DRUG:	Troriluzole (BHV4157)
STUDY NUMBER(S):	BHV4157-207
PROTOCOL(S) TITLE:	A Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of Troriluzole in Generalized Anxiety Disorder
IND NUMBER:	141430
SPONSOR:	Biohaven Pharmaceuticals, Inc
ORIGINAL PROTOCOL DATE:	12 Nov 2018
VERSION NUMBER:	V03 Includes Amendment 01, Amendment 02 and Administrative Letters 01, 02 and 03
VERSION DATE:	01Aug 2019

SUMMARY OF CHANGES

Version Number	**Brief description summary of changes**	**Date**
Version 01 – Original Draft	NA	20 Nov 2018
Version 02 - Amendment 01 and Incorporates Admin Letter 1 and 2	P12 List of Abreviations: - - added Data Monitoring Committee (DMC) - - added Placebo-Control Reminder Script (PCRS) Section 2 Study Objectives - Removed 4 secondary objectives - Moved 3 secondary objectives to exploratory Section 3 Study Endpoints - Removed 4 secondary endpoints - Moved 3 secondary endpoints to exploratory Section 4.3 Table of Assessments - added PCRS - added drug dispensing at Week 8 or Rand Phase - corrected footnote regarding UDS to reflect test performed at Screening and EOS Section 5.3 Exclusion Criteria - changed S-STS reporting period from 12 months to 6 months Section 7.4.4 Laboratory Assessments - f) Urine Drug Screen – removed benzodiazepenes and tricyclic antidepressants. Updated frequency of test to Screening and EOS. Section 7.4.4.2 - changed PGX sample collection to Baseline and End of Study (Wk 8) Section 7.5.7 - Updated the DSST description to clarify that subjects must decode the symbols “within 2 minutes”, Section 11 - Miscellaneous statistical updates have been made Section 12.1 - Added Data Safety Monitoring Committee Section 17.2 - Removed the appendix for the declaration of Helsinki. Minor administrative corrections have also been made throughout the protocol	6-Feb 2019

Version 03 - Amendment 01 and 02 Incorporates Admin Letter 1, 2 and 3	Section 4.3 Table of Assessments - Lengthened the Extension Phase to 48 Weeks Study Schematic: Updated to reflect 48 week Extension Phase Section 5.3: 4l: Exclusion has been modified to clarify that, in addition to herbal medications, use of herbal supplements is excluded within 30 days of randomization and during the course of the study. Section 7.4.4: Laboratory Assessments: Updated to include serum tests for: •B12; •eGFR; •amylase; and •lipase As well as urinalysis parameters of: •appearance •bilirubin •color Section 9.1.2: Revised to allow for IP temperature excursions between 15^0C and 30^0 C (59^0F -86^0F) Section 11: Miscellaneous statistical updates have been made Section 11.4.2: Added clarification based on FDA reveiwer's comment. *Since the primary intent of this trial is to evaluate the effect of the drug when taken as intended in the protocol, a hypothetical strategy will be employed for the intercurrent event of treatment/study discontinuation (due to any reason). Specifically, the assumption will be that had the subjects not discontinued, their efficacy would have been similar to the efficacy of subjects from the same treatment group who did not discontinue. For other intercurrent events that do not cause treatment/study discontinuation such as modest treatment non-compliance, protocol allowed dose adjustments, or initiation or adjustment of concomitant medications related to other symptoms all observed values will be used.* Minor administrative corrections have also been made throughout the protocol	24-Jul-19

BHV4157-207

A Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of Troriluzole in Generalized Anxiety Disorder

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 Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of Troriluzole in Generalized Anxiety Disorder

Rationale: First-line treatment for Generalized Anxiety Disorder (GAD) includes cognitive behavior therapy, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Nonetheless, up to 50% of patients have an inadequate response to conventional pharmacotherapy[1]. While SSRIs, SNRIs, buspirone and some benzodiazepines have been approved for GAD, the majority of patients do not have an adequate response to pharmacologic treatment.

The proposed study is based on recent preclinical, clinical, and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of GAD [2-8]. In addition. the results from a published clinical study examining the use of riluzole, a glutamate modulating agent, suggested efficacy in patients with GAD [2-4].

Troriluzole is a novel glutamate modulating drug that is being developed for the potential treatment of GAD.

Troriluzole is a tripeptide prodrug of the glutamate modulating agent riluzole that has been optimized for improved bioavailability, pharmacokinetics and dosing. Riluzole is currently only indicated for ALS and has a number of non-desirable attributes that have limited its clinical use. Key limitations of riluzole include:

- *Poor oral bioavailability* —When riluzole is administered in a tablet form, approximately 40% is either not absorbed or is metabolized in the liver before reaching systemic circulation.

- *Negative food effect* —Riluzole must be taken on an empty stomach, at least one hour before or two hours after a meal. Failure to adhere to these guidelines results in lower drug levels and potentially decreased therapeutic effects.

- *Negative effect on liver* —Riluzole has been shown to have dose-dependent liver effects that include elevations on liver function tests. Taking riluzole necessitates regular laboratory monitoring of liver function.

• *Pharmacokinetic variability* —Due to extensive first-pass metabolism and CYP1A2 metabolism.

Troriluzole was developed to address limitations of riluzole that have restricted its broader clinical application. Based on the preclinical features of troriluzole and data from a completed Phase 1 study of troriluzole, we anticipate the clinical pharmacology to offer favorable properties as compared to available riluzole:

1. Troriluzole is expected to have *better oral bioavailability*;
2. Troriluzole is expected to have *no food restrictions imposed*;
3. Troriluzole is designed to release riluzole after bypassing first-pass metabolism and thus confer *lower overall drug burden to the liver*, which may translate into a better safety and tolerability profile;
4. Troriluzole is expected to have *reduced pharmacokinetic variability* and be *dosed only once daily*.

As an optimized prodrug of riluzole, the regulatory pathway for troriluzole will rely on toxicology data with troriluzole in rodents and non-human primates, clinical experience with troriluzole in other clinical disorders such as spinocerebellar ataxia, and the well-characterized safety experience of riluzole, which has been marketed globally for over 20 years and is considered safe and well tolerated.

Target Population:	Male and female outpatient subjects between the ages of 18 - 65 years, inclusive, with a primary DSM-5 diagnosis of Generalized Anxiety Disorder (confirmed by the MINI) who have a Hamilton Anxiety Rating Scale (HAM-A) score of 18 or greater at screening and baseline. Additionally, GAD symptoms in subjects had to be present for ≥ 1 year and at least of moderate severity on the Clinical Global Impression - Severity of Illness Scale at study entry.
Number of Subjects:	Approximately 372 randomized subjects

Objectives:

Primary Objectives

- The primary objective of the study is to evaluate the efficacy of troriluzole compared to placebo after 8-weeks of treatment in subjects with GAD, as measured by the Hamilton Anxiety Rating Scale (HAM-A) scale

Secondary Objectives

- To assess the safety and tolerability of troriluzole, relative to placebo, in subjects with GAD
- Evaluate the efficacy of troriluzole compared to placebo on functional disability as measured by the Sheehan Disability Scale (SDS)
- Evaluate the efficacy of troriluzole compared to placebo on global functioning as measured by the Clinical Global Impression - Severity Scale (CGI-S)

Exploratory Objectives

- Evaluate the effects of troriluzole compared to placebo on cognitive performance as measured by the Digit Symbol Substitution Task (DSST) and the Hopkins Verbal Learning Test-Revised (HVLT-R)
- Evaluate the efficacy of troriluzole compared to placebo on improvement in global functioning as measured by the Clinical Global Impression - Improvement Scale (CGI-I)
- Evaluate the efficacy of troriluzole compared to placebo on depressive symptomatology as measured by the Hamilton Depression Rating Scale-17 (HAM-D-17)
- Evaluate the efficacy of troriluzole compared to placebo on anxiety symptoms as measured by the Penn State Worry Questionnaire (PSWQ)
- To characterize the pharmacokinetics of troriluzole based on sparse sampling
- Evaluate correlates of placebo responsiveness by using the Clinical Trial and Site Scale-B (CTSS-B) as well as other pre-intervention outcome measures and demographic information

Study Design:

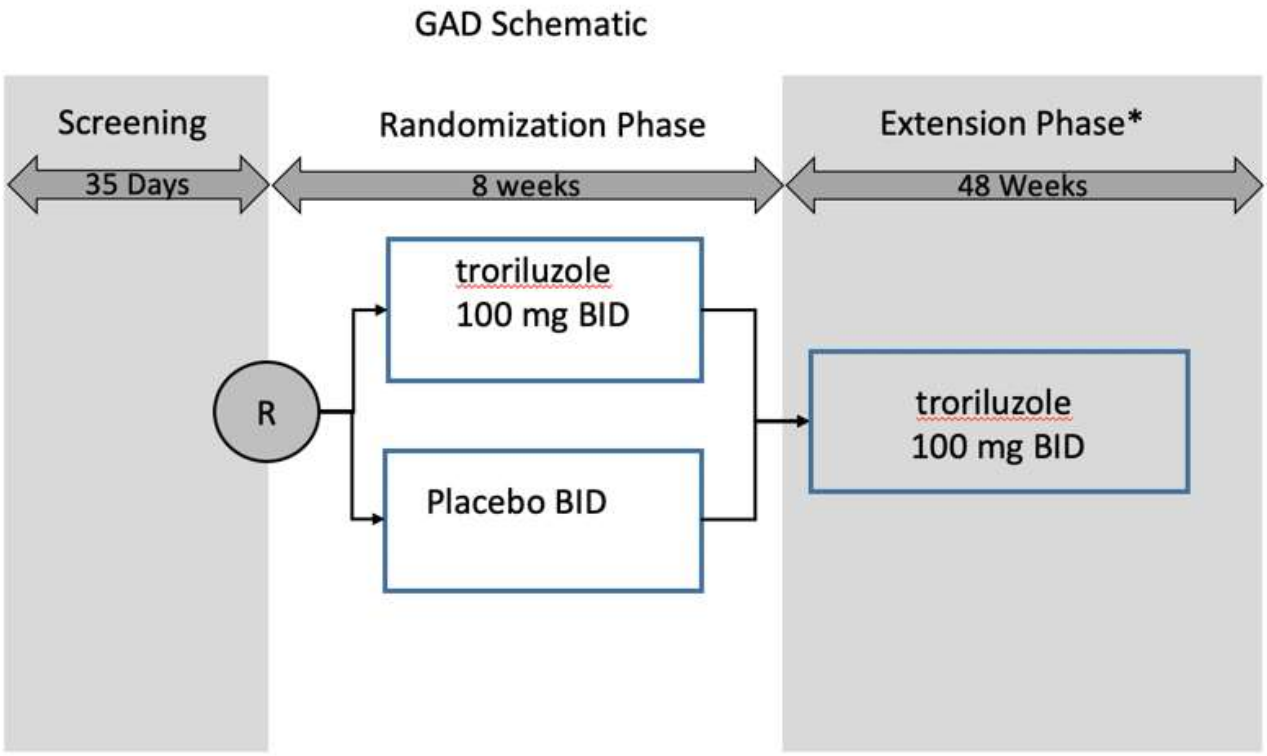
BHV4157-207 is a Phase III, multicenter, randomized, double-blind, placebo-controlled, 2- arm study designed to assess safety, tolerability, and efficacy of troriluzole in subjects with Generalized Anxiety Disorder who have a Hamilton Anxiety Rating Scale (HAM-A) score of 18 or greater at screening and baseline. Additionally, GAD symptoms in subjects had to be present for ≥ 1 year and at least of moderate severity on the Clinical Global Impression Scale-Severity of Illness scale at study entry.

Subjects who qualify will be randomized to receive placebo (BID) or troriluzole (100 mg BID).

Dosing will continue for 8 weeks. Eligible subjects will have the opportunity to continue in a 48 week open label extension phase. Those subjects not continuing in the 48 week extension will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit.

For subjects entering the Extension Phase, their first in-person Extension Visit will be four weeks after the Week 8 Randomization Phase visit. Subjects will undergo visits every fourth week through Week 12 of this phase. Then subjects will undergo visits every 12 weeks up to Week 48 of this phase. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug in the Extension Phase.

STUDY SCHEMATIC*



*Eligible subjects are those subjects who complete the Randomization Phase and for whom the investigator believes open-label treatment offers an acceptable risk-benefit profile.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BE	Bioequivalence
Bid	Twice a Day
BP	Blood Pressure
BID	Twice Daily
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression – Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
Cmax	Maximum Plasma Concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant Medication
CRF	Case Report Form
CTSS-B	Clinical Trial and Site Scale-B
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
DSST	Digit Symbol Substitution Scale
ECG	Electrocardiogram
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
HAM-A	Hamilton Anxiety Rating Scale
HAMD-17	Hamilton Depression Scale 17-Item Version
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

HR	Heart Rate
HRT	Hormone Replacement Therapy
HVLT-R	Hopkins Verbal Learning Test-Revised
IB	Investigator's Brochure
ICF/IC	Informed Consent Form
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
MINI	Mini International Neuropsychiatric Interview
MRI	Magnetic Resonance Imaging
mmHg	Millimeters Mercury
NAA	N-acetylaspartate
NDA	New Drug Application
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
OCD	Obsessive Compulsive Disorder
PCP	Phencyclidine
PK	Pharmacokinetic
po	By Mouth, Orally
PCRS	Placebo-Control Reminder Script
PSWQ	Penn State Worry Questionnaire
qd	Once Daily
RPR	Rapid Plasma Reagin
SAE	Serious Adverse Event

SARA	Scale for Assessment and Rating of Ataxia
SDS	Sheehan Disability Scale
SNRI	Selective Norepinephrine Reuptake Inhibitor
SCA	Spinocerebellar Ataxia
SSRI	Selective Serotonin Reuptake Inhibitor
S-STS	Sheehan Suicidality Tracking Scale
ULN	Upper Limit of Normal
USPI	US Package Insert
WOCBP	Women of Childbearing Potential
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Biohaven Pharmaceuticals, Inc. [Biohaven] is developing a new drug, troriluzole (BHV4157), for the treatment of neurologic and psychiatric disorders. Troriluzole is a novel and optimized prodrug of the glutamatergic agent riluzole. The FDA originally approved riluzole (RILUTEK®) 50 mg twice-a-day (NDA #20-599) for the treatment of patients with Amyotrophic Lateral Sclerosis (ALS). Riluzole, which is only indicated for ALS, has been marketed globally for over 20 years and is considered safe and well tolerated but has a number of non-desirable attributes that have limited its clinical use. Troriluzole is a tripeptide prodrug of the glutamate modulating agent riluzole that has been optimized for improved bioavailability, pharmacokinetics and dosing. The proposed study in GAD is based on recent preclinical, clinical and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of GAD[2-8]. Biohaven hypothesizes that the glutamate modulation effects of troriluzole may address underlying pathologic brain function that is associated with GAD, and thus provide symptomatic benefit in patients suffering from GAD.

1.1.1 Generalized Anxiety Disorder (GAD)

GAD represents a disorder of significant unmet need, affecting approximately 4.3% of the population at some point in their life[9] Approximately one-third of cases are considered severe. GAD is a chronic condition characterized by excessive anxiety and worry that is out of proportion to actual context and causes significant distress or functional impairment. Rates of full remission have been observed to be low [10], with recovery rates from the index episode of less than 60% after a 12-year follow-up. Of those who experienced a recovery, approximately half experienced a recurrence within the same observation period [10], over 25% recurring within 3 years of remission [11] In clinical studies of approved treatments (SSRIs and SNRIs) the rates of remission are typically less than 50%[1]. Patients who experience a partial recovery are more vulnerable to relapse [12]. Further, patients with GAD have increased risk of cardiovascular disease. The social impact includes increased risk of not marrying, absenteeism (average of one week per month), increased risk of suicide, and high healthcare costs. Minimal research has been conducted on the treatment of GAD that has not responded to conventional therapy. Frequently treatment-resistant patients are adjunctively administered benzodiazepines despite the potential for abuse and consequently symptom exacerbation. Based on the unmet medical need described above, additional treatments are required for populations with GAD that has not responded adequately to pharmacotherapy.

1.1.2 Rationale for Troriluzole in the Treatment of GAD

The proposed study is based on recent preclinical, clinical, and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of GAD [2-8] Preclinical data with riluzole (the active metabolite of troriluzole) demonstrated rapid acting antianxiety effects in multiple preclinical models. Efficacy was similar to a benzodiazepine comparator but superior on cognitive tests [7, 8, 13].

Open label data also suggest benefit from the glutamate modulator riluzole in individuals with GAD. In a open-label study by Mathew, 12 of 15 patients treated who completed the trial responded positively to riluzole on the HAM-A over the 8 week course of the trial[2]. As part of this study, subjects received proton magnetic resonance spectroscopy and magnetic resonance imaging scans to measure the effect of riluzole on N-acetylaspartate (NAA), which is a mitochondrial amino acid considered to be a marker of neuronal integrity. In general, responders showed increases in hippocampal NAA compared to nonresponders and a relationship was seen between changes in hippocampal NAA and anxiety symptoms at study end compared to baseline [3]. In addition, MRI showed a positive correlation between hippocampal volume, NAA concentration and HAM-A improvement [4].

The tremendous unmet medical need in anxiety disorders combined with favorable clinical experience with riluzole to date, warrant the identification and clinical development of an optimized formulation of riluzole. The therapeutic potential of riluzole has been suggested by multiple clinical reports and trials on its active metabolite suggesting favorable effects in patients with a variety of psychiatric conditions.

1.1.2.1 Pre-Clinical Studies

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

- No activity at a broad screen of enzymes and receptors, including hERG
- Toxicology studies in rats and monkeys reveal no novel findings relative to what has been reported for riluzole;
- Safety pharmacology studies indicate no clinically relevant changes in hERG, cardiovascular parameters or respiratory parameters. Minimal changes on neurobehavioral parameters at high dose levels are consistent with the known sedative effects of riluzole in rats;
- No signals for carcinogenicity (negative for Ames assay, in vitro chromosomal aberrations and in vivo micronucleus)

1.1.2.2 Clinical Experience

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

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

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

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

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

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

1.1.2.2.1 BHV4157 Phase I

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

1.1.2.2.2 Troriluzole Phase I - Study BHV4157-101

CCI [redacted]

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[redacted]

1.1.2.2.2.1 Study BHV4157-102

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[redacted]

1.1.2.2.2.2 Study BHV4157-103

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1.1.2.2.3 BHV4157 Phase 2 – BHV4157-201

BHV4157-201 was a Phase 2b/3, multicenter, randomized, double-blind, placebo-controlled parallel-group study designed to assess the safety, tolerability, and efficacy of troriluzole in subjects with spinocerebellar ataxia (SCA). Subjects were randomized to receive troriluzole (140 mg PO once daily [QD]) or placebo for 8 weeks. A total of 141 subjects were randomized into the double-blind randomization phase (71 subjects in the troriluzole 140 mg QD group and 70 subjects in the placebo group).

During the double-blind randomization phase, administration of troriluzole at 140 mg QD for 8 weeks was well tolerated in adult subjects with SCA. There were no deaths reported during the randomization phase of this study. Treatment-emergent SAEs were reported for 5 (3.55%) subjects, including 4 troriluzole-treated subjects (asthenia, atrial fibrillation, blood creatine phosphokinase increased, dehydration, back pain and cerebral infarction), and 1 placebo-treated subject (chest discomfort). No clinically meaningful trends in laboratory values were identified in this study. No subject had AST or ALT laboratory abnormalities > 3 X ULN.

Subjects who completed the double-blind randomization phase were offered 96 weeks of open-label treatment with troriluzole (140 mg PO QD) in an extension phase. In the first 48-week portion of the Extension Phase, subjects who experienced a decline (as defined by demonstration of a 2 point or greater decline from baseline on the SARA scale on each of the two most recent consecutive visits accompanied by PI impression of clinical worsening) may be increased to 280 mg daily. One hundred and thirty (131) subjects continued into the open-label extension phase, which is currently on-going. To date, the preliminary safety profile of troriluzole 140 mg QD is consistent with the troriluzole safety profile observed during the randomization phase.

1.1.3 Potential for Drug-Drug Interactions

Troriluzole: Troriluzole, itself, is not expected to interfere with drug metabolism and its cleavage via plasma peptidases renders it unlikely to be affected significantly by liver cytochrome P450 inhibitors. Troriluzole has the following known pharmacokinetic/metabolism parameters:

- Not an inhibitor of CYP3A4, CYP1A2, or CYP2D6
- In CYP induction studies:
    - The estimated EC50 and Emax for CYP1A2 mRNA was 1.44 μM and 3.47-fold induction, respectively;
    - The estimated EC50 and Emax for CYP2B6 mRNA was 12.6 μM and 27.0-fold induction, respectively; and
    - Troriluzole did not increase CYP3A4 mRNA at doses up to 30 μM

Riluzole Metabolism: Troriluzole metabolizes to riluzole. As per the USPI, riluzole metabolism has been assessed in special populations, characterized by hepatic impairment (2 to 3 fold increase in AUC with Child-Pugh Scores of A and B), renal impairment (no effect), age (no effect), gender (no effect), smokers (20% faster elimination) and race (Japanese compared to Caucasians: no effect).

Effect of other drugs on Riluzole metabolism: In vitro studies using human liver microsomal preparations suggest that CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when riluzole is given concurrently with agents that affect CYP1A2 activity. Potential inhibitors of CYP1A2 (e.g., cimetidine, ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, oral contraceptives, thiabendazole, vemurafenib, zileuton) could decrease the rate of riluzole elimination, while inducers of CYP1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

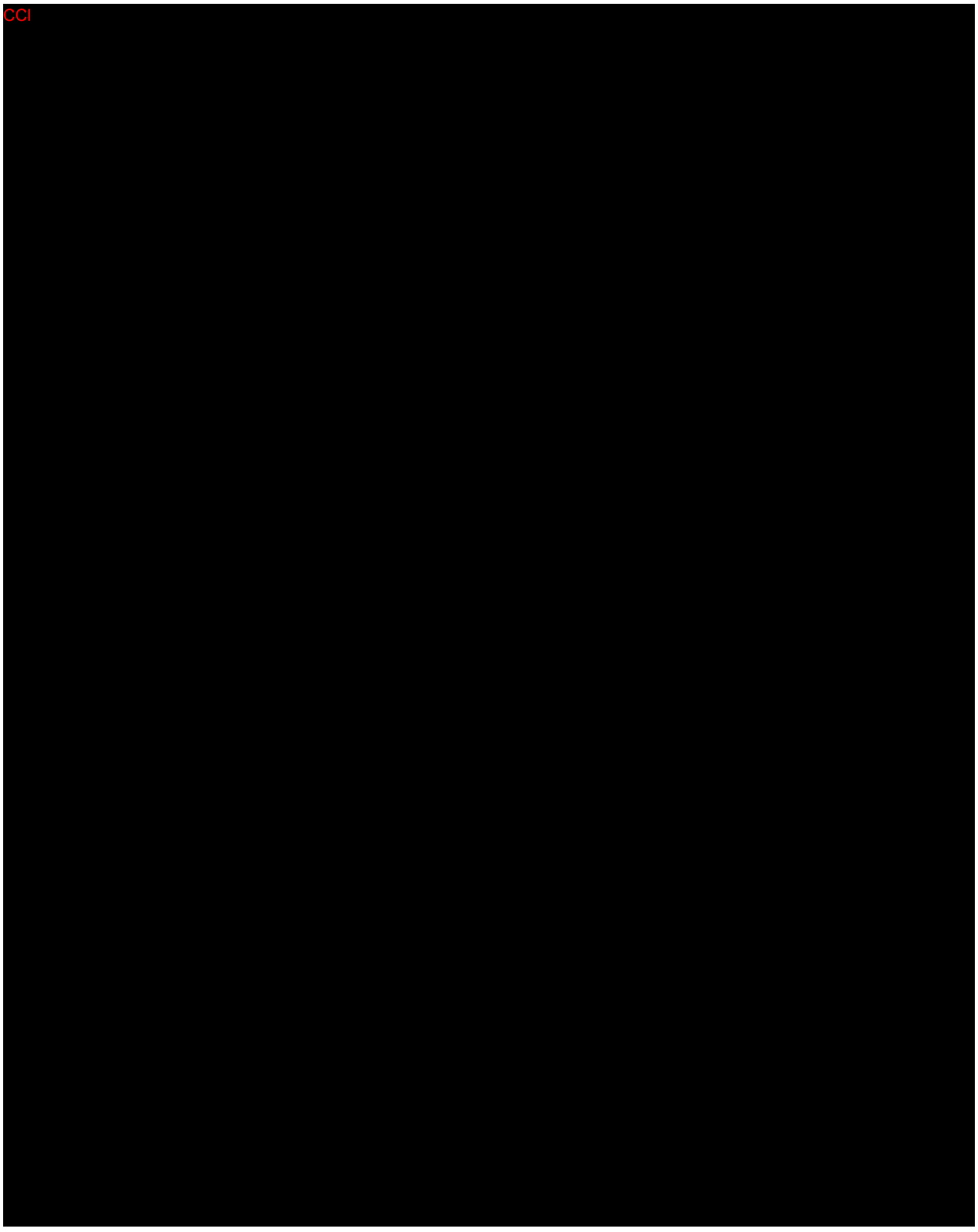
Effect of Riluzole on the Metabolism of Other Drugs: CYP1A2 is the principal isoenzyme involved in the initial oxidative metabolism of riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP1A2 (e.g., theophylline, caffeine, and tacrine). Currently, it is not known whether riluzole has any potential for enzyme induction in humans.

Clinical drug interaction studies for troriluzole have not been conducted yet.

1.1.4 Clinical Adverse Event Profile

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

1.1.4.1 Troriluzole Phase I Studies



1.1.4.2 BHV4157-201: Phase 2 Clinical Adverse Event Profile

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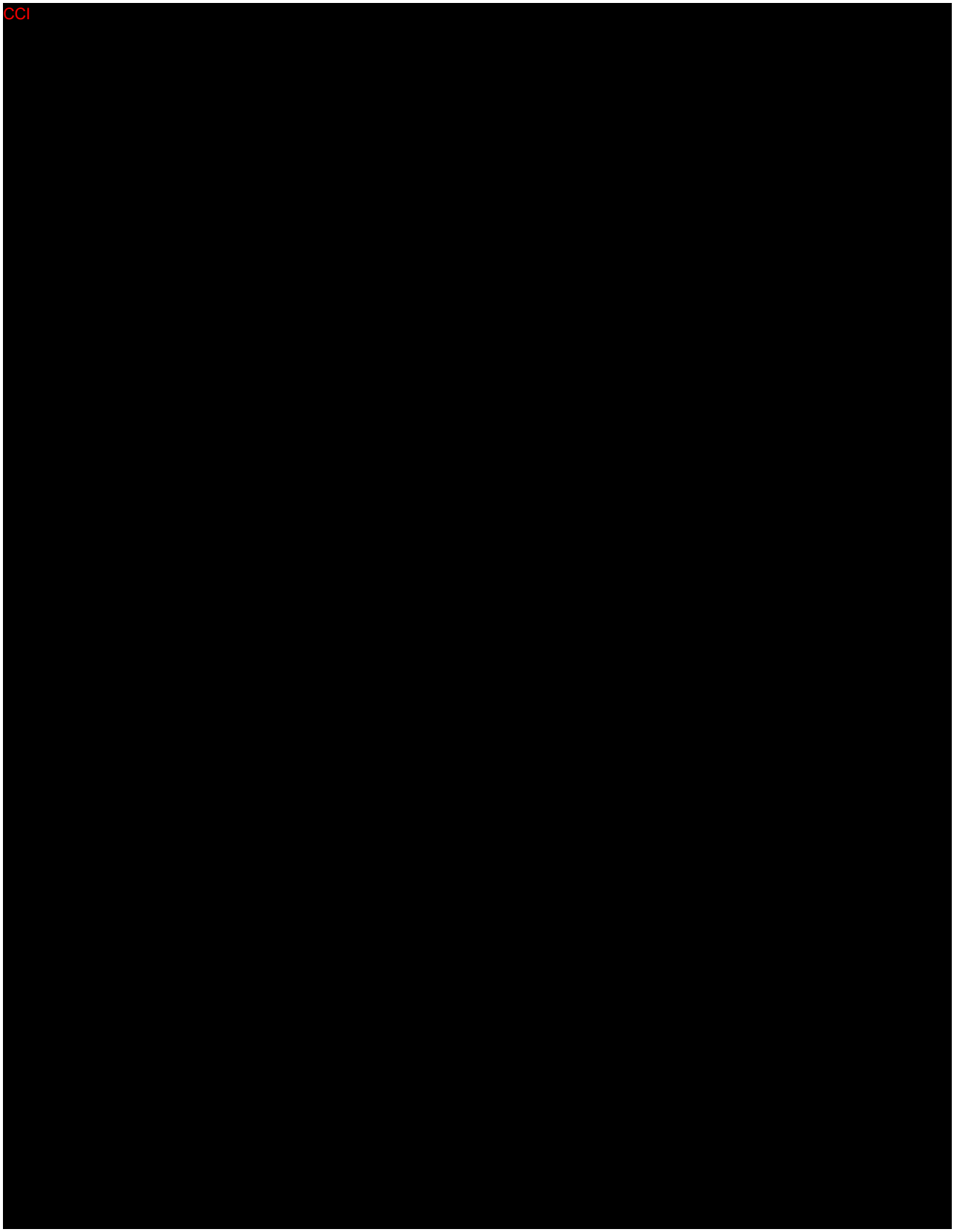

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1.1.4.3 Riluzole

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. The following summarizes relevant information.

Overall, riluzole tablets have been well tolerated in populations with ALS and diverse neuropsychiatric conditions that include Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD) and spinocerebellar ataxia. 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. The AEs occurring greater than 5% and at least 2% more than placebo included asthenia (18% vs 12% placebo) and nausea (14% vs 9%). These two AEs showed trends for a dose response (16). The published literature on the use of riluzole tablets in psychiatric disorders, while generally comprised of case-series, is consistent with this tolerability profile.

The most commonly observed AEs associated with the use of riluzole tablets more frequently than placebo treated patients were:

- asthenia;
- nausea;
- dizziness;
- decreased lung function;
- diarrhea;
- abdominal pain;
- pneumonia;
- vomiting;
- vertigo;
- circumoral paresthesia;
- anorexia; and

- somnolence.

Approximately 14% (n = 141) of the 982 individuals with ALS who received riluzole in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK for asthenia, nausea, abdominal pain, and ALT elevation were dose related. The AEs of asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related. Assessment of pulmonary AEs is confounded by the underlying illness, ALS, which is associated with respiratory symptoms.

1.1.4.3.1 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. No clinically significant LFT changes were observed on study drug in BHV4157-101. In the ongoing clinical trial in SCA, LFTs remain blinded; however, no subjects were required to discontinue study medication due to elevated LFTs.

Riluzole is associated with elevations in aminotransferases that have been reflected in monitoring precautions that will be followed within this protocol. Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 X ULN) four months after starting riluzole; these returned to normal 7 weeks after treatment discontinuation. Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 times ULN. In trials, if ALT levels were < 5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN. There were rare instances of jaundice. There is limited experience with rechallenge of patients who have had riluzole discontinued for ALT > 5 X ULN, but there is the possibility of increased ALT values reoccurring. Therefore, rechallenge is not recommended. In post-marketing experience, cases of clinical hepatitis associated with riluzole have been reported, including one with fatal outcome.

1.1.4.3.2 Neutropenia

Troriluzole has not been associated with hematologic findings in nonclinical toxicology studies to date. In Study BHV4157-101, one subject in the 17.5 mg BID cohort experienced transient and mildly decreased white blood cell count after three days of treatment; however, this subject evidenced moderate decline during the screening period prior to medication administration. The subject's count increased while on continued study drug and normalized within 6 days after onset.

For riluzole, according to the USPI, rare cases of neutropenia were reported. Among approximately 4,000 patients given riluzole for ALS in clinical trials, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.

1.1.4.3.3 Interstitial Lung Disease

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

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

1.1.5 Potential Risk to Fetal Development

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

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

1.2 Study Rationale

1.2.1 Study Design Rationale

Troriluzole is a glutamate modulating drug that is being developed for the potential treatment of spinocerebellar ataxia (SCA), Obsessive Compulsive Disorder (OCD) and Alzeimer's disease. This protocol represents the first trial of troriluzole in Generalized Anxiety Disorder (GAD).

Troriluzole is a novel tripeptide prodrug of the glutamate modulating agent riluzole. The proposed study is based on recent preclinical, clinical and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of GAD[2-8]. While troriluzole has yet to be studied in GAD, studies with riluzole in populations with GAD provide support for the therapeutic potential of troriluzole[2-4]. Trials have also suggested the benefit of riluzole in individuals with OCD [17, 18].

Riluzole has several modes of action; prominent among them, are a reduction in glutamate outflow due to effects on the excitatory amino acid transporters [19]. Given the evidence for the potential role of glutamate in GAD, and that troriluzole is a prodrug of riluzole, it is hypothesized that it would be expected to have therapeutic value in GAD as a glutamate modulating agent.

Troriluzole was developed to advance upon the limitations of riluzole that have restricted its broader clinical application. Riluzole tablets have 60% bioavailability, attributed to high first-pass metabolism in the liver. This is thought to be related to metabolism by the heterogeneously expressed CYP1A2 enzyme, which is also attributable to the high PK variability associated with riluzole. In addition, riluzole is associated with reduced exposure when taken with meals (i.e., a negative food effect), resulting in the guidance to take riluzole within a three hour fast (one hour before or two hours after a meal). Riluzole is also dosed twice a day, has dose-dependent effects on liver function tests and the drug substance itself has other intrinsic limitations including: very low solubility in water, poor oral palatability, pH dependent chemical stability and intense oral numbness if administered directly to the oral mucosa.

In an effort to mitigate the aforementioned limitations of riluzole, several classes of prodrugs were designed, synthesized, and evaluated in multiple in vitro stability assays to predict in vivo drug levels [20]. Troriluzole is a third generation of prodrug development representing multiple years of chemistry effort with optimized in vivo and in vitro features based on stability while transiting the digestive system, enhanced gastrointestinal absorption, avoidance of first pass metabolism, favorable safety pharmacology, metabolic cleavage in the plasma, and enhanced pharmacokinetic properties.

Based on the preclinical features of troriluzole, we anticipate the clinical pharmacology to offer favorable properties as compared to available riluzole:

- Troriluzole is expected to have better oral bioavailability;
- Troriluzole is designed to release riluzole after bypassing first-pass metabolism and thus confer lower overall drug burden to the liver, which may translate into a better safety and tolerability profile as well as reduced pharmacokinetic variability;
- Troriluzole is expected to allow for once daily dosing, thus improving medication compliance;

- Troriluzole is expected to be readily absorbed in both the fasting and fed states; thus, the prodrug is not anticipated to require any special meal restrictions. In contrast, oral riluzole tablets require a 3-hour window of fasting around the two daily doses;

1.2.2 Dose Selection

CCI

[redacted]

1.3 Research Hypothesis

Troriluzole monotherapy is associated with superior therapeutic effects as compared to placebo over an 8 week treatment period in patients with Generalized Anxiety Disorder.

2 STUDY OBJECTIVES

2.1 Primary

- The primary objective of the study is to evaluate the efficacy of troriluzole compared to placebo after 8-weeks of treatment in subjects with GAD, as measured by the Hamilton Anxiety Rating Scale (HAM-A) scale (SIGH-A version).

2.2 Secondary

- To assess the safety and tolerability of troriluzole, relative to placebo, in subjects with GAD
- Evaluate the efficacy of troriluzole compared to placebo on functional disability as measured by the Sheehan Disability Scale (SDS)
- Evaluate the efficacy of troriluzole compared to placebo on global functioning as measured by the Clinical Global Impression - Severity Scale (CGI-S)

2.3 Exploratory

- Evaluate the effects of troriluzole compared to placebo on cognitive performance as measured by the Digit Symbol Substitution Task (DSST) and the Hopkins Verbal Learning Test-Revised (HVLT-R)
- Evaluate the efficacy of troriluzole compared to placebo on improvement in global functioning as measured by the Clinical Global Impression - Improvement Scale (CGI-I)
- Evaluate the efficacy of troriluzole compared to placebo on depressive symptomatology as measured by the Hamilton Depression Rating Scale-17 (HAM-D-17) scale (SIGH-D version)
- Evaluate the efficacy of troriluzole compared to placebo on anxiety symptoms as measured by the Penn State Worry Questionnaire (PSWQ)
- To characterize the pharmacokinetics of troriluzole based on sparse sampling
- Evaluate correlates of placebo responsiveness by using the Clinical Trial and Site Scale-B (CTSS-B) as well as other pre-intervention outcome measures and demographic information

3 STUDY ENDPOINTS

3.1 Primary

- Improvement in generalized anxiety disorder is assessed using the change in the Hamilton Anxiety Rating Scale (HAM-A) total score from baseline to the end of the double-blind phase of the study (Week 8).

3.2 Secondary

- Safety and tolerability are assessed using the frequency of unique subjects with: serious adverse events; adverse events leading to discontinuation; adverse events judged to be related to study medication; and clinically significant laboratory abnormalities that are observed during the double-blind phase.

- Improvement in functional disability is assessed using the change in the Sheehan Disability Scale (SDS) total score from baseline to the end of the double-blind phase.

- Improvement in global clinical condition is assessed using the Clinical Global Impression of Severity Scale (CGI-S) at the end of the double-blind phase of the study.

3.3 Exploratory

- Improvement in cognitive performance is assessed by using the Digit Symbol Substitution Test (DSST) and the Hopkins Verbal Learning Test-Revised (HVLT-R) from baseline to the end of the double blind phase

- Improvement in global clinical condition is assessed using the Clinical Global Impression of Improvement Scale (CGI-I) at the end of the double-blind phase of the study.

- Improvement in depressive symptomatology is measured by the change in the Hamilton Depression Rating Scale-17 (HAM-D-17) from baseline to the end of the double-blind phase

- Improvement in anxiety is assessed using the change in the Penn State Worry Questionnaire (PSWQ) from baseline to the end of the double blind phase

- The pharmacokinetic profile of troriluzole is characterized by blood concentrations observed in treated subjects

- The Clinical Trial and Site Scale-B (CTSS-B) (total score, subitems, other pre-intervention outcome measures and demographics) will be used to characterize correlates of placebo responsiveness (as defined by changes on the HAM-A and SDS)

4 STUDY PLAN

4.1 Study Design and Duration

BHV4157-207 is a Phase III, multicenter, randomized, double-blind, 2-arm placebo- controlled parallel-group study designed to assess safety, tolerability, and efficacy of troriluzole in a population of patients with Generalized Anxiety Disorder who have a Hamilton Anxiety Rating Scale (HAM-A) score of 18 or greater at screening and baseline. Additionally, GAD symptoms in subjects had to be present for ≥ 1 year and at least of moderate severity on the Clinical Global Impression - Severity of Illness Scale at study entry.

Qualifying subjects will receive either troriluzole 100 mg BID or Placebo BID during the randomization phase of the trial. 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 48 weeks of open-label treatment as long as the investigator 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.

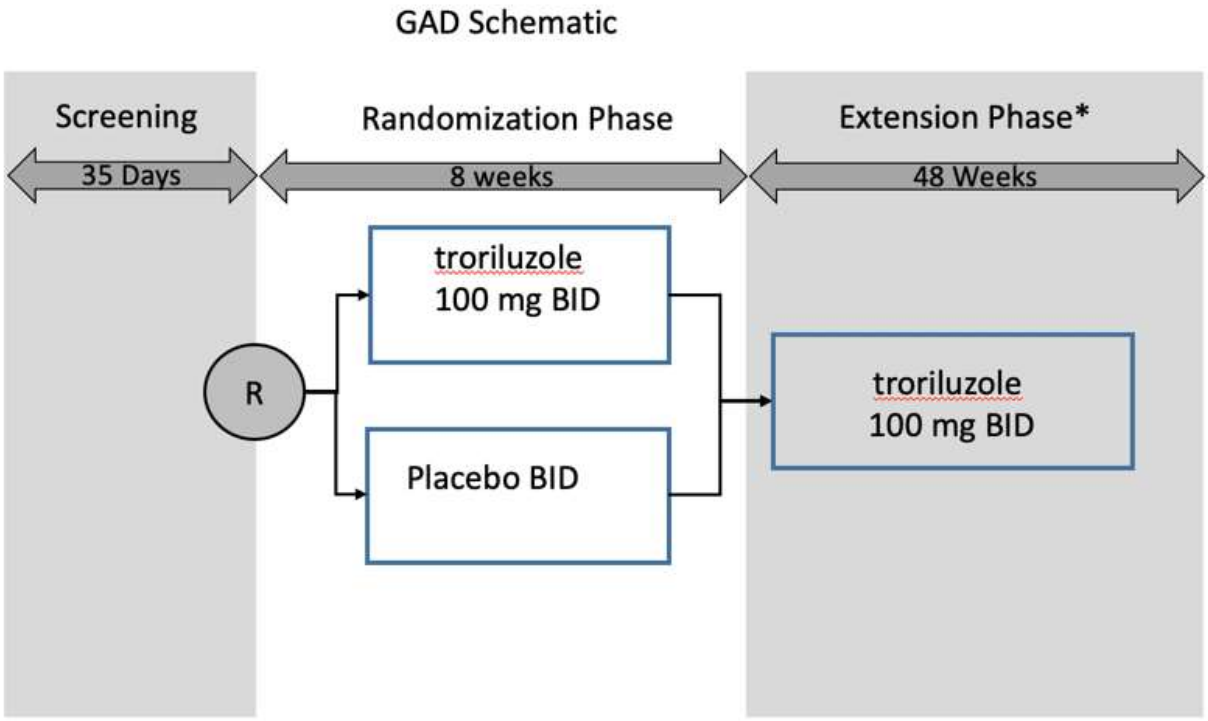
Subjects entering the Extension Phase will have their first Extension Visit four weeks after the Week 8 Randomization Phase visit. Thereafter, subjects will undergo visits every four weeks up through week 12 of the Extension Phase as outlined in Table 2 (Schedule of Assessments/Time & Events- Extension Phase). Subjects will then undergo visits every 12 weeks up to Week 48 of the Extension phase. All subjects will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Extension Phase will continue with the same dose taken at the end of the Randomization Phase.

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

4.2 Study Schematic

Figure 1: Study Schematic



*Eligible subjects are those subjects who complete the Randomization Phase and for whom the investigator believes open-label treatment offers an acceptable risk-benefit profile.

4.3 Schedule of Assessments

Table 2: Schedule of Assessments and Events - Randomization Phase

	Screening Phase [a] (2-35 Days)		**Treatment Phase (8 Weeks) End of Week (+/- 2 days)**				**Follow-up End of Week[b] (+/- 2 days)**
	Screen Visit [a]	**Baseline Visit [a] (Randomization)**	**2**	**4**	**6**	**8 or Early Term**	**10**
Procedure							
Eligibility Assessments							
Informed Consent (IC)	X						
Pharmacogenetic IC	X						
Demographic Data	X						
Inclusion/Exclusion Criteria	X	X					
Medical History [c]	X	X[c]					
Prior & Concomitant Medication [c]	X	X[c]	X	X	X	X	X
SAFER Interview [d]	X						
Psychiatric Evaluation							
Psychiatric History [c]	X	X[c]					
Mini International Neuropsychiatric Interview (MINI)	X						
Safety Assessments							
Physical Examination	X					X	
Vital Signs	X	X	X	X	X	X	X
Physical Measurements (weight and height)	X					X	X
Adverse Event Assessment[c]	X	X	X	X	X	X	X
12 Lead ECG	X	X				X	
Laboratory Assessments including urinalysis [e]	X	X		X		X	
Serology [f]	X						
Serum Pregnancy Test [g]	X	X	X	X	X	X	
Urine Pregnancy Test [g]		X	X	X	X	X	
Urine Drug Screen [h]	X					X	
Blood Alcohol Test [i]	X						

	Screening Phase [a] (2-35 Days)		**Treatment Phase (8 Weeks) End of Week (+/- 2 days)**				**Follow-up End of Week[b] (+/- 2 days)**
	Screen Visit [a]	**Baseline Visit [a] (Randomization)**	**2**	**4**	**6**	**8 or Early Term**	**10**
Sheehan Suicidality Tracking Scale (S-STS)[j]	X	X	X	X	X	X	X
Pharmacokinetic Sampling [k]			X		X	X	
Pharmacogenomic Sampling		X				X	
Clinical Outcome Assessments							
Hamilton Anxiety Rating Scale (HAM-A)	X	X	X	X	X	X	
Placebo-Control Reminder Script (PCRS)[l]	X	X	X	X	X	X	
Sheehan Disability Scale (SDS) [m]		X		X		X	
Hamilton Depression Rating Scale (HAM-D-17)[n]	X[n]	X				X	
Clinical Global Impressions -Improvement Scale (CGI-I)			X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X	X	X	X	X	
Penn State Worry Questionnaire (PSWQ)		X				X	
Cognitive Test Battery [o]		X				X	
Clinical Trial and Site Scale-B (CTSS-B)		X					
Clinical Drug Supplies/Study Supplies							
Randomization		X					
Dispense Study Medication [p]		X		X		X	
Drug Accountability			X	X	X	X	
Return Unused Study Medication				X		X	

[a] Screening/Baseline Phase will be 2 - 35 days. The Baseline Visit may be scheduled but should only occur ***after*** all screening procedures are complete, patient meets inclusion/exclusion criteria, and lab test and ECG results have been received and reviewed by the site. Screening procedures may be performed any time during the Screening Phase. **All Screening safety data must be reviewed by a physician prior to randomization into the Treatment Phase.**

[b] Only for subjects NOT entering the extension phase, or who discontinue early from the Treatment Phase. Subjects entering the extension phase will not require the 2-week post dose visit.

[c] Confirm medical and psychiatric history and update if necessary. Prior & Concomitant medications should be captured for the 30 days prior to screening.

[d] The SAFER Interview will be conducted remotely with the subject by a CRO shortly after the screening visit. A SAFER pass is necessary for randomization.
[e] Laboratory Tests are not required to be fasting.
[f] HBsAg, HCV and HIV antibody, RPR
[g] Serum pregnancy test (b-hcg) conducted at screening and at subsequent visits. Urine pregnancy test conducted prior to dosing at baseline and at subsequent visits. The site may test a patient at any time if pregnancy is suspected.
[h] Urine drug test to be conducted at screening and EOS visit and at unscheduled visit at the discretion of the investigator. Reflex confirmatory drug testing will be conducted for all positive urine drug screen samples. The urine drug screen must be negative for drugs of abuse including cocaine, amphetamines, barbiturates, phencyclidine, cannabis or opioids.
[i] The blood alcohol level must be < 50 mg/dl.
[j] Timeframe for S-STS is 6 months prior to Screening and since last visit for subsequent visits.
[k] Plasma samples for PK will be collected at random at Weeks 2, 6 and 8. Date and time of doses on the day of each visit and the day prior will be collected in case report forms along with time of last meal. PK samples should also be drawn when there are any SAEs or severe AEs during both the Randomization and Extension Phase of the study that are assessed as possibly drug related. Subjects who are able to schedule a morning visit at Weeks 2 and 6 can be instructed to hold their dose of study drug that morning until after a PK trough sample is obtained, if possible and appropriate.
[l] The PCRS is administered prior to the HAM-A at every visit for every subject. There are unique scripts for each phase (Randomization and Extension) please use the appropriate script for each phase and document the time of administration of both the PCRS and HAM-A.
[m] If a subject checks the "not working" box for the Work/School item on the SDS, you MUST check compliance to this instruction, before the visit ends.
[n] HAM-D Item 1 ONLY to be performed at screening. The full HAM-D is required at all other specified visits.
[o] The Cognitive Test Battery performance is assessed by using the Digit Symbol Substitution Task (DSST) and the Hopkins Verbal Learning Test-Revised (HVLT-R).
[p] Study Drug will be dispensed at the baseline visit and subsequent visits per visit schedule. Subjects should take the first dose the day after the baseline visit. Study drug will be dispensed at Week 8 if subject is deemed eligible and agreed to participate in the Extension Phase.

Table 3: Schedule of Assessments and Events - Extension Phase

	Extension Phase (48 Weeks) End of Week (+/- 5 days)						**Follow-up End of Week (+/- 2 days)**
	4	**8**	**12**	**24**	**36**	**48 or Early Term**	**50**
Procedure							
Safety Assessments							
Physical Examination						X	
Vital Signs	X	X	X	X	X	X	X
Physical Measurements (weight and height)			X	X	X	X	
Adverse Event Assessment	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
12 Lead ECG	X		X	X	X	X	
Laboratory Assessments including urinalysis	X	X	X	X	X	X	
Serum Pregnancy Test [a]	X	X	X	X	X	X	
Urine Pregnancy Test[a]	X	X	X	X	X	X	
Urine Drug Screen [b]	X	X	X	X	X	X	
Sheehan Suicidality Tracking Scale (S-STS) [c]	X	X	X	X	X	X	X
Clinical Outcome Assessments							
Hamilton Anxiety Rating Scale (HAM-A)	X	X	X	X	X	X	
Placebo-Control Reminder Script (PCRS) [d]	X	X	X	X	X	X	
Sheehan Disability Scale (SDS)[e]	X	X	X	X	X	X	
Hamilton Depression Rating Scale (HAM-D-17)			X	X	X	X	
Clinical Global Impressions-Improvement Scale (CGI-I)	X	X	X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X	X	X	X	X	
Penn State Worry Questionnaire (PSWQ)	X	X	X	X	X	X	
Clinical Drug Supplies/Study Supplies							
Dispense Study Medication	X	X	X	X	X		
Drug Accountability	X	X	X	X	X	X	
Return Unused Study Medication	X	X	X	X	X	X	

[a] Serum and urine pregnancy tests to be conducted at each visit. The site may test a patient at any time if pregnancy is suspected. Subjects will be provided with urine pregnancy tests to take in between the Visit week 12, 24, 36 and Visit week 48 office visit. Subjects should be instructed to contact the study doctor if they become pregnant at any time during the study. Site should also contact the subject in between the 3-month office visits to remind them of the pregnancy testing requirement, as applicable.
[b]Reflex confirmatory drug testing will be conducted for all positive urine drug screen samples.
[c]Timeframe for S-STS is 6 months prior to Screening and since last visit for subsequent visits.
[d]The PCRS is administered with the HAM-A at every visit for every subject. There are unique scripts for each phase (Randomization and Extension) please use the appropriate script for each phase and document the time of administration of both the PCRS and HAM-A.
[e]If a subject checks the "not working" box for the Work/School item on the SDS, you MUST check compliance to this instruction, before the visit ends.

4.3.1 Screening Phase

The Screening Phase will range from a minimum of 2 days to a maximum of 35. The purpose of the Screening Visit is to ensure that the appropriate subjects are entered into the trial and remain stable during the pre-treatment phase. The investigator will determine that the subject meets eligibility criteria and will collect demographic and medical data presenting a full characterization of the subject. All attempts should be made to obtain medical and pharmacy records to confirm the subject's medical and medication treatment history. It is estimated approximately 372 subjects will enter the randomization phase of the trial.

The SAFER interview will be conducted remotely with the subject by a CRO shortly after the screening visit. A SAFER pass is necessary for the subject to be randomized.

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 troriluzole (100 mg BID) or placebo (BID) (in a 1:1 ratio).

Dosing will continue for 8 weeks. Subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit (unless they are continuing in the Extension Phase).

If subjects have difficulty tolerating BID dosing due to morning dosing of 100 mg (such as experiencing sedation) then the investigator may permit the subject to switch to dosing of 200 mg at night time only (and document this change in the subject's records).

Down titration to 100 mg will only be allowed to address tolerability issues and only with medical monitor approval. If a subject down titrates they will need to stay on that dose for the duration of the Randomization Phase.

- Subjects should take their medication twice a day, doses should be taken in the mornings and evenings approximately 12 hours apart. If tolerability issues arise please refer to Section 9.2.5.

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 372 subjects will enter this phase of the trial.

4.3.3 Extension Phase (if applicable)

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 will have visits in the Extension Phase every four weeks through Week 12 and then every 12 weeks thereafter up to Week 48. All subjects will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase.

If subjects have difficulty tolerating BID dosing due to morning dosing of 100 mg (such as experiencing sedation) then the investigator may permit the subject to switch to dosing of 200 mg at night time only (and document this change in the subject's records).

Down titration to 100 mg will only be allowed to address tolerability issues. Subjects may be rechallenged to increase to 100mg BID during the Extension Phase at the discreation of the investigator.

All visits of the Extension Phase will be open-label.

Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Extension Phase. There is a visit window of +/- 5 days during the Extension Phase of the study.

4.4 Post Study Access to Therapy (if applicable)

No other study drug access is available after the Extension Phase.

5 POPULATION

5.1 Number of Subjects

Approximately 372 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 - 65, inclusive.

3. Target Population

a. Primary diagnosis of generalized anxiety disorder (GAD) either moderate or severe as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as confirmed by the MINI at Screening, in addition to a psychiatric evaluation by a board-certified or Biohaven-approved board-eligible psychiatrist; The duration of illness must be ≥ 1 year;

b. HAM-A Total Score of ≥ 18 at both Screening and Baseline;
c. HAM-A anxiety and tension item scores ≥ 2 at both Screening and Baseline;
d. CGI-S score of ≥ 4 at both Screening and Baseline;
e. Baseline Visit HAM-A Total Score not more than 30% below the Screening Visit HAM-A Total Score;
f. 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;
g. Minimum of 6 years of education or equivalent to complete necessary scales and understand consent forms;
h. Subjects must have adequate hearing, vision, and language skills to perform neuropsychiatric testing and interviews as specified in the protocol;
i. Subjects must be able to understand and agree to comply with the prescribed dosage regimens and procedures; report for regularly scheduled office visits; and reliably communicate with study personnel about adverse events and concomitant medications;
j. It is required that all women of child-bearing potential (WOCBP) who are sexually active agree to use two methods of contraception for the duration of the study (i.e. beginning 30 days prior to baseline and extending to 30 days **after** the last dose of study drug). The two methods should include:
    1. one barrier method (e.g. diaphragm with spermicide, condom with spermicidal gel, intrauterine devices, cervical cap);
    2. and one other method. The other method could include hormonal contraceptives (e.g. oral contraceptives, injectable contraceptives or contraceptive implant) or another barrier method (Section 5.5);
k. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing at Baseline;
l. It is required that men who are sexually active with WOCBP agree to use two methods of contraception for the duration of the study (beginning at first treatment and extending to 90 days after the last dose of study drug).

5.3 Exclusion Criteria

1. **Target Disease Exceptions**
    a. Subjects with a primary DSM-5 psychiatric disorder diagnosis other than GAD within the past 6-months. ***Note: Subjects with a secondary diagnosis of comorbid social anxiety disorder or specific phobia are allowed, if in the investigator's judgement, the diagnosis is not sufficiently prominent and active so as to confound the assessment of GAD symptoms***
    b. Subjects should be excluded at screening or baseline if any medical or psychiatric condition other than GAD, as specified in the inclusion criteria, could predominantly explain or contribute significantly to the subjects' symptoms or that could confound assessment of GAD symptoms;

c. Patients who report a history of inadequate response (per investigator judgement) to three (3) or more adequate trials (including current trial) of any SSRI or SNRI, at an adequate dose and adequate duration (at least 8 weeks) for the treatment of GAD within the 3 years prior to randomization;
d. Current diagnosis of:
    i. Delirium, dementia, amnesic or other cognitive disorder
    ii. Bipolar I or II disorder,
    iii. Schizophrenia or other psychotic disorders, schizoaffective disorder, autism or autistic spectrum disorders, Tourette's disorder, body dysmorphic disorder, hoarding disorder;
    iv. Persistent depressive disorder
    v. Obsessive Compulsive Disorder, Panic Disorder, Post-Traumatic Stress Disorder, Social Anxiety Disorder or Specific Phobia (if primary diagnosis);
e. Major Depressive Disorder or Unspecified Depressive Disorder within the last 6 months prior to Screening;
f. HAM-D-17 item 1 of >1 at Screening or Baseline;
g. HAM-D-17 of > 19 at Baseline;
h. Subjects with clinically significant DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder based on investigator's clinical judgement if no formal diagnosis;
i. Subjects experiencing hallucinations, delusions, or any psychotic symptoms in the past 3 months prior to Screening;
j. Any eating disorder within the last 12 months prior to Screening;
k. Acute suicidality in the last 6 months, or suicide attempt or self-injurious behavior in the last 6 months prior to Screening;
l. Score of >0 on the Sheehan Suicidality Tracking Scale for the period of 6 months prior to screening, and at baseline;
m. Patients who may have received a non-biological investigational agent in any clinical trial within 30 days or a biological agent within 90 days prior to screening;
n. History of psychosurgery, deep brain stimulation (DBS) or electroconvulsive therapy (ECT);
o. Subjects or prisoners who are involuntarily detained or incarcerated for treatment of either a psychiatric or physical illness must not be enrolled into the study.

2. Medical History Exclusions

a. History of substance use disorder (drug or alcohol) in the last 12 months (with the exception of tobacco) as defined by DSM-5 criteria;

b. Positive urine drug screening for cannabis (both medical and recreational use of cannabis are prohibited; (subjects will be expected to refrain from use during the period of the study), amphetamines (including MDMA/ecstasy), cocaine, barbiturate, PCP, and/or opiates at screening or baseline; Note: detectable levels of cannabis are exclusionary unless repeat measurements, before randomization, demonstrate that the previous test results are no longer present;
c. Patients with a blood alcohol level ≥ 50 mg/dl (0.05%). This blood level may be retested prior to randomization, if necessary.
d. Prior or current general medical condition that may confound ability to interpret safety and efficacy results as determined by the Investigator;
e. Clinical history of stroke, TIA, seizure disorder, traumatic brain injury (with sequelae).
f. Patients with a history of Type I or Type II insulin-dependent diabetes mellitus (IDDM);
g. Body mass index >40 kg/m2;
h. Active liver disease or a history of hepatic intolerance to medications that, in the investigator's judgment, is medically significant;
i. Vitamin B12 or folate deficiency Note: Subjects with a B12 deficiency can participate in the study if they are on stable Vitamin B12 replacement for at least 3 months prior to randomization and their B12 levels are within normal limits prior to randomization;
j. Hematologic or solid malignancy diagnosis within 5 years prior to screening. (Note: Subjects with a history of localized skin cancer, basal cell or squamous cell carcinoma, may be enrolled in the study as long as they are cancer free prior to randomization). Subjects with other localized cancers (without metastatic spread) who have previously completed their course of treatment more than 5 years prior to screening, are not currently receiving treatment and have been in remission may be enrolled only if, in the opinion of the investigator, there is no expectation for recurrence or further cancer treatment during the study period. Antihormonal therapy (e.g., tamoxifen) is allowed if the subject's cancer is in remission and the subject is on stable maintenance therapy to reduce their risk of recurrence;
k. Any unstable cardiovascular (includes uncontrolled hypertension), pulmonary, gastrointestinal, or hepatic disease 30 days prior to screening;
l. End-stage cardiovascular disease (e.g., Congestive Heart Failure New York Heart Association/CHF NYHA Class III or IV or unstable angina);
m. History of, or current positive rapid plasma reagin [RPR] test and a positive confirmatory test;

n. History of chronic pulmonary disease or chronic pulmonary symptoms;
o. Immunocompromised subjects. Note: Subjects taking a systemic immunosuppressive agent may be randomized only if they are on a stable dose, have no clinically relevant immunosuppression, and have a white blood count (WBC) within normal limits;
p. History of medically significant gastrointestinal (GI) illnesses including:
    i. A current diagnosis of active, peptic ulceration or gastrointestinal bleeding within the last 6 months and/or chronic inflammatory bowel disease at screening;
    ii. A history of any gastrointestinal surgery that impacts the absorption of study drug such as gastric bypass or reductive surgery;
    iii. Chronic or frequent episodes of loose stools;
q. History or evidence of any medical, neurological or psychological condition that would expose the subject to an undue risk of a significant adverse event or interfere with assessments of safety and efficacy during the course of the trial as determined by the clinical judgment of the investigator;
r. Women who are pregnant or breastfeeding;

3. Physical and Laboratory Test Findings

a. Uncontrolled hypertension at screening (e.g., repeated diastolic measurements ≥ 96 mmHg);
b. Diagnosis of hypothyroidism by a screening thyroid stimulating hormone (TSH) value > the upper limit of normal (ULN) and free thyroxine (T4) < the lower limit of normal (Note: Subjects with history of hypothyroidism may participate in the study, provided they are euthyroid on stable thyroid replacement therapy for at least 3 months prior to screening, and therapy is expected to remain stable during the course of the study;
c. Hepatic test abnormalities at screening (may be repeated one time for confirmation in screening prior to baseline):
    i. Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or GGT > 1.5 times the upper limit of normal; or
    ii. Total bilirubin > 2 times the upper limit of normal (ULN; unless subject has documented history of Gilbert's Syndrome in which case subject may be enrolled with permission of the Sponsor).
d. P-Amylase or Lipase values greater than 1.5 times the upper limit of normal at screening (ULN) (may be repeated one time for confirmation in screening prior to baseline);
e. HbA1c > 7.0% at screening;
f. Pathologic renal findings at screening as defined by the presence of either of the following criteria:

i. Estimated glomerular filtration rate (eGFR) according to the re- expressed abbreviated (four-variable) Modification of Diet in Renal Disease (MDRD) Study equation < 30 ml/min/ 1.73m2; The MDRD estimation is calculated as follows: eGFR (mL/min/1.73m2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black). [Scr: Standardized serum creatinine];
ii. Creatinine ≥ 2mg/dL

g. Hematologic abnormalities at screening:
   i. Hemoglobin < 10 g/dL; or
   ii. WBC < 3.0 x 103/mm3; or
   iii. Platelet count < 100,000/mm3; or
   iv. Neutrophils, Absolute ≤ 1000/mm^3
h. Human Immunodeficiency Virus (HIV) positive at screening (indicated by positive confirmatory test);
i. HBsAg or HCV positive at screening;
j. QTcF (Fridericia) interval ≥ 470 msec during the screening/baseline period or uncontrolled arrhythmia or frequent premature ventricular contraction (PVCs) (> 5/minute) or Mobitz Type II second or third degree atrioventricular (AV) block or left bundle branch block, or right bundle branch block with a QRS duration ≥ 150 msec or intraventricular conduction defect with a QRS duration ≥ 150 msec or evidence of acute or sub-acute myocardial infarction or ischemia or other ECG findings that, in the investigator's opinion, would preclude participation in the study;
k.

4. Prohibited Treatments and/or Therapies

a. Previous treatment with riluzole;
b. Patients who would likely require prohibited concomitant therapy after randomization (Refer to Section 5.4)
c. Use of a mono-amine-oxidase (MAO) inhibitor is prohibited 30 days prior to randomization (baseline visit) and during the study;
d. Patients who have been treated within 7 days or 5 half lives (whichever is longer) prior to randomization with any other psychotropic medications such as but not limited to the following: antipsychotics, antiepileptics (including gabapentin [Neurontin], pregabalin [Lyrica], cambamazepine [Tegretol], lamotrigine [Lamictal], divalproex sodium [Depakote], valproic acid [Depakene], topiramate [Topamax]), lithium, diphenhydramine, N-acetylcysteine, ketamine, memantine;
e. Stimulants are prohibited within 14 days prior to randomization and during the study
f. Patients who have been treated with any antidepressant agents in the 7 days prior to Randomization.

g. Patients who have been treated with fluoxetine (Prozac) in the 30 days prior to Randomization;
h. Patients who have been treated with sleeping agents of any kind within seven days prior to Randomization; Note: zolpidem, zaleplon, or eszopiclone used as sleeping agents, are permitted during the study up to 3 days per week. Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled efficacy assessments. See Section 5.4
i. The use of a depot neuroleptic is prohibited 6 months prior to randomization (baseline visit) and during the study;
j. Use of varenicline (Chantix) is prohibited 30 days prior to randomization (baseline visit) and during the randomization phase of the study;
k. Anxiolytic use (including benzodiazepines prn and buspirone) is prohibited within 7 days of randomization and during the study. For subjects who have been on regular, daily benzodiazepine use, benzodiazepine use is prohibited 30 days prior to randomization and during the study. Note: Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing are allowed on a prn basis.
l. Herbal medication and herbal supplement use within 14 days of randomization and during the course of the study are prohibited.
m. Patients receiving psychotherapy (e.g., individual, group, marriage or family therapy) unless participation has been regular (e.g., weekly) for at least 3 months prior to the Screening Visit and no significant change in frequency is anticipated through the Week 8 visit;
n. Transcranial Magnetic Stimulation (TMS) is prohibited within three months prior to screening and during the study.
o. Patients taking medications that are CYP1A2 inhibitors or inducers (see Appendix II) should not be taking these medications for at least 5 half-lives prior to randomization and during the study.

5.4 Prohibited Concomitant Medication

Clinically appropriate dose tapering of prohibited medications may only be done during the Screening Phase.

During the course of the study, patients should stay on their usual medication regimes (i.e. those not excluded by the protocol) at stable doses.

The use of the following medications are prohibited or restricted as follows:

1) Use of a mono-amine-oxidase (MAO) inhibitor is prohibited 30 days prior to randomization (baseline visit) and for the duration of the study;

2) Patients who have been treated within 7 days or 5 half lives (whichever is longer) prior to randomization with any other psychotropic medications such as but not limited to the following: antipsychotics, antiepileptics (including gabapentin [Neurontin], pregabalin [Lyrica], cambamazepine [Tegretol], lamotrigine [Lamictal], divalprioic acid [Depakote], valproic acid [Depakene], topiramate [Topamax]), lithium, diphenhydramine, N-acetylcysteine, ketamine, memantine;
3) Stimulants are prohibited within 14 days prior to randomization and during the study.
4) Antidepressant agents are prohibited within the 7 days prior to randomization and during the study.
5) Fluoxetine (Prozac) is prohibited within the 30 days prior to randomization and during the study.
6) Sleeping agents of any kind within seven days prior to randomization; Note: zolpidem, zaleplon, or eszopiclone used as sleeping agents, are permitted during the study, no more than 3 days per week. Note: Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled efficacy assessments.
7) The use of a depot neuroleptic is prohibited 6 months prior to randomization (baseline visit);
8) Use of varenicline (Chantix) is prohibited 30 days prior to randomization (baseline visit) and during the randomization phase of the study;
9) Anxiolytic use (including benzodiazepines prn and buspirone) is prohibited within 7 days of randomization and during the study. For subjects who have been on regular, daily benzodiazepine use, benzodiazepine use is prohibited 30 days prior to randomization and during the study. Note: Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing prn are allowed on a prn basis.
10) Herbal over-the-counter preparations or supplements taken to manage symptoms of GAD, such as, but not limited to: hypericum perforatum (St. John's Wort), omega-3 fatty acids, S-adenosyl methionine (SAM-e) or kava extracts should not be taken for two weeks prior to randomization and during the study.

CYP1A2 Inhibitors and Inducers: Troriluzole should be used with caution with medications that are inhibitors or inducers of the CYP1A2 enzyme system due to the potential for drug interactions. Subjects should be monitored appropriately when taking a CYP1A2 inhibitor or inducer. The following medications are prohibited at least 5 half-lives prior to randomization and during the study (Appendix II):

- Strong to moderate CYP1A2 inhibitors which may increase the risk of riluzole associated adverse events.
- Strong to moderate CYP1A2 inducers which may result in decreased efficacy
- Hepatotoxic drugs (e.g. allopurinol, methyldopa, sulfasalazine) which may increase the risk for hepatotoxicity

Oral contraceptives which contain ethinyl estradiol (CYP1A2 inhibitor) are allowed.

Hypnotic Use: New use of hypnotics should be avoided. For the management of persistent sleeping difficulties or insomnia, subjects may receive the following medications at no higher than the indicated doses, no more than 3 days per week. Note: Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled efficacy assessments:

- Zolpidem tartrate (Ambien): up to 10 mg at bedtime (HS) as needed (prn);
- Zolpidem tartrate extended-release (Ambien CR): up to 12.5 mg at HS prn;
- Zaleplon (Sonata): up to 20 mg at HS prn
- Eszopiclone (Lunesta): up to 3 mg at HS prn.

Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing prn are allowed. Subjects should be encouraged to avoid taking a benzodiazepine the morning of a study visit. Benzodiazepines should not be initiated during the Randomization Phase of the study.

Other medications: Other medications not explicitly called out herein are allowed during the Randomization Phase, provided they (1) have been prescribed for a sufficient duration (at least 30 days) that the investigator can adequately assess tolerability and deems them to be well-tolerated; (2) do not limit subject's ability to perform key rating scales by the impression of the investigator; (3) the regimen and dose (± 25%) have been stable for at least 30 days prior to screening and are not anticipated to change during the Randomization Phase; (4) could not adversely affect assessment of safety or efficacy.

Any medication adjustments or the initiation of new medications are recommended to be addressed during the Extension Phase, preferably no sooner than ***after*** four weeks of treatment during this phase so as not to confound assessment of safety / tolerability.

Lorazepam up to 2 mg/day (or equivalent benzodiazepine) can be used prn during the Extension Phase when clinically required per investigator judgement. Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled efficacy assessments.

Medications for the short term treatment of intercurrent illness are allowed if needed, provided they are not otherwise excluded as noted above.

The generic name (where possible), start date, end date and dosing information for any medication (prescriptions or non-prescription) taken within 1 month prior to the screeing visit will be recorded in the concomitant medication electronic case report form.

5.4.1 Other Restrictions and Precautions

In order to ensure that appropriate concomitant therapy is administered, it is essential that subjects be instructed not to take any medication, either non-prescription or prescription therapy prescribed by another physician, without prior consultation with the investigator.

Patients should not undergo any elective medical procedure without prior consultation with the Investigator. An elective procedure (minor surgery, dental surgery, orthopedic surgery etc…) that might require hospitalization or anesthesia should be deferred until after the study whenever clinically appropriate.

5.5 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-menopausal is defined as:

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

The requisite drug interaction studies to determine the interaction of troriluzole with oral contraceptives have not been completed to date. It is therefore not possible to determine the efficacy of oral contraceptives as an effective method of contraception for WOCBP who are participating in this study. Oral estrogen and progestin hormonal contraceptives as a sole method of contraception are therefore prohibited. It is required that all WOCBP use two methods of contraception for the duration of the study (i.e. beginning at 30 days prior to baseline) through 30 days **after** the last dose of study drug. The two methods should include one barrier method (e.g. diaphragm with spermicidal gel, condom with spermicidal gel, intrauterine devices, cervical cap) and one other method. The other method could include oral contraceptives (e.g. oral contraceptives, injectable contraceptives or contraceptive implant) or another barrier method.

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

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

5.6 Deviation from Inclusion/Exclusion Criteria

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

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

The sponsor will provide investigational product which will include troriluzole (100 mg) capsules and matching placebo.

Sites will also be provided with a Regulatory binder, and IWRS Manual. Source document creation is the responsibility of the site. 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.

7 ELIGIBILITY ASSESSMENTS

7.1 MINI International Neuropsychiatric Interview (MINI)

The MINI is a structured interview for the diagnosis of psychiatric disorders that will be conducted at screening to confirm the diagnosis of GAD and assess for the presence of other major psychiatric conditions.

7.2 SAFER Interview

The SAFER Interview is a structured interview conducted remotely by a CRO (telephone call to subject) shortly after the screening visit is completed to confirm the diagnosis, treatment history and GAD severity. A SAFER pass is necessary for randomization. This will be conducted by trained personnel who are qualified psychiatrists and psychologists. Additional details about this interview will be provided in the Informed Consent Form.

7.3 Medical and Psychiatric 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, patient history of GAD and other psychiatric history.

7.4 Safety Assessments

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

7.4.1 Vital Signs and Physical Measurements (Height and Weight)

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

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

1. The site should attempt to use the same scale to weigh a given subject throughout the study;

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

7.4.2 Electrocardiogram (ECG)

A 12-Lead ECG will be recorded during the scheduled visits as specified in the Schedule of Assessments/Time & Events and as medically necessary.

7.4.3 Physical Exam

Subjects will undergo a complete physical exam in both the Randomization and Extension Phase of the study. The Physical Exam should include at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, lymph nodes, lungs, cardiovascular, abdomen, skin, and musculoskeletal evaluation by the Principal Investigator or a medically qualified delegate. If a subject is discontinued for any reason, an attempt should be made to conduct a final physical exam.

7.4.4 Laboratory Assessments

Laboratory testing will include the following:

a) Hematology: hemoglobin, hematocrit, platelets, CBC with differential and absolute neutrophil count
b) Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, BUN, uric acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1c, TSH, T4, B12, eGFR, P-Amylase, and Lipase;
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) Serum pregnancy test will be conducted at screening, baseline and all scheduled visits. Urine pregnancy tests will be performed prior to dosing at baseline and at scheduled visits, at study visits where lab assessments are not performed, or at the discretion of the Investigator. Subjects will be provided with urine pregnancy tests to take in between the Week 12, Week 24, Week 36 and Week 48 office visits during the Extension Phase;
e) HBsAg, HCV, HIV antibody detection, and RPR (reflex testing will be done for any positive RPR) will be performed at screening.
f) Urine Drug Screen for cannabis (medical and recreational), amphetamines (including MDMA/ecstasy), cocaine, barbiturate, PCP and opiates at screening and EOS visit. Reflex confirmatory testing will be conducted on all positive urine drug screen samples.
g) Blood alcohol level.

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 the source document. In addition, if warranted repeat labs can be drawn.

7.4.4.1 Pharmacokinetics

A pharmacokinetic sample will be collected at Week 2, Week 6, and Week 8 of the Randomization Phase. Subjects should take their dose at their routine time on the days of these visits. Date and time of doses on the day of each visit and the day prior will be collected in case report forms along with time of last meal for entry into the eDC system. Subjects who are able to schedule a morning visit for Week 2 and Week 6 can be instructed to hold their dose of study drug that morning until after a PK trough sample is obtained, if possible and appropriate.

Additionally, PK samples should be drawn if there are any SAEs in either the Randomization or Extension Phase of the study that are assessed as possibly drug-related or severe AEs that could be drug-related.

7.4.4.2 Pharmacogenetics

A pharmacogenetics blood sample will be obtained at baseline and end of study (Week 8 Randomization Phase) for possible future exploratory analysis investigating how genetic variation may determine troriluzole efficacy and safety. All subjects will sign a pharmacogenomics ICF indicating whether they are consenting to or not consenting to provide a pharmacogenetic blood sample. All subjects will be informed that consenting to provide a blood sample for pharmacogenetic analysis is optional and does not affect participation in the study.

DNA samples will be stored indefinitely from subjects who have provided written informed consent unless a written request for destruction of the sample is provided by the subject to the site which conducted the Biohaven-sponsored clinical trial. This written request provided by the subject requesting destruction of the subject's pharmacogenetic samples should be provided by the site to the sponsor.

7.4.4.3 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.

7.4.4.4 Evaluation of Laboratory Assessments

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

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

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

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

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

If any visit shows ALT or AST>5x ULN, the Investigator will assess this as 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
    - Epstein-Barr virus serology
- Assess AEs
- Consider gall bladder or ductal imaging studies if presentation suggests potential for gall stones.

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

7.4.5 Sheehan Suicidality Tracking Scale (Sheehan STS)

The Sheehan STS (S-STS) is a prospective, clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors[21, 22]. The S-STS will be completed on a paper form at the site. At the screening visit, the recall period for completing the S-STS is 6 months prior; at all other visits, the recall period for completing the S-STS is since the last visit. Subjects who have a S-STS score > 0 should be evaluated by the investigator. If the investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject's safety and obtain mental health evaluation must be implemented. The subject must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the Sponsor.

7.5 Clinical Outcome Assessments

Training will be provided for all clinical outcome assessments through either didactic, video certification, and/or online training.

The order of the tests should include the administration of the HAM-A prior to other clinical / safety outcome assessments, followed by the other clinical outcome assessments.

7.5.1 Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a clinician-administered scale used extensively in research and clinical practice to both rate severity of GAD and to monitor improvement during treatment. It is designed to rate the severity of anxiety as well as the type of symptoms in patients with GAD. The HAM-A will be utilized as the primary efficacy assessment of the patient's level of anxiety and must be administered utilizing a structured interview guide, the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A) [23].

The scale consists of 14 items. Each item is scored on a scale of 0 (not present) to 4 (severe) with a total score range of 0-56. Subscale scores can be calculated for psychic anxiety factor (sum of HAM-A items anxious mood, tension, fears, insomnia, concentration, depressed mood, and behavior at interview), and somatic anxiety factor (sum of HAM-A items somatic muscular, somatic sensory, cardiovascular, respiratory, gastrointestinal, genitourinary and autonomic symptoms).

Raters must be trained and pre-approved by sponsor or sponsor representative (i.e. CRO) to rate subjects on the HAM-A. Raters must complete training and receive their certification prior to administering the HAM-A to study subjects.

7.5.2 Placebo-Control Reminder Script (PCRS)

The Placebo-Control Reminder Script (PCRS) is a statement read by a clinician to a subject prior to every administration of the HAM-A throughout the study. It is intended to provide a standardized method for educating subjects on what it means to be in a placebo-controlled study, expectations regarding clinical benefit, and how to interact with study staff, to minimizing the placebo effect.

7.5.3 Sheehan Disability Scale (SDS)

The Sheehan Disability Scale (SDS) is a patient-rated measure of functional disability in domains of work, social and family life. The SDS has demonstrated sensitivity to treatment effects in numerous randomized controlled trials in populations with varied diagnoses (70). The assessment is a three item questionnaire measuring disease-related disruption of work, social life and family life. Respondents evaluate impairment on an 11 point scale from 0 -10 with anchor definitions. The 3 items can also be summed into a single dimensional measure of global functional impairment that rages from 0 (unimpaired) to 30 (highly impaired).

Subjects may indicate that item 1 of the SDS (Work/School) is not applicable to them by checking a box labeled "*I have not worked / studied at all during the past week for reasons unrelated to the disorder.*" For these subjects item 1 of the SDS is not scored. However, subjects that were unable to work or study due to reasons related to the disorder must complete item 1.

If a subject checks the "not working" box for the Work/School item, you MUST check compliance to this instruction, before the visit ends.

7.5.4 Clinical Global Impression (CGI)

Subjects will be rated on the seven-point Severity of Illness (CGI-S) and Global Improvement (CGI-I) scales of the CGI. The CGI-S is rated during the screening phase as a screening assessment to determine eligibility for entry into the study.

A Sponsor approved rater, preferably a psychiatrist, should administer the CGI. All efforts should be made to ensure that the same clinician administers the CGI-S and CGI-I for a given patient. Notation in the subject's study records should substantiate the CGI ratings.

7.5.5 Hamilton Depression Rating Scale 17 Item Version (HAM-D-17)

The HAM-D 17 score, derived from the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) will be used as a secondary assessment of the patient's level of depression.

Although the HAM-D consists of 21 items, the scoring is based on the first 17. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0-2.

7.5.6 Penn State Worry Questionnaire (PSWQ)

The Penn State Worry Questionnaire (PSWQ) is a self-administered, 16-item, Likert-type scale designed to measure worry. Possible range of scores is 16-80. Each item is scored 1-5. Items 1, 3, 8, 10 and 11 are reversed scored.

7.5.7 Cognitive Test Battery

The Cognitive Test Battery will consist of the Digit Symbol Substitution Task (DSST) and the Hopkins Verbal Learning Test-Revised (HVLT-R).

The DSST requires that subjects fill in a series of symbols correctly coded withing 2 minutes. The higher the score the better the performance.

The Hopkins Verbal Learning Test-Revised (HVLT-R) is one test with a set of six forms intended to measure verbal learning and memory in individuals ages 16 and older. The six forms of the HVLT-R are designed to allow frequent, rapid retesting. Each test includes a list of 12 nouns; the examiner reads the list to the examinee, who repeats as many words as remembered, in any order. This process is repeated three times; 20-25 minutes later, examinees are asked again to recall as many words as possible; for the final task, the examiner reads a list of 24 words (including the 12 words from the list) and asks the examinee after each whether the word was on the list [24].

7.5.8 Clinical Trial and Site Scale-B (CTSS-B)

The Clinical Trial and Site Scale-B (CTSS-B) is a scale to assess potential domains associated with placebo response. The scale is a patient reported assessment and consists of 26 items. Items 1-24 are rated on a scale from 1 ("Completely Disagree") to 9 ("Completely Agree").

Items 25 and 26 are rated on a scale of 1 ("Very much better") to 7 ("Very much worse"). The CTSS-B is a modified version of an assessment developed by Feltner et al. [25].

8 EARLY DISCONTNUATION OF STUDY

All subjects who discontinue study treatment early should complete the 2-Week Post Dose Visit. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e. is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

9 STUDY DRUG MANAGEMENT

9.1 Description of Study Drug

9.1.1 Investigational Product

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

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 100 mg and matching placebo.

9.1.2 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), in a secure, temperature controlled, limited access area. The medications will be stored in a locked, environmentally-controlled medication room with restricted access. Container(s) will bear a label containing at least the name of the study drug, lot and/or batch number and storage conditions.

9.2 Dose and Administration

9.2.1 Randomization Phase

During the randomization phase, all subjects will be randomized to receive troriluzole 100 mg BID or placebo BID.

It is recommended that all patients ingest study drug twice per day (BID) once in the morning and once in the evening (approximately 12 hours apart). Study drug can be taken without regard to meals.

If subjects have difficulty tolerating BID dosing due to morning dosing of 100 mg (such as experiencing sedation) then the investigator may permit the subject to switch to dosing of 200 mg at night time only (and document this change in the subject's records).

Down titration to 100 mg will only be allowed to address tolerability issues and only with medical monitor approval. If a subject down titrates they will need to stay on that dose for the duration of the Randomization Phase.

9.2.2 Extension Phase

Subjects completing the Randomization Phase will be offered approximately 48 weeks of troriluzole treatment as long as the PI believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will receive open-label troriluzole. Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase. Subjects will continue to ingest study drug twice per day (BID) once in the morning and once in the evening (approximately 12 hours apart). Study drug can be taken without regard to meals.

If subjects have difficulty tolerating BID dosing due to morning dosing of 100 mg (such as experiencing sedation) then the investigator may permit the subject to switch to dosing of 200 mg at night time only (and document this change in the subject's records).

Down titration to 100 mg will only be allowed to address tolerability issues. Subjects may be rechallenged to increase to 100mg BID during the Extension Phase at the discreation of the investigator.

All visits of the Extension Phase will be open-label.

9.2.3 Method of Assigning Patient Identification

The investigator or designee will need to access an Interactive Web-based Response System (IWRS) in order to register each subject in each study phase. Initially the investigator or designee will enter the subject into the study at the Screening Visit after informed consent is obtained and a subject number is assigned. After completion of all screening evaluations, all eligible subjects will be randomized via IWRS at the Baseline Visit, in a 1:1 ratio to receive either placebo (BID) or troriluzole (100 mg BID). Treatment assignments will be obtained by the investigator (or designee) via the IWRS system.

Investigational sites will access the IWRS at each scheduled IP dispensing visit throughout the Randomization Phase to dispense drug. 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 or to indicate that the subject will continue into the Extension Phase.

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 IP dispensing visit throughout the Extension Phase to dispense drug.

Study medication will be assigned via the IWRS system in the Randomization and 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.

9.2.4 Selection and Timing of Dose and Administration

During the randomization phase of the study, subjects will be randomized to receive placebo (BID) or troriluzole (100 mg BID). Open label BHV -4157 will be provided during the extension phase. Study Drug will be dispensed at the baseline visit. Subjects should take the first dose the day after the baseline visit. Study medication should be administered twice per day (BID) once in the morning and once in the evening (approximately 12 hours apart).

9.2.5 Dose Modifications

Randomization Phase: Subjects will receive 100 mg BID or Placebo BID for eight (8) weeks.

If subjects have difficulty tolerating 100 mg BID dosing (such as experiencing sedation) then the investigator may permit the subject to switch to dosing of 200 mg at night time or morning only (and document this change in the subject's records).

Down titration to 100 mg once daily (QD) will only be allowed to address tolerability issues and only with medical monitor approval. If a subject down titrates to 100 mg QD they will need to stay on that dose for the duration of the Randomization Phase.

Extension Phase: Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase. Subjects receiving placebo in the randomization phase will be switched in a blinded manner to 100 mg BID or 100 mg QD. Subjects who enter the Extension Phase on 100 mg QD due to tolerability issues can be rechallenged to increase to 100 mg BID based on investigator judgement.

For subjects who do not tolerate their study treatment the investigator may permit them to switch to night time dosing (200 mg QD at night) if there is reason to believe that may help tolerability. Any such changes must be documented by the investigator. If the subject is receiving 100 mg QD

and this switch in dosing time does not result in acceptable tolerability then dosing should be discontinued.

9.3 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 subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that patient may be broken by the treating physician.

Before breaking the blind of an individual subject's treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. Unblinding will be managed via the IWRS system.
A pharmacokineticist, IWRS vendor, and pharmacovigilance role may be unblinded before data are unblinded for the primary endpoint and all subjects complete the Randomized Phase of the study. Except as noted above, other members of the BHV research team will remain blinded. For purposes of the DMC, periodic analysis will be carried out by the unblinded safety biostatistics team independent and firewalled from the team directly involved with the design and primary analysis of the trial. A report will be prepared for the DMC as outlined in the DMC charter.

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

9.4 Treatment Compliance

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

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

9.5 Destruction and Return of Study Drug

All unused and/or partially used study drug can be sent back to the drug depot for destruction only after being inspected and reconciled by the responsible BHV Study monitor or the sponsor's designee.

If it is site policy to destroy study drug on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to the applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused study drugs can only be

destroyed after being inspected and reconciled by the responsible BHV Study monitor or the sponsor's designee.

10 ADVERSE EVENTS

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

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

10.1 Serious Adverse Events

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

10.1.1 Definition of Serious Adverse Event (SAE)

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

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

- Potential drug induced liver injury (see section 10.1.7).

10.1.2 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 an 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.

10.1.3 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.

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 or related.

10.1.4 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, potential drug induced liver injury and pregnancies 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 CCI immediately via telephone, upon observing or learning of the event. CCI will then immediately notify the Biohaven Medical Monitor of the event. The SAE form must then be submitted to CCI 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 the SAE information in the Electronic Data Capture (EDC) system (i.e.: event term, start stop dates, causality, severity).

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

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

- CCI

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

- CCI

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

SAE Telephone Contact: Dr. PPD PPD

If only limited information is initially available, 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.

10.1.5 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 troriluzole) 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.

10.1.6 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 CCI 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 CCI

10.1.7 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 10.1.4.

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.

10.2 Non-serious Adverse Events

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

10.2.1 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.

11 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

11.1 General Procedures

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

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

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

Unless otherwise specified, the randomization phase and the open-label extension phase will be analyzed separately. For subjects receiving troriluzole during both phases, summary statistics will be provided for data from both phases combined.

11.2 Sample Size

The sample size for this study will be approximately 372 randomized subjects.

From a review of generalized anxiety disorder by Hidalgo[26], data from 7 adult studies (treatment duration between 4 to 12 weeks) provided the standard deviation for change from baseline ranging from 6.0 to 8.7; the average standard deviation was 7.4.

With an expected Week 8 difference between treatment groups to be 2.5 points on the HAM-A total scale, 372 subjects provide 90% power based on a 2-sample t-test with a common standard deviation of 7.4. The previous is based on an assumption of no premature discontinuations, if premature discontinuations occur at a rate of up to 25%, the power to detect a 2.5 point difference may be as low as 80%.

11.3 Populations for Analysis

The following analysis sets are defined for this protocol:

- Enrolled subjects: Patients who signed an informed consent form and were assigned a Patient Identification number (PID)

- Randomized subjects: Enrolled subjects who received a treatment assignment from the Interactive Web Response System (IWRS).

- Treated subjects: Enrolled subjects who received at least 1 dose of blinded study therapy (troriluzole or placebo) or open-label troriluzole.

- Modified Intent to Treat (mITT) subjects: Randomized subjects that received at least one dose of blinded study therapy and provided at least one post-baseline efficacy assessment during the randomization phase

11.4 Statistical Methods

11.4.1 Demographic and Baseline Characteristics

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

Demographic information will be summarized descriptively by treatment group and overall (i.e., treatment groups combined).

11.4.2 Primary Endpoint(s)

As the primary objective of this study is based on the evaluation of severity of patients' symptomology, the estimand for the primary endpoint will be the effect due to the initially randomized treatments if taken as directed, a de jure efficacy estimand. The target population will be the mITT population. The primary endpoint will be the change from baseline in the HAM-A score, troriluzole relative to placebo, at Week 8 of the randomization phase. This treatment effect will be summarized as the difference in change from baseline in the HAM-A between the groups receiving troriluzole and placebo.

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

The change from baseline in the HAM-A score, will be analyzed using Mixed Model for Repeated Measures (MMRM). The model will include treatment, visit and the treatment-by-visit interaction as fixed effects, and the baseline value of the HAM-A and baseline Ham-A by visit interaction as covariates. The covariance structure will be initially specified as unstructured. If the model fails to converge, then a Huynh-Feldt structure may be used, followed by an AR(1)

structure. The troriluzole and placebo groups will be compared at the end of the double-blind phase using a single degree of freedom contrast, with Kenwood-Rogers degrees of freedom, and significance assessed at a two-sided alpha level of 0.05. Sensitivity analyses will include, but not limited to a multiple imputation method employing a jump to reference method. Details of these analyses are provided in the statistical analysis plan.

Additional analyses on the HAM-A Scale will included analysis of the change from baseline Psychic Anxiety and Somatic Anxiety subscales as well as analyses of the percentage of HAM-A responders and remitters. Response is defined a a 50% or greater reduction in the HAM-A Total Score from baseline to endpoint. Remission is defined as a HAM-A Total Score <= 7 at Weeks 6 and 8. Details of these analyses are provided in the statistical analysis plan.

11.4.3 Secondary and Exploratory Endpoint(s)

Continuous change-from-baseline efficacy endpoints will be analyzed using the same methodology as the primary endpoint. Further details on the secondary and exploratory analyses are provided in the SAP.

11.4.4 Adjustment for Multiplicity

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

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

11.4.5 Missing Data

Studies similar to the randomized phase of this study showed ~25% of the subjects fail to complete the blinded randomized portion of the study[27][28]. Hence, we expect a similar rate of discontinuation during the randomized phase of this study. As part of sensitivity analyses for the primary and secondary endpoints, the missing data will be multiply imputed for the primary endpoint using reference methods (e.g. jump to reference). Further details on the handling of missing data, including for the SDS, are provided in the statistical analysis plan.

11.4.6 Analysis of Safety

The investigators determine the intensity of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available. AEs will be presented by system organ class and preferred term, ordered by the overall frequency of events. If a subject

had an adverse event with different intensities over time, then only the greatest intensity is reported in a study phase.

The frequencies of the following safety events are summarized by treatment group and overall for treated subjects: SAEs; all AEs, non-serious AEs; AEs by intensity; AEs by relatedness and clinically relevant laboratory abnormalities.

Graphical and tabular displays of on-treatment liver function test results are provided

11.5 Schedule of Analyses

This study will be monitored by a Data Safety Monitoring Board which will review interim summaries of the data during the trial. Please see section 12.1 for details.

An initial analysis of the data will be conducted after the last subject completes their Week 8 visit. This will only include analyses of efficacy data from the double-blind phase of the study, however safety analyses will include data from double-blind as well as the extension phase.

A final analysis of the study will be completed after the last subject completes their last study visit. This will summarize all efficacy data collected in the open-label phase, and summarize all safety, laboratory and other data collected through the entire study.

Additional analyses may be conducted during the open-label phase of the study to support regulatory and administrative requirements.

12 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).

12.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized for this study. The DMC will review the safety of all patients enrolled in trials on an regular basis.

The DMC will review the protocol, and will identify the data parameters and format of the information to be regularly reported. The DMC will meet in person or by conference call approximately quarterly. The DMC will typically receive reports with data by treatment group (e.g. blinded group A, group B etc.) or, if requested by the DMC, completely unblinded.

Based on the review of safety data, the DMC will make recommendations regarding the conduct of the study to the clinical team. These may include continuing the study as designed, amending safety monitoring procedures, modifying the protocol or the informed consent form, or recommending the termination of the study.

For purposes of the DMC, data analysis will be carried out by the unblinded safety biostatistics team independent and firewalled from the team directly involved witht the study design and primary analyses, and a report will be prepared for the DMC.

For further details please refer to the DMC charter.

12.2 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.

12.3 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.

A separate ICF will be obtained for the collection of blood for pharmacogenetic samples for possible future exploratory analysis investigating how genetic variation may determine troriluzole efficacy and safety. All subjects will sign a pharmacogenomics ICF indicating whether they are consenting to or not consenting to provide a pharmacogenetic blood sample. All subjects will be informed that consenting to provide a blood sample for pharmacogenetic analysis is optional and does not affect participation in the study. The investigator or the investigator's designee is responsible for verifying the patient's consent prior to obtaining the pharmacogenetic blood sample.

The approval of the pharmacogenetic ICF may occur separately from the consent form for other study related procedures and assessments. In instances were IRB approval for pharmacogenetics samples is not obtained, samples for genetic analysis will not be collected.

DNA samples will be stored indefinitely from subjects who have provided written informed consent unless a written request for destruction of the sample is provided by the subject to the site which conducted the Biohaven-sponsored clinical trial. This written request provided by the subject to the site requesting destruction of the subject's pharmacogenetic samples should be provided by the site to the sponsor.

12.4 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.

12.5 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.

12.6 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.

12.7 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.

13 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.

14 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.

15 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.

16 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 researchers for the purpose of advancing the understanding of neurologic or psychiatric illness, rating scales, or trial methodology for the affected population. In any publication of this data, confidentiality of individual subjects will be protected.

17 APPENDICES

17.1 APPENDIX I - Names of Study Personnel

Sponsor:	Biohaven Pharmaceutical Holding Company Limited c/o Biohaven Pharmaceuticals, Inc. PPD New Haven, CT 06510
Medical Monitor and Medical Monitor Back-up:	PPD PPD PPD PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 PPD PPD PPD PPD PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 PPD PPD PPD PPD PPD PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 PPD PPD
Clinical Research Organizations:	CCI PPD PPD PPD

17.2 APPENDIX II - Potent and Moderate Inhibitors and Inducers of the CYP1A2 Enzyme System*

CYP1A2 Potent and Moderate Inhibitors

Amiodarone
Artemisinin
Atazanavir
Cimetidine
Ciprofloxacin
Efavirenz
Enoxacin
Fluoroquinolones
Furafylline
Interferon
Methoxsalen
Mexiletine
Mibefradil
Tacirne
Thiabendazole
Ticlopidine
Vemurafenib
Zileuton

CYP1A2 Potent and Moderate Inducers

Barbiturates
Beta-naphthoflavone
Carbamazepine
Insulin
Methylcholanthrene
Modafinil
Nafcillin
Omeprazole
Primidone
Rifampin

*This list is not exhaustive.

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of Troriluzole in Generalized Anxiety Disorder

Study No: BHV4157-207

Draft Original Protocol Date: 16 Nov 2018

Protocol Version No: V03

Protocol Version Date: 01 Aug 2019

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

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56 and 312 and according to applicable local requirements.
- The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	**Signature Approval**	**Date**
Author/Protocol Writer: PPD PPD Biohaven Pharmaceuticals (I confirm, QC completed for required elements)		
Clinical Operations: PPD PPD PPD Biohaven Pharmaceuticals		
Biostatistics: PPD PPD PPD Biohaven Pharmaceuticals		
Medical Lead: PPD PPD PPD Biohaven Pharmaceuticals		
Regulatory Affairs: PPD PPD PPD PPD Biohaven Pharmaceuticals		