

1. Target Disease Exceptions

a. Any medical condition other than one of the hereditary ataxias specified in the inclusion criteria that could predominantly explain or contribute significantly to the subjects' symptoms of ataxia (for example, alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, paraneoplastic disease, head injury, idiopathic late onset ataxia, multisystem atrophy) or that can confound assessment of ataxia symptoms (for example, stroke, arthritis);

b. MMSE score < 24;

[redacted]

d. SARA total score of > 30 points at screening; 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.

[redacted]

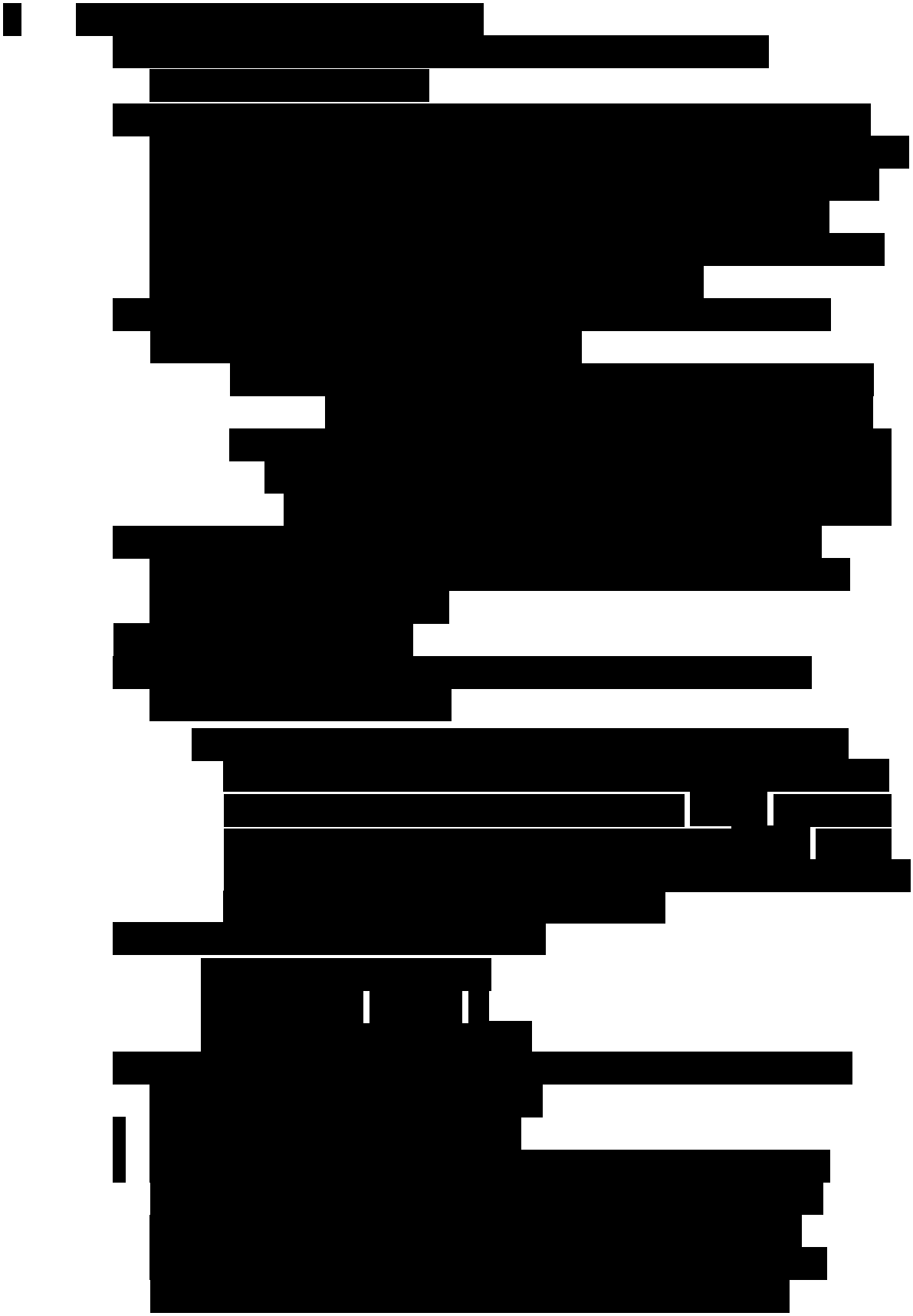
2. Medical History Exclusions

a. Clinical history of stroke. Note: Subjects with a history of transient ischemic attack (TIA) may be enrolled, if it occurred at least 3 months prior to screening and the subject is prescribed appropriate treatment [e.g., platelet aggregation inhibitors];

[redacted]

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

[redacted]



5.4 Prohibited Concomitant Medication

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]

Woman 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 menopause is defined as:

- Amenorrhea greater than or equal to 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level > 35mIU/mL 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 performed to date. It is therefore not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP who participating this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited. It is required that all WOCBP use 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 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.

5.5 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 AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

The sponsor will provide investigational product which will include including troriluzole, 140 MG capsules and matching placebo.

Sites will also be provided with a Regulatory binder, Rating Scale Binder, IVRS Manual and a Source Document Template. Instructions on all 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.

Eligibility Assessments

6.1.1 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.

6.1.2 Neurological 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.

6.1.3 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.

6.2 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.

The SARA rating (primary outcome measure) must NOT be performed by the staff (including principal investigator) who are evaluating test lab results during the 8 week randomization phase. Specifically, these tests include Serum Chemistry, Hematology and Urinalysis acquired after baseline (i.e., Week 4 scheduled labs, potentially other unscheduled tests, through Week 8 scheduled labs). After completion of the Week 8 visit assessments and sign-off on SARA ratings as final, a SARA rater who is the principal investigator may evaluate labs that will be acquired within the Extension Phase. Based on this requirement, a site may potentially need to identify a qualified physician or other medical personnel who can be available to review lab tests during the randomization phase for each subject. This is further described in Section 6.3.1.

6.2.1 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.

1) The same scale should be used to weigh a given subject throughout the study.

2) Scales should be calibrated and zeroed just prior to each subject's weigh-in session.

3) A subject should void just prior to being weighed.

4) Weight should be recorded before a meal (if applicable) and at approximately the same time each day.

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

6.2.2 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 to determine clinical significance. If a site is unable to identify a cardiologist for this task, the Medical Lead at [redacted] can review the ECG to determine clinical significance.

6.2.3 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.

6.2.4 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, creatinine, BUN, uric acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase or Lipase, TSH, and T4;
c) Urinalysis: macroscopic examination, pH, specific gravity, ketones, nitrites, urobilinogen, leukocyte esterase, protein, creatinine, 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. Any local lab results that are out of range must be brought to the attention of the Biohaven Medical Monitor.

[redacted]

6.2.4.4 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. 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.

6.2.4.5 *Evaluation of Laboratory Assessments*

As described above, the SARA rating (primary outcome measure) must NOT be performed by the staff (including principal investigator) who are evaluating test lab results during the 8 week randomization phase. Specifically, these tests include Serum Chemistry, Hematology and Urinalysis acquired after baseline (i.e., Week 4, potentially other unscheduled tests, through Week 8 scheduled labs). After completion of the Week 8 visit assessments and sign-off on SARA ratings as final, a SARA rater who is the principal investigator may evaluate lab tests acquired in the Extension Phase. Based on this requirement, a site may potentially need to identify a qualified Lab Monitor (i.e., physician or other medical personnel) who can be available to review labs during the randomization phase for each subject. This requirement does not apply during the Extension Phase.

The rationale for this process is to assure adequate blinding while maintaining subject safety. Riluzole itself is associated with low rates of transient increases in transaminases. According to the US Prescribing information for riluzole (the active metabolite of troriluzole), the rates of markedly elevated transaminases (AST or ALT > 5x ULN) are approximately 2%. The rates of less elevated transaminases (i.e., AST or ALT > 3x ULN) are approximately 8%. While troriluzole was designed to diminish risk for LFT changes (e.g., diminished first-pass liver metabolism, approximately 30% lower molar burden than the 100 mg dose of riluzole), the study is designed to address the possibility of such increases while maintaining the integrity of the primary outcome measure. Other lab abnormalities, based on known literature of riluzole, could include decreased neutrophil count. The Lab Monitor should manage any non-LFT lab

abnormalities as medically warranted to assure subject safety. The SARA Rater (who may be the PI) should be shielded from the nature of any additional evaluation triggered by these lab tests.

The management of abnormal LFTs are described herein. Scheduled LFTs (ALT, AST, bilirubin, alkaline phosphatase) at the Week 4 and Week 8 visits will be evaluated by the Lab Monitor (LM), who will be a physician or other qualified medical personnel designated by the PI and who has no involvement in the conduct of the SARA Ratings.

If AST or ALT values are between 3x ULN and <5x ULN, then the Lab Monitor, potentially with administrative assistance from the Study Coordinator, 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 the Week 4 visit shows ALT or AST>5x ULN, the Lab Monitor will notify the PI and the PI will assess this as a potential 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
    - Ebstein-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 8 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.

Other Safety Assessments

6.2.5 Sheehan Suicidality Tracking Scale (Sheehan STS)

The Sheehan 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. 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.

6.3 Clinical Outcome Assessments

The clinical outcome assessments and other interviews/scales (e.g., Sheehan STS) 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 SARA prior to other clinical / safety outcome assessments [redacted]

6.3.1 The Scale for the Assessment and Rating of Ataxia (SARA)

The SARA was developed as a clinician-administered instrument to measure severity of symptoms in patients with SCA. While there are multiple scales available, the SARA has been tested in the most patients with SCA to date. It has been demonstrated to have excellent inter-rater reliability [i.e., intraclass correlations of > 0.95 (61, 62)], good test- retest reliability [intraclass coefficient of 0.90 (61)], high internal consistency [Cronbach's alpha of > 0.94 (61, 62)], sensitivity to change over time in populations with SCA (2, 63, 64) and able to detect treatment effects (65). In addition, the SARA scores were highly correlated with measures of activities of daily living, such as the Barthel Index (typically used in stroke) and the Unified Huntingtons Disease Rating Scale Part IV (typically used in Huntingtons Disease).

The SARA scores range from 0 (no ataxia) to 40 (severe). The SARA takes approximately 15 minutes to administer. Assessed items include:

1. Gait (rated 0 to 8)
2. Stance (0 to 6)
3. Sitting (0 to 4)

4. Speech disturbance (0 to 6)
5. Finger chase (0 to 4)
6. Nose-finger test (0 to 4)
7. Fast alternating hand movements (0 to 4)
8. Heel-shin slide (0 to 4)

Once each of the 8 categories has been assessed, the total score is calculated to determine the severity of ataxia. For motor activities of the four extremities (items 5-8), assessments are performed bilaterally and the mean values are used to obtain the total score.

Raters must be pre-approved by sponsor or sponsor representative (i.e. CRO) to rate subjects on the SARA

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.5 Early Discontinuation from the Study

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 stopped taking study medication 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).

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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 matching placebo). Troriluzole will be provided as a loose filled capsule in the Randomization Phase and as loose filled or formulated capsules (dependent on lot) in the Extension Phase. Formulated capsules have black markings on the capsule which differentiates them from the loose filled capsules. Study BHV4157-102 demonstrated bioequivalence of the two formulations.

7.1.2 Packaging, Shipment and Storage

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 manufacturing and/or expiry/retest date. Individual subject doses will be dispensed according to the randomization scheme in appropriate envelopes/containers indicated with at least the project number, the period number and the subject number/ spare number.

7.2 Dose and Administration

Subjects will receive placebo (QD) or troriluzole (140 mg QD) loose filled capsules in the Randomization Phase and loose filled or formulated capsules (dependent on lot) in the Extension Phase. Formulated capsules have black markings on the capsule which differentiates them from the loose filled capsules

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

- If subjects have difficulty tolerating morning dosing (such as experiencing sedation) then the investigator may permit the subject to switch to night time dosing (and document this change).

For subjects who experienced decline (as defined below) over at least 9 months of treatment with 140 mg troriluzole in the first Extension Phase, the PI may offer an increased dose of 280 mg daily based on anticipated tolerability (e.g., the patient was tolerating the 140 mg dose well). Decline will be defined as demonstration of a 2 point or greater decline from Randomization Phase baseline on the SARA scale on two most recent consecutive visits (at least one month apart) accompanied by PI opinion clinical worsening.

Subjects who are dosed with 280 mg troriluzole in the Expanded Extension phase may continue dosing at their regular time if they experienced no adverse events. Otherwise, consideration should be given to bedtime dosing so as to mitigate impact of adverse events such as sedation. In addition, the PI may consider splitting dosing (twice daily) based upon an adverse event profile that may suggest improved tolerability with such a regimen.

7.2.1 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 will be assigned. After completion of all screening evaluations, all eligible subjects will be randomized, in a 1:1 ratio [redacted] to receive either placebo (QD) or troriluzole (140mg QD). 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 8 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 to track patient enrollment.

Open Label Extension study medication will be supplied in bulk bottles. Bottle numbers will be assigned via the IWRS system in the Extension Phase. 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.

For all subjects entering the Expanded Extension Phase, including those who are re-entering the study (as described in section 4.3.3) bottle numbers will be assigned manually and sites will be responsible for recording the bottle numbers on the Drug Accountability Form provided in the Regulatory Binder. Subjects re-entering the study will retain the same subject number as assigned at the initial Screening Visit.

7.2.2 Selection and Timing of Dose and Administration

Subjects will receive placebo (QD) or troriluzole (140 mg QD). Study medication should be administered in the morning without regard to meals.

See Section 7.2 for subjects who are dosed with 280 mg troriluzole in the extension phase.

7.2.3 Dose Modifications

For subjects who do not tolerate their study treatment, the investigator may permit them to switch to night time dosing if there is reason to believe that may help tolerability. In addition, the investigator may permit up to one week of every other day dosing prior to re-instituting daily dosing. Any such changes must be documented by the investigator. If these procedures do not result in acceptable tolerability then dosing should be discontinued.

See Section 7.2 for subjects who are dosed with 280 mg troriluzole in the Expanded Extension phase.

7.3 Blinding and Unblinding

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

Before breaking the blind of an individual patient's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the patient'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 patient is

receiving active product without the need for unblinding. Unblinding will be managed via the IWRS system.

The Biostatistician, or designee, will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of sample from a control group of patients. A pharmacokinetics and IWRS randomization manager may all be unblinded before data is more generally unblinded. These summaries will not reveal individual patients' treatment assignments. Except as noted above, other members of the BHV research team and CRO will remain blinded until after the primary analysis is completed.

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

7.4 Treatment Compliance

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

Patients have to 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 patient from the trial should be considered.

7.5 Destruction and Return of Study Drug

If study drugs (those supplied by the sponsor or sourced by the investigator) are to be destroyed 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 BHV Study monitor or the sponsor's designee.

Study drug will not be returned. All unused and/or partially used study drug may be destroyed on site providing the site has an applicable standard operating procedure on file.

8 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a 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 relate 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.

8.1 Serious Adverse Events

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

8.1.1 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 BHV-4157;
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are (but not limited to):
    - Intensive treatment in an emergency room or at home for allergic bronchospasm;
    - Blood dyscrasias or convulsions that do not result in inpatient hospitalization;

- Development of drug dependency or drug abuse;
- Potential drug induced liver injury (see section 8.1.6).

8.1.2 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.

Classification of Adverse Events

The severity of all AEs must be recorded in the eCRF and on the SAE Form, if applicable. The severity or intensity of an AE refers to the extent to which it affects the subject's daily activities. The severity of events should be graded as mild, moderate or severe. Refer to the BHV4157-201 SAE Reporting and Management Plan for definitions of each grading criteria.

The Investigator's assessment of an AEs relationship to study drug is part of the documentation process but is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The relationship or association of the study drug in causing or contributing to the AE will be characterized as either not related, unlikely related, possibly related, or related. Refer to the BHV4157-201 SAE Reporting and Management Plan for definitions of each criteria.

8.1.3 Collection and Reporting 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 8.1.4), potential drug induced liver injury (see section 8.1.6) and pregnancies (see section 8.1.5) 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 [redacted] immediately via telephone, upon observing or learning of the event. [redacted] will then immediately notify the Biohaven Medical Monitor of the event. The SAE form must then be submitted to [redacted] 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 [redacted]

The Serious Adverse Event Report Form (SAERF) should be submitted [redacted] by facsimile (FAX).

North America: [redacted]

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

North America: [redacted]

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.

8.1.4 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.

8.1.5 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 [redacted] 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 [redacted]

8.1.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

- 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.

8.2 Non-serious Adverse Events

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

8.2.1 Collection and Reporting of Non-Serious Adverse Events

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 clinically significant 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.

9 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.

9.1 General Procedures

Analysis populations: Efficacy data will be assessed using the Full Analysis Set (FAS) consisting of all patients with at least one dose of test treatment and at least one efficacy observation. No missing data will be imputed as missing data are assumed to be missing at random. Safety data will be assessed using the Safety Analysis Set (SAF), which includes all patients exposed to at least 1 dose of study treatment.

Statistical analyses: Descriptive statistics are planned for all outcome measures collected in this study. The randomization phase and the extension phase will be analyzed separately. For patients receiving troriluzole during both phases, summary statistics will be provided for data from both phases combined.

9.2 Sample Size

The sample size for this study will be approximately 120 randomized subjects to accommodate for dropouts and based on the rationale that follows.

[redacted] For this trial, conservatively assuming a TRUE underlying difference between treatments of 1.24 units and pooled SD=2.01, N=112 (56/group) has ~90% power to yield a statistically significant (alpha=0.050, 2-sided) difference between treatments in change from baseline to week 8 in SARA score. This calculation is via 2-sample t-test, which is likely conservative compared to the planned repeated measures analysis planned for this trial to leverage the likely correlation of response between weeks 4 and 8. [redacted]

9.3 Statistical Methods

9.3.1 Primary Endpoint(s)

The primary endpoint is change from baseline to week 8 in SARA score; the primary objective is the comparison of troriluzole versus placebo. The primary analysis will be carried out via a Mixed Model for Repeated Measures (MMRM) analysis model using the FAS population. [redacted]

[redacted]

9.3.2 Secondary Endpoint(s)

Continuous secondary, change-from-baseline, endpoints will be analyzed via analysis of covariance model [redacted] Binary endpoints will be summarized by counts and percents by treatment; p-values for comparisons between weeks will be provided by exact binomial test.

9.3.3 Analysis of Safety

Safety outcome measures (adverse events, laboratory variables, ECG and vital signs) will be descriptively summarized by treatment group for the SAF population. For adverse events, treatment-emergent adverse events (TEAEs) are defined as those that developed, worsened, or became serious after first dose of test treatment. They will be summarized by counts and percents. Observed values and change from baseline in lab variables and vital signs will be summarized by count, mean, median, SD, minimum, and maximum. The primary endpoint will be assessed when all subjects complete the 8 week randomization phase. In addition, during the extension phase, data may be locked, analyses conducted, and reports produced as required to support safety monitoring, administrative concerns, and regulatory requirements.

9.3.4 Demographic and Baseline Characteristics

Demographic information will be summarized (n, mean, SD, minimum, maximum for continuous endpoints; n and % for categorical endpoints) by treatment group and for treatment groups combined. This will be for the Safety Analysis Set; however, if substantial difference exists between the numbers of patients in the SAF and the FAS, then a separate similar summary will be provided for the FAS.

10 ETHICS AND RESPONSIBILITIES

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).

10.1 Data and Safety Monitoring Committee

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 cases of emergency will be followed.

10.2 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.

10.3 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.

10.4 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.

10.5 Records Management and Retention

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.

10.6 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.

10.7 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.

11 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.

12 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.

13 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.

14 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.

15 REFERENCES

[redacted]

3. Custer SK, Garden GA, Gill N, Rueb U, Libby RT, Schultz C, Guyenet SJ, Deller T, Westrum LE, Sopher BL, La Spada AR. Bergmann glia expression of polyglutamine-expanded ataxin-7 produces neurodegeneration by impairing glutamate transport. Nat Neurosci. 2006;9(10):1302-11. Epub 2006/08/29. doi: 10.1038/nn1750. PubMed PMID: 16936724.
4. Cvetanovic M. Decreased expression of glutamate transporter GLAST in Bergmann glia is associated with the loss of Purkinje neurons in the spinocerebellar ataxia type 1. Cerebellum (London, England). 2015;14(1):8-11. Epub 2014/09/27. doi: 10.1007/s12311-014-0605-0. PubMed PMID: 25255716.
5. Shakkottai VG, do Carmo Costa M, Dell'Orco JM, Sankaranarayanan A, Wulff H, Paulson HL. Early changes in cerebellar physiology accompany motor dysfunction in the polyglutamine disease spinocerebellar ataxia type 3. J Neurosci. 2011;31(36):13002-14. Epub 2011/09/09. doi: 10.1523/jneurosci.2789-11.2011. PubMed PMID: 21900579; PMCID: PMC3170039.
6. Groeneveld GJ, van Kan HJ, Torano JS, Veldink JH, Guchelaar HJ, Wokke JH, van den Berg LH. Inter- and intraindividual variability of riluzole serum concentrations in patients with ALS. J Neurol Sci. 2001;191(1-2):121-5. Epub 2001/10/26. PubMed PMID: 11677002.
7. Martinet M, Montay G, Rhodes G. Pharmacokinetics and metabolism of riluzole. Drugs Today. 1997;33(8):587-94.
8. Sanderink GJ, Bournique B, Stevens J, Petry M, Martinet M. Involvement of human CYP1A isoenzymes in the metabolism and drug interactions of riluzole in vitro. J Pharmacol Exp Ther. 1997;282:1465-72.
9. McDonnell ME, Vera MD, Blass BE, Pelletier JC, King RC, Fernandez-Metzler C, Smith GR, Wrobel J, Chen S, Wall BA, Reitz AB. Riluzole prodrugs for melanoma and ALS: design, synthesis, and in vitro metabolic profiling. Bioorg Med Chem. 2012;20(18):5642-8. Epub 2012/08/16. doi: 10.1016/j.bmc.2012.07.004. PubMed PMID: 22892214; PMCID: PMC3495316.
10. Aminoff M, Greenberg D, Simon R. Clinical Neurology. 9ed: McGraw-Hill Education; 2015.
11. Ropper AH, Samuels MA, Klein JP. Adams and Victors Principles of Neurology. 10ed. New York: McGraw-Hill Education; 2014.
12. Kasumu A, Bezprozvanny I. Deranged calcium signaling in Purkinje cells and pathogenesis in spinocerebellar ataxia 2 (SCA2) and other ataxias. Cerebellum. 2012;11(3):630-9. doi: 10.1007/s12311-010-0182-9. PubMed PMID: 20480274; PMCID: 3257360.
13. Sankaranarayanan A, Raman G, Busch C, Schultz T, Zimin PI, Hoyer J, Kohler R, Wulff H. Naphtho[1,2-d]thiazol-2-ylamine (SKA-31), a new activator of KCa2 and

KCa3.1 potassium channels, potentiates the endothelium-derived hyperpolarizing factor response and lowers blood pressure. Mol Pharmacol. 2009;75(2):281-95. Epub 2008/10/29. doi: 10.1124/mol.108.051425. PubMed PMID: 18955585; PMCID: PMC2635097.

14. Maltecca F, Baseggio E, Consolato F, Mazza D, Podini P, Young SM, Jr., Drago I, Bahr BA, Puliti A, Codazzi F, Quattrini A, Casari G. Purkinje neuron Ca2+ influx reduction rescues ataxia in SCA28 model. J Clin Invest. 2015;125(1):263-74. Epub 2014/12/09. doi: 10.1172/jci74770. PubMed PMID: 25485680; PMCID: PMC4382234.

15. USPI. RILUTEK ASPI, Approved April 20162016.

16. Lacomblez L, G. B, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet. 1996;347(9013):1425-31.

17. Le Liboux A, Lefebvre P, Le Roux Y, Truffinet P, Aubeneau M, Kirkesseli S, Montay G. Single- and multiple-dose pharmacokinetics of riluzole in white subjects. J Clin Pharmacol. 1997;37:820-7.

18. Benavides J, Camelin JC, Mitrani N, Flamand F, Uzan A, Legrand JJ, Gueremy C, Le Fur G. 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission--II. Biochemical properties. Neuropharmacology. 1985;24(11):1085-92.

19. Mizoule J, Meldrum B, Mazadier M, Croucher M, Ollat C, Uzan A, Legrand JJ, Gueremy C, Le Fur G. 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission--I. Anticonvulsant properties. Neuropharmacology. 1985;24(8):767-73.

20. Doble A. The pharmacology and mechanism of action of riluzole. Neurology. 1996;47(6 Suppl 4):S233-41.

21. Pittenger C, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. CNS Drugs. 2008;22(9):761-86. Epub 2008/08/14. doi: 2294 [pii].

22. Zarate CA, Manji HK. Riluzole in psychiatry: a systematic review of the literature. Expert Opin Drug Metab Toxicol. 2008;4(9):1223-34. Epub 2008/08/30. doi: 10.1517/17425255.4.9.1223. PubMed PMID: 18721116.

23. Cheramy A, Barbeito L, Godeheu G, Glowinski J. Riluzole inhibits the release of glutamate in the caudate nucleus of the cat in vivo. Neurosci Lett. 1992;147(2):209-12.

24. Doble A, Hubert JP, Blanchard JC. Pertussis toxin pretreatment abolishes the inhibitory effect of riluzole and carbachol on D-[3H]aspartate release from cultured cerebellar granule cells. Neurosci Lett. 1992;140(2):251-4.

25. Martin D, Thompson MA, Nadler JV. The neuroprotective agent riluzole inhibits release of glutamate and aspartate from slices of hippocampal area CA1. Eur J Pharmacol. 1993;250(3):473-6.

26. Jehle T, Bauer J, Blauth E, Hummel A, Darstein M, Freiman TM, Feuerstein TJ. Effects of riluzole on electrically evoked neurotransmitter release. Br J Pharmacol. 2000;130(6):1227-34.

27. Benoit E, Escande D. Riluzole specifically blocks inactivated Na channels in myelinated nerve fibre. Pflugers Arch. 1991;419(6):603-9.

28. Hebert T, Drapeau P, Pradier L, Dunn RJ. Block of the rat brain IIA sodium channel alpha subunit by the neuroprotective drug riluzole. Mol Pharmacol. 1994;45(5):1055-60.

29. Zona C, Siniscalchi A, Mercuri NB, Bernardi G. Riluzole interacts with voltage-activated sodium and potassium currents in cultured rat cortical neurons. Neuroscience. 1998;85(3):931-8.
30. Urbani A, Belluzzi O. Riluzole inhibits the persistent sodium current in mammalian CNS neurons. Eur J Neurosci. 2000;12(10):3567-74.
31. Huang CS, Song JH, Nagata K, Yeh JZ, Narahashi T. Effects of the neuroprotective agent riluzole on the high voltage-activated calcium channels of rat dorsal root ganglion neurons. J Pharmacol Exp Ther. 1997;28(3):1280-90.
32. Stefani A, Spadoni F, Bernardi G. Differential inhibition by riluzole, lamotrigine, and phenytoin of sodium and calcium currents in cortical neurons: implications for neuroprotective strategies. Exp Neurol. 1997;147(1):115-22.
33. Duprat F, Lesage F, Patel AJ, Fink M, Romey G, Lazdunski M. The neuroprotective agent riluzole activates the two P domain K(+) channels TREK-1 and TRAAK. Mol Pharmacol. 2000;57(5):906-12.
34. Xu L, Enyeart JA, Enyeart JJ. Neuroprotective agent riluzole dramatically slows inactivation of Kv1.4 potassium channels by a voltage-dependent oxidative mechanism. J Pharmacol Exp Ther. 2001;299(1):227-37.
35. Ahn HS, Choi JS, Choi BH, Kim MJ, Rhie DJ, Yoon SH, Jo YH, Kim MS, Sung KW, Hahn SJ. Inhibition of the cloned delayed rectifier K+ channels, Kv1.5 and Kv3.1, by riluzole. Neuroscience. 2005;133(4):1007-19.
36. Ahn HS, Kim SE, Jang HJ, Kim MJ, Rhie DJ, Yoon SH, Jo YH, Kim MS, Sung KW, Hahn SJ. Interaction of riluzole with the closed inactivated state of Kv4.3 channels. J Pharmacol Exp Ther. 2006;319(1):323-31.
37. Azbill RD, Mu X, Springer JE. Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes. Brain Res. 2000;871(2):175-80.
38. Dunlop J, Beal McIlvain H, She Y, Howland DS. Impaired spinal cord glutamate transport capacity and reduced sensitivity to riluzole in a transgenic superoxide dismutase mutant rat model of amyotrophic lateral sclerosis. J Neurosci. 2003;23(5):1688-96.
39. Frizzo ME, Dall'Onder LP, Dalcin KB, Souza DO. Riluzole enhances glutamate uptake in rat astrocyte cultures. Cell Mol Neurobiol. 2004;24(1):123-8.
40. Fumagalli E, Funicello M, Rauen T, Rauen T, Gobbi M, Mennini T. Riluzole enhances the activity of glutamate transporters GLAST, GLT1 and EAAC1. Eur J Pharmacol. 2008;578(2-3):171-6.
41. Sung B, Lim G, Mao J. Altered expression and uptake activity of spinal glutamate transporters after nerve injury contribute to the pathogenesis of neuropathic pain in rats. J Neurosci. 2003;23(7):2899-910.
42. Chowdhury GM, Banasr M, de Graaf RA, Rothman DL, Behar KL, Sanacora G. Chronic riluzole treatment increases glucose metabolism in rat prefrontal cortex and hippocampus. J Cereb Blood Flow Metab. 2008.
43. Banasr M, Chowdhury GM, Terwilliger R, Newton SS, Duman RS, Behar KL, Sanacora G. Glial pathology in an animal model of depression: reversal of stress-induced cellular, metabolic and behavioral deficits by the glutamate-modulating drug riluzole. Mol Psychiatry. 2008.
44. Brennan BP, Hudson JI, Jensen JE, McCarthy J, Roberts JL, Prescot AP, Cohen BM, Pope HG, Jr., Renshaw PF, Ongur D. Rapid enhancement of glutamatergic neurotransmission in bipolar depression following treatment with riluzole.

Neuropsychopharmacology. 2010;35(3):834-46. Epub 2009/12/04. doi: 10.1038/npp.2009.191. PubMed PMID: 19956089; PMCID: Pmc3055603.
45. Zafra F, Hengerer B, Leibrock J, Thoenen H, Lindholm D. Activity dependent regulation of BDNF and NGF mRNAs in the rat hippocampus is mediated by non-NMDA glutamate receptors. EMBO J. 1990;9(11):3545-50.
46. Lauterborn JC, Lynch G, Vanderklish P, Arai A, Gall CM. Positive modulation of AMPA receptors increases neurotrophin expression by hippocampal and cortical neurons. Journal of Neuroscience. 2000;20(1):8-21.
47. Hayashi T, Umemori H, Mishina M, Yamamoto T. The AMPA receptor interacts with and signals through the protein tyrosine kinase Lyn. Nature. 1999;397(6714):72-6.
48. Legutko B, Li X, Skolnick P. Regulation of BDNF expression in primary neuron culture by LY392098, a novel AMPA receptor potentiator. Neuropharmacology. 2001;40(8):1019-27.
49. Hardingham GE. Pro-survival signalling from the NMDA receptor. Biochem Soc Trans. 2006;34(Pt 5):936-8. PubMed PMID: 17052231.
50. Hardingham GE, Bading H. Coupling of extrasynaptic NMDA receptors to a CREB shut-off pathway is developmentally regulated. Biochimica et Biophysica Acta. 2002;1600(1-2):148-53.
51. Hardingham GE, Bading H. The Yin and Yang of NMDA receptor signalling. Trends in Neurosciences. 2003;26(2):81-9.
52. Hardingham GE, Fukunaga Y, Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways.[see comment]. Nature Neuroscience. 2002;5(5):405-14.
53. Mizuta I, Ohta M, Ohta K, Nishimura M, Mizuta E, Kuno S. Riluzole stimulates nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor synthesis in cultured mouse astrocytes. Neurosci Lett. 2001;310(2-3):117-20.
54. Katoh-Semba R, Asano T, Ueda H, Morishita R, Takeuchi IK, Inaguma Y, Kato K. Riluzole enhances expression of brain-derived neurotrophic factor with consequent proliferation of granule precursor cells in the rat hippocampus. FASEB J. 2002;16(10):1328-30.
55. Fumagalli E, Bigini P, Barbera S, De Paola M, Mennini T. Riluzole, unlike the AMPA antagonist RPR119990, reduces motor impairment and partially prevents motoneuron death in the wobbler mouse, a model of neurodegenerative disease. Exp Neurol. 2006;198(1):114-28.
56. Du J, Suzuki K, Wei Y, Wang Y, Blumenthal R, Chen Z, Falke C, Zarate CA, Manji HK. The anticonvulsants lamotrigine, riluzole, and valproate differentially regulate AMPA receptor membrane localization: relationship to clinical effects in mood disorder. Neuropsychopharmacology. 2007;32(4):793-802.
57. Mohammadi B, Krampfl K, Moschref H, Dengler R, Bufler J. Interaction of the neuroprotective drug riluzole with GABA(A) and glycine receptor channels. Eur J Pharmacol. 2001;415(2-3):135-40.
58. He Y, Benz A, Fu T, Wang M, Covey DF, Zorumski CF, Mennerick S. Neuroprotective agent riluzole potentiates postsynaptic GABA(A) receptor function. Neuropharmacology. 2002;42(2):199-209.

59. Mohammadi B, Lang N, Dengler R, Bufler J. Interaction of high concentrations of riluzole with recombinant skeletal muscle sodium channels and adult-type nicotinic receptor channels. Muscle Nerve. 2002;26(4):539-45.
60. Niciu MJ, Kelmendi B, Sanacora G. Overview of glutamatergic neurotransmission in the nervous system. Pharmacol Biochem Behav. 2012;100(4):656-64. Epub 2011/09/06. doi: 10.1016/j.pbb.2011.08.008. PubMed PMID: 21889952; PMCID: Pmc3253893.
61. Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, Giunti P, Globas C, Infante J, Kang JS, Kremer B, Mariotti C, Melegh B, Pandolfo M, Rakowicz M, Ribai P, Rola R, Schols L, Szymanski S, van de Warrenburg BP, Durr A, Klockgether T, Fancellu R. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology. 2006;66(11):1717-20. Epub 2006/06/14. doi: 10.1212/01.wnl.0000219042.60538.92. PubMed PMID: 16769946.
62. Yabe I, Matsushima M, Soma H, Basri R, Sasaki H. Usefulness of the Scale for Assessment and Rating of Ataxia (SARA). J Neurol Sci. 2008;266(1-2):164-6. Epub 2007/10/24. doi: 10.1016/j.jns.2007.09.021. PubMed PMID: 17950753.
63. Jacobi H, Rakowicz M, Rola R, Fancellu R, Mariotti C, Charles P, Durr A, Kuper M, Timmann D, Linnemann C, Schols L, Kaut O, Schaub C, Filla A, Baliko L, Melegh B, Kang JS, Giunti P, van de Warrenburg BP, Fimmers R, Klockgether T. Inventory of Non-Ataxia Signs (INAS): validation of a new clinical assessment instrument. Cerebellum (London, England). 2013;12(3):418-28. Epub 2012/10/24. doi: 10.1007/s12311-012-0421-3. PubMed PMID: 23090211.
64. Schmitz-Hubsch T, Fimmers R, Rakowicz M, Rola R, Zdzienicka E, Fancellu R, Mariotti C, Linnemann C, Schols L, Timmann D, Filla A, Salvatore E, Infante J, Giunti P, Labrum R, Kremer B, van de Warrenburg BP, Baliko L, Melegh B, Depondt C, Schulz J, du Montcel ST, Klockgether T. Responsiveness of different rating instruments in spinocerebellar ataxia patients. Neurology. 2010;74(8):678-84. Epub 2010/02/24. doi: 10.1212/WNL.0b013e3181d1a6c9. PubMed PMID: 20177122.
65. Zesiewicz TA, Greenstein PE, Sullivan KL, Wecker L, Miller A, Jahan I, Chen R, Perlman SL. A randomized trial of varenicline (Chantix) for the treatment of spinocerebellar ataxia type 3. Neurology. 2012;78(8):545-50. Epub 2012/02/11. doi: 10.1212/WNL.0b013e318247cc7a. PubMed PMID: 22323747.
66. Schmitz-Hubsch T, Giunti P, Stephenson DA, Globas C, Baliko L, Sacca F, Mariotti C, Rakowicz M, Szymanski S, Infante J, van de Warrenburg BP, Timmann D, Fancellu R, Rola R, Depondt C, Schols L, Zdzienicka E, Kang JS, Dohlinger S, Kremer B, Melegh B, Filla A, Klockgether T. SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. Neurology. 2008;71(7):486-92. Epub 2008/08/13. doi: 10.1212/01.wnl.0000324863.76290.19. PubMed PMID: 18695159.
67. Group HS. Unified Huntington's Disease Rating Scale: reliability and consistency. Huntington Study Group. Mov Disord. 1996;11(2):136-42. Epub 1996/03/01. doi: 10.1002/mds.870110204. PubMed PMID: 8684382.
68. Weyer A, Abele M, Schmitz-Hubsch T, Schoch B, Frings M, Timmann D, Klockgether T. Reliability and validity of the scale for the assessment and rating of ataxia: a study in 64 ataxia patients. Mov Disord. 2007;22(11):1633-7. Epub 2007/05/23. doi: 10.1002/mds.21544. PubMed PMID: 17516493.
69. Lo RY, Figueroa KP, Pulst SM, Lin CY, Perlman S, Wilmot G, Gomez C, Schmahmann J, Paulson H, Shakkottai VG, Ying S, Zesiewicz T, Bushara K, Geschwind

M, Xia G, Subramony SH, Ashizawa T, Kuo SH. Coenzyme Q10 and spinocerebellar ataxias. Mov Disord. 2015;30(2):214-20. Epub 2014/12/03. doi: 10.1002/mds.26088. PubMed PMID: 25449974; PMCID: PMC4674072.

70. Kathy Harnett Sheehan and David V. Sheehan. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol. 2008 Mar;23(2):70-83. PMID: 18301121

71. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. Cerebellum (London, England). 2007;6(3):254-67. Epub 2007/09/06. doi: 10.1080/14734220701490995. PubMed PMID: 17786822.

72. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatry Clin Neurosci. 2004;16(3):367-78. Epub 2004/09/21. doi: 10.1176/jnp.16.3.367. PubMed PMID: 15377747.

16 APPENDICES

16.1 APPENDIX I – Names of Study Personnel

Sponsor:	[redacted]
Medical Monitor and Medical Monitor Back-up:	
Clinical Research Organizations:	