PROTOCOL TITLE: A randomized, double-blind, placebo-controlled trial ofadjunctive Troriluzole in Obsessive Compulsive Disorder

NCT NUMBER: NCT03299166

DATE: 13-Oct-2022

DRUG:	Troriluzole (BHV4157)
STUDY NUMBER(S):	BHV4157-202
PROTOCOL(S) TITLE:	A randomized, double-blind, placebo-controlled trial of adjunctive Troriluzole in Obsessive Compulsive Disorder
IND NUMBER:	135590
SPONSOR:	Biohaven Pharmaceutical Holding Company Limited
DRAFT ORIGINAL PROTOCOL DATE:	09 Aug 2017
VERSION NUMBER:	V10 Includes Amendment 01, Amendment 02, Amendment 03, Amendment 04, Amendment 05, Amendment 06, Amendment 07, Amendment 08, Amendment 09, and Administrative Letter 1 dated: 25Aug17
VERSION DATE:	13 Oct 2022

SUMMARY OF CHANGES

Version Number	Brief description summary of changes	Date
Version 06 – Amendment 01, 02, 03, 04 and 05 – Incorporates Admin Letter 01	The protocol has been updated to clarify that current SOC therapy must be monotherapy. **Section 5.3:** 2p: Added exclusion criteria that women who are pregnant or breastfeeding are excluded from study participation. 4h: 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 5.4:** Added exclusion for use of cannabidiol (CBD) oil. **Section 9.1.2:** Revised to allow for IP temperature excursions between 15°C and 20°C (59°F -68°F) **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.*	3 June 2019

Version 07 – Amendment 01, 02, 03, 04, 05 and 06 – Incorporates Admin Letter 01	Added additional window for Week 12 visit in order to proactively account for any subjects that may potentially be out of visit window due to concerns related to COVID-19 pandemic. Allowing remote safety visits if needed due to COVID-19 concerns. **Section 4.3** Added additional guidance regarding remote visits in the event that in-office visits are not feasible due to COVID-19 concerns. Footnote B and N modified to address potential extended Week 12 visit window and the dispensing/shipment of additional study drug **Section 4.3.2** Added additional window for Week 12 visit in order to proactively account for any subjects that may potentially be out of visit window due to concerns related to COVID-19 pandemic. Allowing remote safety visits if needed due to COVID-19 concerns. **Section 7.7.4** Added language permitting local safety lab draws in cases where subjects may be may potentially be out of visit window due to concerns related to COVID-19 pandemic.	16 Mar 2020
Version 08 – Amendment 01, 02, 03, 04, 05, 06 and 07 – Incorporates Admin Letter 01	**Section 9.2.3:** Revised to permit extended dosing period between Week 8 and Week 12, if necessary, due to COVID-19 concerns, and to not permit entrance into the Extension Phase until a Randomization Phase Week 12 visit is conducted in the office. **Section 9.4:** Revised to permit overnight shipment of study drug, if necessary, due to COVID-19 concerns. General typographical errors have been corrected and administrative updates have been made throughout.	19 Oct 2020

Version 09 – Amendment 01, 02, 03, 04, 05, 06 07, and 08 – Incorporates Admin Letter 01	**Section 4.3** Revised Schedule of Assessments to add an Additional Expanded Extension Phase, which provides eligible subjects with an additional 48 weeks of open-label treatment with troriluzole.	15 Dec 2021

Version 10 – Amendment 01, 02, 03, 04, 05, 06 07, 08 and 09 – Incorporates Admin Letter 01	**Study Design and Study Schematic** Revised Study Design sections and Study Schematic to add an additional 48 weeks of open-label treatment with troriluzole to the Additional Expanded Extension Phase. **Section 4.3** Revised Schedule of Assessments to add an additional 48 weeks of open-label treatment with troriluzole to the Additional Expanded Extension Phase (Table 7). **Sections 4.3, 4.3.2, 7.7.4 and 10.1.4** Revised to reflect change in Medical Monitor from PPD PPD to PPD PPD **Section 17.1 Appendix I** Revised to reflect change in Medical Monitor from PPD PPD to PPD PPD and addition of back-up Medical Monitor PPD PPD General typographical errors have been corrected and administrative updates have been made throughout.	13 Oct 2022

BHV4157-202

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ADJUNCTIVE TRORILUZOLE IN OBSESSIVE COMPULSIVE 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 randomized, double-blind, placebo-controlled trial of adjunctive troriluzole in Obsessive Compulsive Disorder

Rationale: First-line treatment for Obsessive Compulsive Disorder (OCD) includes cognitive behavior therapy and selective serotonin reuptake inhibitors (SSRIs). Nonetheless, up to 60% of patients have an inadequate response to conventional pharmacotherapy [1]. While SSRIs and clomipramine have been approved for OCD, the majority of patients do not have an adequate response to pharmacologic treatment, and some seek invasive neurosurgical procedures to ameliorate symptoms.

The proposed study is based on recent preclinical, clinical, genetic and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of OCD. In multiple published clinical case studies, the use of agents that modulate brain glutamate have been suggested to have efficacy in patients with refractory OCD [2-8] .

Troriluzole is a novel glutamate modulating drug that is being developed for the potential treatment of OCD as adjunctive therapy to standard of care treatments in subjects who have experienced an inadequate response to current pharmacotherapy.

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:

- Troriluzole is expected to have *better oral bioavailability*;
- Troriluzole is expected to have *no food restrictions imposed*;
- 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;
- 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 Obsessive Compulsive Disorder (confirmed by the MINI) who have had an inadequate response to Standard of Care medications, including their current standard of care. An inadequate response to their current standard of care is defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 19 or greater despite at least 10 weeks of treatment at Baseline [8] with the maximum tolerated dose of an SSRI, clomipramine, venlafaxine or desvenlafaxine. Additionally, OCD 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 item.

Number of Subjects: Approximately 226 randomized subjects

Objectives:

Primary Objectives

- The primary objective of the study is to evaluate the efficacy of Troriluzole as adjunctive therapy in subjects with OCD who have had an inadequate response to SSRI, clomipramine, venlafaxine or desvenlafaxine treatment

Secondary Objectives

- To assess the safety and tolerability of troriluzole, relative to placebo, in subjects with OCD
- 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)
- Evaluate the efficacy of troriluzole compared to placebo on obsessive symptomatology as measured by the change in the Yale Brown Obsessive Compulsive Scale (Y-BOCS) obsessions subscale

Exploratory Objectives

- Evaluate the efficacy of troriluzole compared to placebo on depressive symptomatology as measured by the Quick Inventory of Depressive Symptomatology - Self Report (QIDS-SR)
- Evaluate the efficacy of troriluzole compared to placebo on anxiety symptoms as measured by the Beck Anxiety Inventory (BAI)
- Evaluate the efficacy of troriluzole compared to placebo on insight regarding obsessional beliefs as measured by the Brown Assessment of Beliefs Scale (BABS)
- To assess pharmacodynamic effects of troriluzole vs. placebo on markers of synaptic plasticity as measured by plasma levels of BDNF and proBDNF
- To characterize the pharmacokinetics of troriluzole based on sparse sampling

Study Design:

BHV4157-202 is a Phase IIb/III, multicenter, randomized, double-blind, placebo-controlled, 2- arm study designed to assess safety, tolerability, and efficacy of troriluzole as adjunctive therapy when added to standard of care treatment in subjects with Obsessive Compulsive Disorder who failed to respond adequately to prior pharmacotherapy. Current treatment failure is defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 19 or greater despite at least 8 weeks of treatment at screening and at least 10 weeks of treatment at baseline with an adequate dose of an SSRI, clomipramine, venlafaxine or desvenlafaxine.

Subjects who are stable on Standard of Care (SOC) medication and having an inadequate response (as defined above) will be randomized to additionally receive placebo (QD) or troriluzole (200 mg QD, after four weeks at 140 mg QD).

Dosing will continue for approximately 12 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 12 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. Subjects who complete the 48 week extension may have the opportunity to receive an additional 48 weeks of open-label treatment with troriluzole in an Expanded Extension Phase depending on when they completed the first 48 weeks. Those subjects not continuing in the 48 week Expanded Extension Phase will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit.

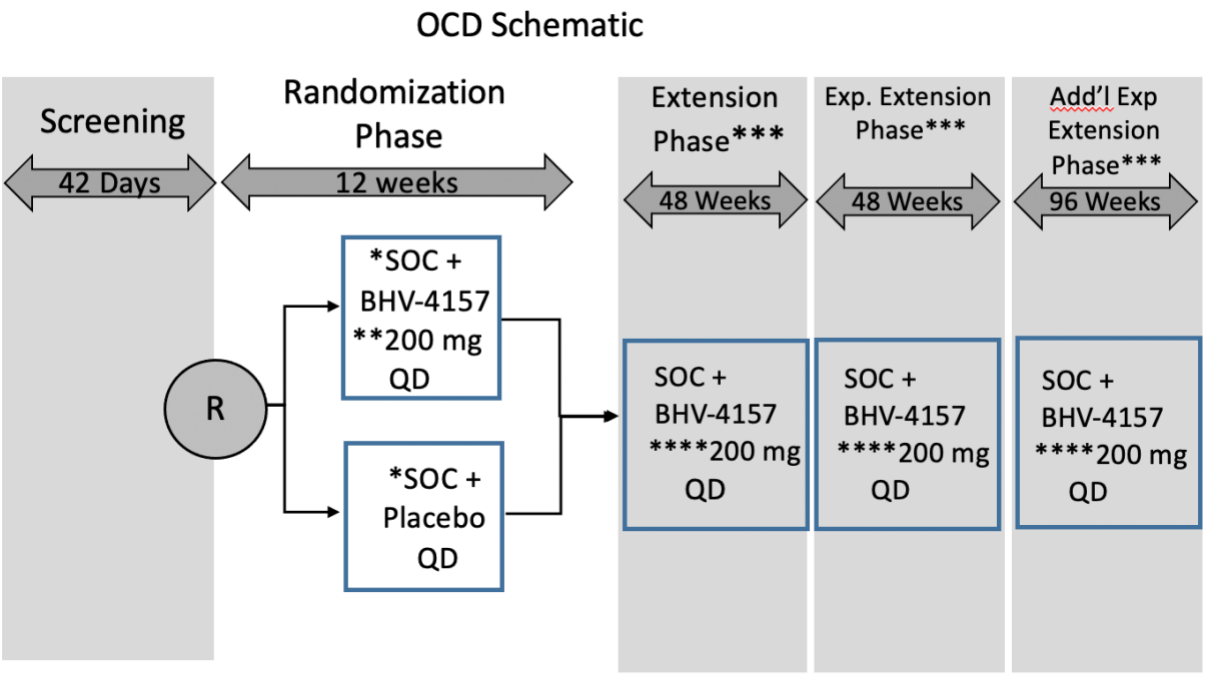
For subjects completing the initial 48 week Extension Phase and continuing directly into the Expanded Extension Phase with no dose interruption, their first in-person expanded extension visit will be 12 weeks after the extension week 48 visit. Subjects will undergo visits every 12 weeks up to Week 96 of this phase. Subjects who complete the 48 week Expanded Extension Phase may have the opportunity to receive an additional 96 weeks of open-label treatment with troriluzole in the Additional Expanded Extension Phase, for a total of 192 weeks of open-label treatment, depending on when they completed the first 96 weeks. Those subjects not continuing in the Additional Expanded Extension Phase will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit.

Subjects who previously completed the initial 48 week Extension Phase and have exited the study will have the opportunity to return and receive an additional 48 weeks of open-label treatment with troriluzole provided it has not

been more than 3 months since they completed the study and the PI believes it offers an acceptable risk-benefit profile. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug.

Subjects who completed the Expanded Extension Phase and have exited the study will have the opportunity to return and receive an additional 48 weeks of open-label treatment with troriluzole in an Additional Expanded Extension Phase provided it has not been more than 4 weeks since they completed the study and the PI believes it offers an acceptable risk-benefit profile. Subjects who complete the initial 48 weeks of the Additional Expanded Extension Phase will have the opportunity to continue and receive an additional 48 weeks of open-label treatment provided the PI believes it offers an acceptable risk-benefit profile. All subjects will undergo a post study drug termination visit two weeks after the last dose of study drug.

STUDY SCHEMATIC*



*Subjects should have been taking an adequate maximum tolerated dose, as defined in the Inclusion Criteria 3.b.2 of an SSRI, clomipramine, venlafaxine or desvenlafaxine for at least 8 weeks prior to Screening and 10 weeks at Baseline.
**Subjects will receive 140mg for the first four (4) weeks and then will be increased to 200mg for the duration of the study. Down titration will only be allowed to address tolerability issues.
***Eligible subjects will include those who perceived benefit in earlier phases and for whom the PI believes extended treatment with BHV4157 would offer an acceptable risk-benefit profile.
****Subjects entering the Extension, Expanded Extension or Additional Expanded Extension phase will continue with the same dose taken at then end of the Randomization Phase, Extension or Expanded Extension phase. Subjects on placebo at the end of the Randomization Phase will be switched in a blinded manner to 140mg for the first four weeks and then will be increased to 200mg for the duration of the Extension Phase of the study. Down titration after the first four weeks of the Extension Phases of the study will only be allowed to address tolerability issues. Subjects who enter the Extension Phases of the study on 140mg for tolerability issues can be re-challenged to receive 200mg after the first four weeks at PI discretion.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
Bid	Twice Daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Cmax	Maximum Plasma Concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant Medication
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
GCP	Good Clinical Practice
HR	Heart Rate
IB	Investigator's Brochure
ICF	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
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level

NOAEL	No Observed Adverse Event Level
PK	Pharmacokinetic
po	By Mouth, Orally
qd	Once Daily
SAE	Serious Adverse Event
SOC	Standard of Care
SSRI	Selective Serotonin Reuptake Inhibitor
ULN	Upper Limit of Normal
USPI	US Package Insert
WHO	World Health Organization

1 INTRODUCTION AND RATIONALE

1.1 Background

Biohaven Pharmaceutical Holding Company Limited [Biohaven] is developing a new drug, troriluzole, for the treatment of OCD as well as for other 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 is only indicated for ALS and 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 OCD is based on recent preclinical, clinical and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of OCD [6-10]. Biohaven hypothesizes that the pleiotropic effects of riluzole (e.g., glutamate modulation) may target mechanisms underlying pathologic brain function that is associated with OCD, and thus provide symptomatic benefit in patients suffering from OCD.

1.1.1 Obsessive Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is a prevalent psychiatric disease, affecting 2-3% of the general population [11]. According to the National Comorbidity Survey, approximately half of OCD cases are characterized as severe [1]. Patients with OCD suffer from intrusive, obsessional thoughts that are typically ego-dystonic and commonly engage in time-consuming compulsive behaviors in in an attempt to attenuate their anxiety. The anxiety associated with OCD symptoms can be intense and persist chronically over time. Existing therapies, including pharmacotherapy and well-established cognitive-behavioral techniques, can significantly reduce symptoms in many patients. However, persistent residual symptoms are the norm and can lead to markedly restricted lives even in treated patients; and a substantial number of patients are treatment refractory [12]. Indeed, treatment refractory OCD is a sufficiently debilitating condition that it is the only psychiatric disease for which psychosurgery still remains an established therapy of last resort [13,14]. Augmentation strategies with neuroleptic medications can improve the effectiveness of selective serotonin inhibitors (SRIs) therapy but do not eliminate OCD symptoms [15,16]. Additionally, neuroleptic medications are associated with adverse effects including tardive dyskinesia, extrapyramidal symptoms and metabolic syndrome. The clinical observation that few patients experience a complete response to SRIs or dopamine antagonists suggests that other neurochemical systems are involved in the pathophysiology of OCD. Novel pharmacological treatments are needed to improve treatment outcomes.

1.1.2 Rationale for Troriluzole in the Treatment of OCD

The proposed study is based on recent preclinical, clinical, genetic and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of OCD [4,5,9,10,17-25]. The Glutamate transporter gene SLC1A1 has been associated with the transmission of OCD in some studies, providing some genetic evidence of the association between altered glutamate neurotransmission and OCD [24]. Further genome-wide association studies have identified the glutamate related SAPAP/DLGAP proteins as additional genes of interest [26,27].

Neuroimaging studies have also consistently identified increased blood flow, metabolism and brain activity in the orbitofrontal cortex (OFC), striatum, and thalamus of individuals with OCD [28]. The striatum is the primary input nucleus of the basal ganglia, a network of subcortical structures; the OFC is the major target of cortical input to the basal ganglia and the thalamus is a major output; it projects back to the cortex, forming a feedback loop. These structures, which are hyperactive in OCD, thus constitute part of the cortico-striato-thalamo-cortical (CSTC) circuitry. Information flows through this circuitry in two parallel loops: the direct pathway, which provides net positive feedback to the cortex, and the indirect pathway, which provides net negative feedback. Activity in these parallel circuitries exists in a tightly regulated dynamic balance. A leading explanatory model for OCD suggests that overactivity in the direct pathway relative to the indirect pathway results in a disinhibited thalamus and the creation of a self-perpetuating circuit between the thalamus and the orbitofrontal cortex that drives OCD symptoms [29,30]. Clinical studies support this model. Compared to controls, treatment naïve OCD patients have significantly increased glutamatergic activity as measured by proton magnetic resonance spectroscopy (1H-MRS) [31,32]. Moreover, treatment with an SRI was associated with a significant decline in caudate glutamate concentration in those individuals who responded to SRI treatment [31-34]. These clinical findings are consistent with pharmacological studies demonstrating an SRI-induced inhibition of glutamate release [35].

Open label data and small clinical studies also suggest benefit from the glutamate modulator riluzole in individuals with OCD [8,36,37]. In a study by Emamzadehfard [4], patients treated with riluzole augmentation of the SSRI fluvoxamine showed significantly greater reductions in their Y-BOCS score and more patients achieved remission compared to placebo over the 10 week course of the trial. Riluzole has several modes of action; prominent among them, are an inhibition of presynaptic glutamate release and increased glutamate cycling due to effects on the excitatory amino acid transporters (EAATs) located on glia [38].

1.1.3 Troriluzole

1.1.3.1 Pre-Clinical Studies

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[redacted]

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[redacted]

1.1.3.2 Clinical Experience

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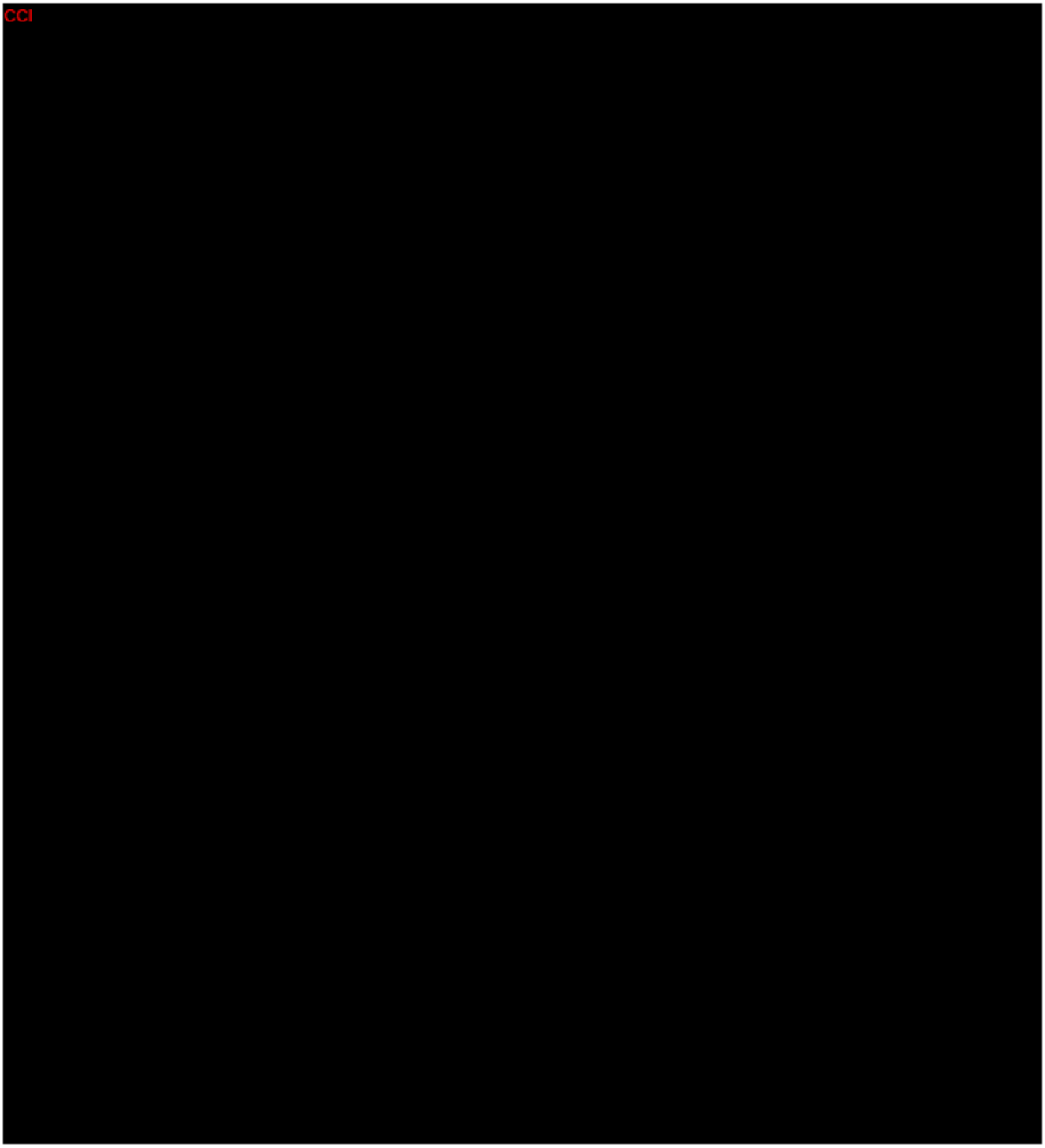
[redacted]

1.1.3.2.1 Troriluzole Phase I - Study BHV4157-101



1.1.3.2.2 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 completing the double-blind randomization phase were offered 48 weeks of open-label treatment with troriluzole (140 mg PO QD) in an extension phase. One hundred and thirty (131) subjects continued into the open-label extension phase, which was ongoing as of October 2017. At that time, the preliminary safety profile of troriluzole 140 mg QD was consistent with the troriluzole safety profile observed during the randomization phase.

1.1.4 Potential for Drug-Drug Interactions

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

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., 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.

1.1.5 Clinical Adverse Event Profile

1.1.5.1 Troriluzole

CCI

[redacted]

1.1.5.2 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.

1.1.5.2.1 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.

1.1.5.2.2 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.

1.1.5.2.3 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.

1.1.6 Potential Risk to Fetal Development

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

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

1.2 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) as well as Obsessive Compulsive Disorder (OCD). This protocol represents the first trial of troriluzole in OCD.

Troriluzole is a novel tripeptide prodrug of the glutamate modulating agent riluzole. The proposed study is based on recent preclinical, clinical, genetic and neuroimaging studies that implicate glutamatergic hyperactivity in the pathogenesis of OCD [24,26,27,44]. While troriluzole has yet to be studied in OCD, studies with riluzole in populations with OCD provide support for the therapeutic potential of troriluzole. In addition to open label data suggesting the benefit of riluzole in individuals with OCD [8,36,37], one recent placebo-controlled, double-blind trial of riluzole augmentation of SSRI treatment in patients with refractory or moderate to severe OCD showed riluzole to be effective in a subset of patients [4].

Riluzole has several modes of action; prominent among them, are a reduction in glutamate outflow due to effects on the excitatory amino acid transporters [38]. Given the evidence for the role of elevated brain glutamate in OCD, and that troriluzole is a prodrug of riluzole, it is hypothesized that it would be expected to have therapeutic value in OCD 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 [8-10]. In addition, riluzole is associated with reduced exposure when taken with meals (i.e., a negative food effect), resulting in the guidance to take riluzole within a three hour fast (one hour before or two hours after a meal).

Riluzole is also dosed twice a day, has dose-dependent effects on liver function tests and the drug substance itself has other intrinsic limitations including: very low solubility in water, poor oral palatability, pH dependent chemical stability and intense oral numbness if administered directly to the oral mucosa.

Troriluzole 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:

- **Improved Bioavailability**—Troriluzole is a substrate for the gut transporters (PepT1). This is thought to increase the bioavailability of the drug as compared to orally dosed riluzole, meaning that more of the compound is absorbed by the body into the blood stream and can have an active effect. Studies have shown that administration of agents through peptide transporters significantly increases the absorption of drugs with otherwise poor oral bioavailability.

- **No Negative Food Effect**—Troriluzole shows no food effect in human studies, meaning that the drug will not be associated with special meal restrictions, a phenomenon potentially attributable to enhanced uptake by intestinal transporters specific to the peptide-containing moiety of troriluzole. This is in contrast to oral riluzole tablets, which require a 3-hour window of fasting around its two daily doses to reach therapeutic levels, currently a dose-limiting factor of riluzole.

- **Lower Overall Drug Burden to the Liver**—As a prodrug that mitigates first-pass liver metabolism and enhances bioavailability, therapeutic concentrations of the active metabolite riluzole can be achieved with a lower molar drug load as compared to riluzole tablets. In addition, release of the active metabolite over time will result in a reduced bolus hepatic concentration as compared to that associated with riluzole tablets. Taken together, we believe these attributes of troriluzole will reduce the potential for adverse liver effects.

- **Optimized Dosing Regimen and Compliance**—Troriluzole has been developed as a convenient once-daily dose, which could improve regimen compliance for patients. We believe these are important features to optimize long-term health outcomes in the treatment of patients with chronic diseases.

1.2.2 Pharmacokinetics and Dose Selection Rationale

1.3 Research Hypothesis

Troriluzole is superior to placebo as adjunctive therapy when added to Standard of Care Treatment over a 12 week period in patients with Obsessive Compulsive Disorder with an inadequate response to SSRI, clomipramine, venlafaxine or desvenlafaxine treatment.

2 STUDY OBJECTIVES

2.1 Primary

- The primary objective of the study is to evaluate the efficacy of troriluzole as adjunctive therapy in subjects with OCD who have had an inadequate response to SSRI, clomipramine, venlafaxine or desvenlafaxine treatment

2.2 Secondary

- To assess the safety and tolerability of troriluzole, relative to placebo, in subjects with OCD
- Evaluate the efficacy of troriluzole compared to placebo on functional disability as measured by the SDS
- Evaluate the efficacy of troriluzole compared to placebo on global functioning as measured by the Clinical Global Impression- Severity Scale (CGI-S)
- Evaluate the efficacy of troriluzole compared to placebo on obsessive symptomatology as measured by the change in the Y-BOCS obsessions subscale

2.3 Exploratory

- Evaluate the efficacy of troriluzole compared to placebo on depressive symptomatology as measured by the QIDS-SR
- Evaluate the efficacy of troriluzole compared to placebo on anxiety symptoms as measured by the BAI
- Evaluate the efficacy of troriluzole compared to placebo on insight regarding obsessional beliefs as measured by the BABS
- To assess pharmacodynamic effects of troriluzole vs. placebo on markers of synaptic plasticity as measured by plasma levels of BDNF and proBDNF
- To characterize the pharmacokinetics of troriluzole based on sparse sampling

3 STUDY ENDPOINTS

3.1 Primary

- Improvement in obsessive-compulsive symptomatology is assessed using the change in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score from baseline to the end of the double-blind phase of the study (Week 12).

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.
- Improvement in obsessive symptomatology is assessed using the change in the Y-BOCS obsessions subscale score from baseline to the end of the double-blind phase of the study.

3.3 Exploratory

- Improvement in depressive symptomatology is measured by the change in the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR) from baseline to the end of the double-blind phase.
- Improvement in anxiety is assessed using the change in the Beck Anxiety Inventory (BAI) from baseline to the end of the double blind phase.
- Improvement of insight into obsessive-compulsive beliefs is measured by the change in the Brown Assessment of Beliefs Scale (BABS) from baseline to the end of the double-blind phase.
- The impact on markers of synaptic plasticity is assessed using the change in plasma BDNF and proBDNF levels from baseline to the end of the double-blind phase.
- The pharmacokinetic profile of troriluzole is characterized by blood concentrations observed in treated subjects.

4 STUDY PLAN

4.1 Study Design and Duration

BHV4157-202 is a Phase IIb/III, multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group study designed to assess safety, tolerability, and efficacy of troriluzole as adjunctive therapy in a population of patients with Obsessive Compulsive Disorder who have had an inadequate response to Standard of Care treatment. Treatment failure on the subjects' current standard of care is defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 19 or greater despite at least 8 weeks of treatment at Screening and 10 weeks of treatment, at Baseline, with an adequate dose of an SSRI, clomipramine, venlafaxine or desvenlafaxine medication.

Subjects who are stable on Standard of Care (SOC) medication and are having an inadequate response (as defined above) will be randomized to additionally receive once a day dosing of troriluzole or matching placebo.

Subjects will receive either troriluzole (140mg) or Placebo for the first four weeks and then will be increased to 200 mg (or matching placebo) for the duration of the study. Down titration after the first four weeks of the Randomization Phase will only be allowed for tolerability purposes.

Dosing will continue for approximately 12 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 PI believes open-label treatment offers an acceptable risk-benefit profile. Subjects who agree to enter the Extension Phase will not complete the follow-up safety visit and should continue dosing as specified.

Subjects entering the Extension Phase will have their first Extension Visit four weeks after the Week 12 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 on placebo in the Randomization Phase will be switched in a blinded manner to 140 mg for the first four weeks and then will be increased to 200 mg for the duration of the study. Down titration after the first four weeks of the Extension Phase will only be allowed for tolerability purposes. All Visits after week 4 will be open label. Subjects who enter the Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg after Extension Week 4 at PI discretion.

Subjects who complete the 48-week Extension Phase and are continuing directly into the 48-week Expanded Extension Phase with no dose interruption will have their first visit 12 weeks after the Extension Week 48 visit. Therafter, subject will undergo visits every 12 weeks until

Week 96 of the Expanded Extension Phase as outlined in Table 3 (Schedule of Assessments/Time and Events – Expanded Extension Phase – Continuing Subjects).

Subjects who previously completed the Extension Week 48 visit and exited the study, will have the opportunity to return and receive an additional 48 weeks of open-label treatment with troriluzole provided it has not been more than 3 months since they completed the study and the PI believes it offers an acceptable risk-benefit profile. Returning subjects who have been off study medication for less than 4 weeks will undergo an abbreviated Baseline visit before re-entering the study. Returning subjects who have been off study medication for 4 weeks or more will be required to undergo a full Baseline visit. In addition, for returning subjects, safety laboratory assessments will be performed 4 and 8 weeks after re-starting study medication. Thereafter, study visits in the Expanded Extension Phase will be every 12 weeks until Week 48 of the Expanded Extension Phase as outlined in Table 4 (Schedule of Assessments/Time and Events – Expanded Extension Phase – Returning Subjects). All subject will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Expanded Extension Phase will continue with the same dose taken at the end of the initial Extension Phase. Down titration after the first four weeks of the Expanded Extension Phase will only be allowed for tolerability purposes. Subjects who enter the Expanded Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg after the first 4 weeks at PI discretion.

Subjects who complete the 48-week Expanded Extension Phase and are continuing directly into the 96-week Additional Expanded Extension Phase with no dose interruption will have their first visit 12 weeks after the 48th week of the Expanded Extension (EE Week 96 or EE Week 48 as identified in protocol version 08). Therafter, subject will undergo visits every 12 weeks until Week 96/144/192 of the Additional Expanded Extension Phase as outlined in Table 5 and Table 7 (Schedule of Assessments/Time and Events – Additional Expanded Extension Phase – Continuing Subjects).

Subjects who previously completed the Expanded Extension Week 48/96 visit and exited the study, will have the opportunity to return and receive an additional 48 weeks of open-label treatment with troriluzole provided it has not been more than 4 weeks since they completed the study and the PI believes it offers an acceptable risk-benefit profile. Returning subjects will undergo an abbreviated Baseline visit before re-entering the study. In addition, for returning subjects, safety laboratory assessments will be performed 4 and 8 weeks after re-starting study medication. Subjects who complete the initial 48 weeks of the Additional Expanded Extension Phase will have the opportunity to continue and receive an additional 48 weeks of open-label treatment provided the PI believes it offers an acceptable risk-benefit profile. Thereafter, study visits in the Additional Expanded Extension Phase will be every 12 weeks until Week 96 of the Additional Expanded Extension Phase as outlined in Table 6 (Schedule of Assessments/Time and Events – Additional Expanded Extension Phase – Returning Subjects). All subject will undergo a termination visit two weeks after the last dose of study drug.

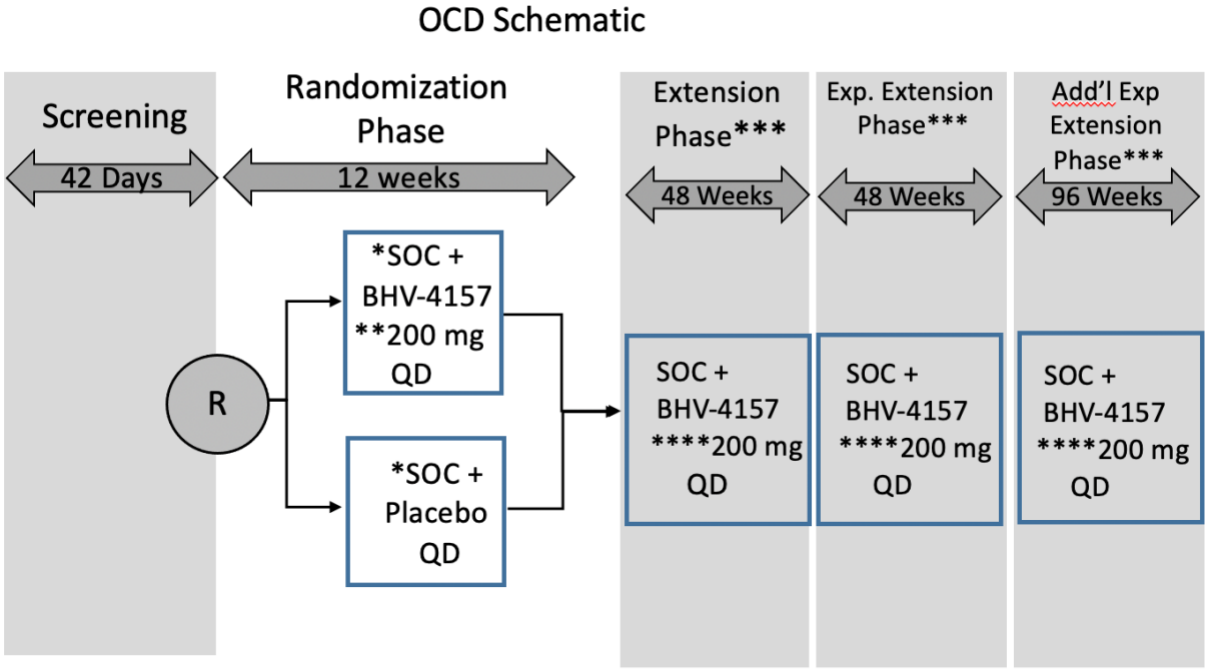
Subjects entering the Additional Expanded Extension Phase will continue with the same dose taken at the end of the Expanded Extension Phase. Down titration after the first four weeks of the Expanded Extension Phase will only be allowed for tolerability purposes. Subjects who enter the

Additional Expanded Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg after the first 4 weeks at PI discretion.

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

4.2 Study Schematic

Figure 1: Study Schematic



*Subjects should have been taking an adequate maximum tolerated dose, as defined in the Inclusion Criteria 3.b.2 of an SSRI, clomipramine, venlafaxine or desvenlafaxine for at least 8 weeks prior to Screening and 10 weeks at Baseline.
**Subjects will receive 140mg for the first four (4) weeks and then will be increased to 200mg for the duration of the study. Down titration will only be allowed to address tolerability issues.
***Eligible subjects will include those who perceived benefit in earlier phases and for whom the PI believes extended treatment with BHV4157 would offer an acceptable risk-benefit profile.
****Subjects entering the Extension, Expanded Extension or Additional Expanded Extension phase will continue with the same dose taken at then end of the Randomization Phase, Extension or Expanded Extension phase. Subjects on placebo at the end of the Randomization Phase will be switched in a blinded manner to 140mg for the first four weeks and then will be increased to 200mg for the duration of the Extension Phase of the study. Down titration after the first four weeks of the Extension Phases of the study will only be allowed to address tolerability issues. Subjects who enter the Extension Phases of the study on 140mg for tolerability issues can be re-challenged to receive 200mg after the first four weeks at PI discretion.

4.3 Schedule of Assessments

Every effort should be made to conduct the study visits as planned. However, due to concerns related to the COVID-19 pandemic, study participants may be unable to come into the office for their study scheduled visit, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed) note the following guidance: Under these circumstances, the investigator should contact the sponsor medical monitor to discuss the most appropriate course of action. Remote safety visits will be allowed on a case by case basis, if a patient is unable to come to the site for evaluation and the investigator determines that a remote visit offers an acceptable risk-benefit approach and is appropriate for a particular subject. The investigator should discuss the specific requirements for the remote safety visit with the sponsor medical monitor, which will be based on the study visit number and the clinical status of the participant. If the remote visit requires laboratory testing, local labs must be able to be obtained, reviewed by the site and a redacted version forwarded to Biohaven when available for review. Shipping of study drug from the site to the patient via overnight tracked and certified courier will also be allowed.

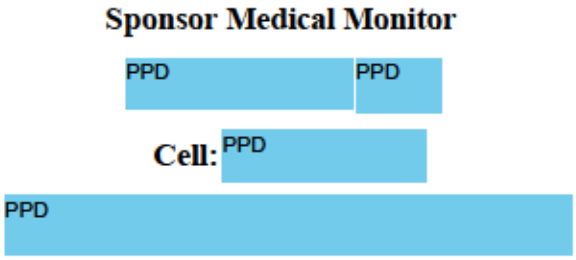


Table 1: Schedule of Assessments and Events - Randomization Phase

Visit	Screening[a]	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 or early term[bc]	Week 2 Post Last Dose[d]
Day	-2 to -42	0		28		56	84	98
Eligibility Assessments								
Informed Consent	X							
Pharmacogenetic Informed Consent	X							
Inclusion/Exclusion	X	X						
MINI	X							
MMSE	X							
Borderline Personality Disorder Module (BPD Module)	X							
MGH-TRQ-OCD[e]	X							
Medical History	X							
Demographic Assessment	X							
Disease History	X							
SAFER Interview[f]	X							
Safety Assessments								
Adverse Event Assessment	X	X		X		X	X	X
Telephone Check-in[m]			X		X			

Visit	Screening[a]	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 or early term[bc]	Week 2 Post Last Dose[d]
Day	-2 to -42	0		28		56	84	98
Includes AE assessment and concomitant medication review								
Laboratory Assessments including urinalysis[g]	X	X		X		X	X	
Serology[h]	X							
Pregnancy testing[i]	X	X		X		X	X	
Urine drug test[j]	X	X					X	
Physical Exam	X						X	
Physical Measurements	X						X	
Vital Signs	X	X		X		X	X	X
12-Lead ECG	X	X					X	
Concomitant Medication Review	X	X		X		X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X		X		X	X	X
Clinical Outcome Assessments								
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X	X		X		X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X		X		X	X	
Sheehan Disability Scale (SDS)[n]	X	X		X		X	X	
Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)	X	X		X		X	X	
Beck Anxiety Inventory (BAI)	X	X		X		X	X	

Visit	Screening[a]	Baseline	Week 2	Week 4	Week 6	Week 8	Week 12 or early term[bc]	Week 2 Post Last Dose[d]
Day	-2 to -42	0		28		56	84	98
Brown Assessment of Beliefs (BABS)	X	X					X	
Biomarker and Other Assessments								
BDNF and proBDNF Blood Sample		X					X	
Pharmacokinetics Blood Sample[k]				X		X	X	
Pharmacogenomics Blood Sample		X					X	
Clinical Drug Supply								
Randomization		X						
Dispense Study Drug[l]		X		X		X	X[b, o]	
Drug Accountability				X		X	X	

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

[a] Screening window is minimum of 2 days to maximum of 42 days. Screening can be as short as 2 days as long as the subjects has been on at least 8 weeks of their current SOC OCD therapy at an adequate dose at Screening and at least 10 weeks of their current SOC OCD therapy (SSRI, clomipramine, venlafaxine or desvenlafaxine) at an adequate dose by the Baseline Visit.

[b] Study drug will be dispensed at Week 12 if subject is deemed eligible and agreed to participate in the Extension Phase. Subjects will not be allowed to transition to the Extension Phase until they have an in-person Week 12 visit.

[c]Every effort should be made to conduct the Week 12 visit and maintain the +/- 7 day window. However, due to concerns related to the COVID-19 pandemic, the Week12 visit window may be modified beyond the +/- 7 day window, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed) note the following guidance. Under these circumstances, the last visit window may be extended up to 6 weeks (up to a maximum treatment duration of 18 weeks), but every attempt should be made to conduct the visit as close to the date the visit is due as possible. If the visit window is modified, and the investigator determines that a remote visit offers an acceptable risk-benefit approach and is appropriate for a particular subject, participants should be evaluated remotely for safety only (e.g., via phone) at the time of the scheduled Week 12 visit to perform and document appropriate safety assessments including the Sheehan Suicidality Tracking Scale (STS). If the remote visit requires laboratory testing, local labs must be able to be obtained, reviewed by the site and a redacted copy submitted to the study Medical Monitor. Study

medication may be sent to the participant via tracked and certified courier. For any such cases, the investigator should discuss the specific circumstances of each case with the sponsor medical monitor: PPD PPD; CellPPD PPD

[d] Only for subjects NOT entering the Extension Phase. Subjects entering the Extension Phase will not require the 2-week post dose visit.

[e] The subject must have an inadequate response to the standard of care treatment, as defined in the protocol. The MGH-TRQ-OCD will be used to capture information on past treatments.

[f] 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.

[g] Laboratory assessments are not required to be fasting.

[h] HBsAg, HCV, HIV antibody, RPR

[i] Serum pregnancy test (b-hcg) conducted at screening. Urine pregnancy test conducted at subsequent visits. To be done prior to dosing at baseline. The site may test a patient at any time if pregnancy is suspected.

[j] Urine drug test to be conducted at screening, baseline and EOS visit and at unscheduled visit at the discretion of the investigator. Reflex confirmatory drug testing will be conducted by the lab vendor for all positive urine drug screen samples.

[k] Plasma samples for PK will be collected at random at Weeks 4, 8 and 12. Date and time of doses on the day of visits and 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 that are possibly drug related. Subjects who are able to schedule a morning visit for Week 4 and Week 8 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] Study Drug will be dispensed at the baseline visit. Subjects should take the first dose in the morning the day after the baseline visit.

[m] Telephone calls to subjects will be made between visits during the first and second months of the Randomization Phase (Weeks 2 and 6) to monitor subject condition, any new concomitant medications and adverse events.

[n] 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.

[o] If the study site needs to send drug overnight via certified and tracked courier and this is acceptable to the institution because a visit is absolutely not possible because of the COVID-19 pandemic, this is permissible per study. The sponsor should be consulted prior to shipping drug.

Table 2: Schedule of Assessments and Events - Extension Phase

Visit	Ext Wk 2	Ext Wk4	Ext Wk 6	Ext Wk 8	Ext Wk 12	Ext Wk 24	Ext Wk 36	Ext Wk 48 or early term	Wk2 Post last dose
Safety Assessments									
Adverse Event Assessment		X		X	X	X	X	X	X
Telephone Check-in[b] *Includes AE assessment and concomitant medication review*	X		X						
Laboratory Assessments		X		X	X	X	X	X	
Pregnancy testing[a]		X		X	X	X	X	X	
Urine drug test		X		X	X	X	X	X	
Physical Exam								X	
Physical Measurements						X		X	
Vital Signs		X		X	X	X	X	X	X
12-Lead ECG		X			X	X	X	X	
Concomitant Medication Review		X		X	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)		X		X	X	X	X	X	X
Clinical Outcome Assessments									
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)		X		X	X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)		X		X	X	X	X	X	
Sheehan Disability Scale (SDS)[c]		X		X	X	X	X	X	
Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)		X		X	X	X	X	X	
Beck Anxiety Inventory (BAI)		X		X	X	X	X	X	

Brown Assessment of Beliefs (BABS)		X			X				
Biomarker and Other Assessments									
BDNF and proBDNF Blood Sample								X	
Clinical Drug Supply									
Dispense Study Drug		X		X	X	X	X		
Drug Accountability		X		X	X	X	X	X	

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

[a]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Extension Phase. *Note: test will be sent home at Week 12 and at Week 24 and should be performed once between each 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] Telephone calls to subjects will be made between visits during the first and second months of the Extension Phase (Weeks 2 and 6) to monitor subject condition, any new concomitant medications and adverse events.

Table 3: Schedule of Assessments and Events – Expanded Extension Phase (continuing subjects)

Visit	Exp Ext Wk 60	Exp Ext Wk 72	Exp Ext Wk 84	Exp Ext Wk 96 or early term	Wk2 Post last dose
Safety Assessments					
Adverse Event Assessment	X	X	X	X	X
Laboratory Assessments		X		X	
Labs: LFT tests only: (ALT, AST, BILI, GGT)	X		X		
Pregnancy testing[a]	X	X	X	X	
Urine drug test	X	X	X	X	
Physical Exam		X		X	
Physical Measurements		X		X	
Vital Signs	X	X	X	X	X
12-Lead ECG	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X
Clinical Outcome Assessments					
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X	X	X	
Sheehan Disability Scale (SDS)[b]	X	X	X	X	
Clinical Drug Supply					
Dispense Study Drug	X	X	X		
Drug Accountability	X	X	X	X	

Visit window is +/- 7 days during the expanded extension phase.
[a]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Expanded Extension Phase. *Note: test will be sent home at Week 60, Week 72 and at Week 84 and should be performed once between each visit.
[b] 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.

Table 4: Schedule of Assessments and Events – Expanded Extension Phase (returning subjects)

Visit	Baseline Visit[a]	Abbreviated Baseline Visit[b]	Exp Ext Wk 4	Exp Ext Wk 8	Exp Ext Wk 12	Exp Ext Wk 24	Exp Ext Wk 36	Exp Ext Wk 48 / early term	Wk2 Post last dose
Eligibility Assessments									
Informed Consent	X	X							
Safety Assessments									
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Laboratory Assessments	X					X		X	
Lab: LFT tests only (ALT, AST, BILI, GGT)			X	X	X		X		
Pregnancy testing[c]	X				X	X	X	X	
Urine drug test	X				X	X	X	X	
Physical Exam	X					X		X	
Physical Measurements	X				X	X	X	X	
Vital Signs	X	X			X	X	X	X	X
12-Lead ECG	X				X	X	X	X	
Concomitant Medication Review	X	X			X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X	X	X	X	X
Clinical Outcome Assessments									
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X				X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X				X	X	X	X	
Sheehan Disability Scale (SDS)[d]	X				X	X	X	X	

Clinical Drug Supply									
Re-enter subject in IWRS	X	X							
Dispense Study Drug	X	X			X	X	X		
Drug Accountability			X	X	X	X	X	X	

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

[a]Baseline Visit is needed for returning subjects who completed dosing in the initial Extension Phase ≥ 4 weeks prior to returning to the study and entering the Expanded Extension Phase.

[b]Abbreviated Baseline Visit only needed for returning subjects who completed dosing in the initial Extension Phase < 4 weeks prior to returning to the study and entering the Expanded Extension Phase.

[c]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Expanded Extension Phase. *Note: A test will be sent home at Week 12, 24 and at Week 36 and should be performed once between each visit.

[d] 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.

Table 5: Schedule of Assessments and Events – Additional Expanded Extension Phase (continuing subjects)

Visit	Add'l Exp Ext Wk 60/108	Add'l Exp Ext Wk 72/120	Add'l Exp Ext Wk 84/132	Add'l Exp Ext Wk 96/144 or early term	Wk2 Post last dose
Safety Assessments					
Adverse Event Assessment	X	X	X	X	X
Laboratory Assessments		X		X	
Labs: LFT tests only: (ALT, AST, BILI, GGT)	X		X		
Pregnancy testing[a]	X	X	X	X	
Urine drug test	X	X	X	X	
Physical Exam		X		X	
Physical Measurements		X		X	
Vital Signs	X	X	X	X	X
12-Lead ECG	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X
Clinical Outcome Assessments					
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X	X	X	
Sheehan Disability Scale (SDS)[b]	X	X	X	X	
Clinical Drug Supply					
Dispense Study Drug	X	X	X	X[c]	
Drug Accountability	X	X	X	X	

Visit window is +/- 7 days during the additional expanded extension phase.
[a]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Additional Expanded Extension Phase. *Note: test will be sent home at Week 60/108, Week 72/120 and at Week 84/132 and should be performed once between each visit.

[b] 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.
[c] Only subjects continuing in the Additional Expanded Extension Phase for an additional 48 weeks of Open-Label treatment will be dispensed IP at this visit.

Table 6: Schedule of Assessments and Events – Additional Expanded Extension Phase (returning subjects)

Visit	Abbreviated Baseline Visit[a]	Add'l Exp Ext Wk 4	Add'l Exp Ext Wk 8	Add'l Exp Ext Wk 12	Add'l Exp Ext Wk 24	Add'l Exp Ext Wk 36	Add'l Exp Ext Wk 48 / early term	Wk2 Post last dose
Eligibility Assessments								
Informed Consent	X							
Safety Assessments								
Adverse Event Assessment	X	X	X	X	X	X	X	X
Laboratory Assessments					X		X	
Lab: LFT tests only (ALT, AST, BILI, GGT)		X	X	X		X		
Pregnancy testing[b]				X	X	X	X	
Urine drug test				X	X	X	X	
Physical Exam					X		X	
Physical Measurements				X	X	X	X	
Vital Signs	X			X	X	X	X	X
12-Lead ECG				X	X	X	X	
Concomitant Medication Review	X			X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X	X	X	X
Clinical Outcome Assessments								
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)				X	X	X	X	

Clinical Global Impressions-Severity Scale (CGI-S)				X	X	X	X	
Sheehan Disability Scale (SDS)[c]				X	X	X	X	
Clinical Drug Supply								
Re-enter subject in IWRS	X							
Dispense Study Drug	X			X	X	X	X[d]	
Drug Accountability		X	X	X	X	X	X	

Visit window is +/- 7 days during the additional expanded extension phase.
[a]Abbreviated Baseline Visit is needed for returning subjects who completed dosing in the Additional Expanded Extension Phase < 4 weeks prior to returning to the study and entering the Additional Expanded Extension Phase.
[b]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Additional Expanded Extension Phase. *Note: A test will be sent home at Week 12, 24 and at Week 36 and should be performed once between each visit.
[c] 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.
[d] Only subjects continuing in the Additional Expanded Extension Phase for an additional 48 weeks of Open-Label treatment will be dispensed IP at this visit.

Table 7: Schedule of Assessments and Events – Additional Expanded Extension Phase (all continuing subjects)

Visit	Add'l Exp Ext Wk 60/108/156	Add'l Exp Ext Wk 72/120/168	Add'l Exp Ext Wk 84/132/180	Add'l Exp Ext Wk 96/144/192 or early term	Wk2 Post last dose
Safety Assessments					
Adverse Event Assessment	X	X	X	X	X
Laboratory Assessments		X		X	
Labs: LFT tests only: (ALT, AST, BILI, GGT)	X		X		
Pregnancy testing[a]	X	X	X	X	
Urine drug test	X	X	X	X	
Physical Exam		X		X	
Physical Measurements		X		X	
Vital Signs	X	X	X	X	X
12-Lead ECG	X	X	X	X	
Concomitant Medication Review	X	X	X	X	X
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X
Clinical Outcome Assessments					
Yale-Brown Obsessive Compulsive Scale (Y-BOCS)	X	X	X	X	
Clinical Global Impressions-Severity Scale (CGI-S)	X	X	X	X	
Sheehan Disability Scale (SDS)[b]	X	X	X	X	
Clinical Drug Supply					
Dispense Study Drug	X	X	X		
Drug Accountability	X	X	X	X	

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

[a]In addition to urine pregnancy tests conducted at each study visit, subjects will be provided with urine pregnancy tests to take in between every 3-month office visit during the Additional Expanded Extension Phase. *Note: test will

be sent home at Week 60/108/156, Week 72/120/168 and at Week 84/132/180 and should be performed once between each visit.
[b] 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 42. The purpose of the Screening Visit is to ensure that the appropriate patients are entered into the trial. Screening can be as short as 2 days as long as the subject has been on at least 8 weeks of their current SOC OCD therapy at an adequate dose at Screening and at least 10 weeks of their current SOC OCD therapy (SSRI, clomipramine, venlafaxine or desvenlafaxine) at an adequate dose by the baseline visit. The investigator will determine that the patient meets eligibility criteria and will collect demographic and medical data presenting a full characterization of the patient. 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 370 subjects will enter the screening 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 for randomization.

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 (200 mg QD) or placebo (QD) (in a 1:1 ratio) in addition to their SOC medication. Subjects will receive 140mg or placebo for the first four (4) weeks and will then be increased to 200mg or placebo for the duration of the study. Down titration to 140 mg will only be allowed to address tolerability issues

Dosing will continue for 12 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). Telephone calls will be made to the subject at the week 2 and 6 time points during this phase. The purpose of the telephone call is to check on the subject's symptoms, any new concomitant medications and the possibility of adverse events.

Subjects completing the Randomization Phase will be offered approximately 96 weeks of open-label treatment as long as the PI believes open-label treatment offers an acceptable risk-benefit profile.

- Subjects should take their medication in the mornings. If tolerability issues arise please refer to Section 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 226 subjects will enter this phase of the trial.

Every effort should be made to conduct the Week 12 visit and maintain the +/- 2 day window. However, due to concerns related to the COVID-19 pandemic, the Week 12 visit window may be modified beyond the +/- 2 day window, in order to minimize any potential risks to study participant safety and to comply with governmental and local institutional guidance (e.g., study site has a policy that a clinical research visit must be delayed) note the following guidance. Under these circumstances, the visit window may be extended (up to a maximum treatment duration of 18 weeks), but every attempt should be made to conduct the visit as close to the date the visit is due as possible. If the visit window is modified, and the investigator determines that a remote visit offers an acceptable risk-benefit approach and is appropriate for a particular subject, participants should be evaluated remotely (e.g., via phone) at the time of the scheduled Week 12 visit to perform and document appropriate safety assessments. If the remote visit requires laboratory testing, local labs must be able to be obtained and reviewed by the site. Study medication may be sent to the participant via tracked and certified courier. For any such cases, the investigator should discuss the specific circumstances of each case with the sponsor medical monitor.

Sponsor Medical Monitor

PPD PPD

Cell: PPD

PPD

4.3.3 Extension Phase

Subjects will have visits in the Extension Phase every four weeks through Week 12 and then every 12 weeks thereafter up to Week 48. All subjects will undergo a termination visit two weeks after the last dose of study drug. Telephone calls will be made to the subject at the week 2 and 6 time points during this phase. The purpose of the telephone call is to check on the subject's symptoms, any new concomitant medications and the possibility of adverse events.

Subjects entering the Extension phase will continue on the same dose that was taken at the end of the Randomization phase. Subjects receiving placebo in the randomization phase will be switched in a blinded manner to 140mg for the first 4 weeks, and will then be increased to 200mg (at the Week 4 visit). Down titration will only be allowed to address tolerability issues. All visits starting at week 4 of the Extension Phase will be open-label. Subjects who enter the Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension Week 4 at PI discretion. If a subject has to delay the Randomization Phase Week 12 visit due to concerns about COVID-19, the site should contact the Sponsor immediately upon learning about the cancelation so that the Sponsor can provide instruction on providing study drug. Subjects will not be allowed to transition to the Extension Phase until they have an in-person Week 12 visit.

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

4.3.4 Expanded Extension Phase (if applicable)

Subjects who complete the initial 48 week Extension Phase and are continuing directly into the Expanded Extension Phase with no dose interruption will have visits every 12 weeks until Week 96 of the Expanded Extension Phase. Subjects who previously completed the initial 48 week Extension Phase and who have left the study will have the opportunity to re-enter the study provided it has not been more than 3 months since completing the study. Returning subjects who have been off study medication for less than 4 weeks, will have an abbreviated Baseline visit before re-entering the study. Those who have been off study medication for 4 weeks or more will undergo a full Baseline Visit. In addition, for returning subjects, safety laboratory assessments will be performed 4 and 8 weeks after re-starting study medication. Thereafter, study visits in the Expanded Extension Phase will be every 12 weeks until Week 48. Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Expanded Extension Phase. There is a visit window of +/- 7 days during this phase of the study.

4.3.5 Additional Expanded Extension Phase (if applicable)

Subjects who complete the 48 week Expanded Extension Phase and are continuing directly into the Additional Expanded Extension Phase with no dose interruption will have their first visit 12 weeks after the 48th week of the Expanded Extension (EE Week 96 or EE Week 48 as identified in Protocol version 08). Thereafter, subjects will undergo visits every 12 weeks until Week 96/144/192 of the Additional Expanded Extension Phase. Subjects who previously completed the Expanded Extension Week 48/96 and who have left the study will have the opportunity to re-enter the study and receive an additional 48 weeks of open label treatment provided it has not been more than 4 weeks since completing the study. Returning subjects will have an abbreviated Baseline visit before re-entering the study. In addition, for returning subjects, safety laboratory assessments will be performed 4 and 8 weeks after re-starting study medication. Thereafter, study visits in the Additional Expanded Extension Phase will be every 12 weeks until Week 96. Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Additional Expanded Extension Phase. There is a visit window of +/- 7 days during this phase of the study.

All subjects will undergo a termination visit two weeks after the last dose of study drug.

4.4 Post Study Access to Therapy (if applicable)

There is an extension phase, an expanded extension phase and an additional expanded extension phase of this trial for up to 192 weeks of open-label treatment as described in Sections 4.3.3, 4.3.4 and 4.3.5. No other study drug access is available after the extension.

5 POPULATION

5.1 Number of Subjects

Approximately 226 subjects are expected to be randomized in this study.

5.2 Inclusion Criteria

5.2.1 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.

5.2.2 Age and Sex

a. Male and female outpatient subjects between the ages of 18 - 65, inclusive.

5.2.3 Target Population

a. Primary diagnosis of obsessive-compulsive disorder (OCD) as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition as confirmed by the MINI at Screening; The duration of the subject's illness must be ≥ 1 year;

b. Subjects must be currently experiencing non-response or inadequate response to their current Standard of Care (SOC) medication defined as:

1. Subjects Y-BOCS total score must be ≥ 19 at Screening and Baseline, reflecting moderate or severe OCD symptoms.

2. Subjects must currently be on a selective serotonin reuptake inhibitor (SSRI) or clomipramine, venlafaxine or desvenlafaxine monotherapy treatment for an adequate duration and at an adequate dose defined as:

a. Adequate Duration: At least 8 weeks at screening and 10 weeks of SSRI, clomipramine, venlafaxine or desvenlafaxine at Baseline.

b. Adequate Dose: Defined by the USPI labeling. Refer to table below:

Generic	Brand	Class	Dose Range[3]
Citalopram[1,2]	Celexa	SSRI	20-40mg
Escitalopram[2]	Lexapro	SSRI	10-20mg
Fluoxetine	Prozac	SSRI	20-60mg
Fluvoxamine	Luvox	SSRI	100-300mg
Paroxetine	Paxil	SSRI	40-60mg
Sertraline	Zoloft	SSRI	50-200mg
Clomipramine	Anafranil	TCA	100-250mg
Venlafaxine[2]	Effexor XR	SNRI	75-225 mg
Desvenlafaxine[2]	Pristiq	SNRI	50 mg

[1]Doses above 40 mg/day
Citalopram are not recommended due to the risk of QT prolongation. 20 mg/day of citalopram is the maximum recommended dose for patients who are greater than 60 years of age, subjects with hepatic impairment, and for CYP219 poor metabolizers or those subjects taking cimetidine or another CYP2C19 inhibitor.
[2]Citalopram, escitalopram, venlafaxine, and desvenlafaxine are not FDA approved for OCD. APA guidelines for OCD include the use of citalopram, escitalopram and venlafaxine. Doses listed are for major depressive disorder.

[3] Higher doses of SSRI (except for citalopram), clomipramine, venlafaxine or desvenlafaxine are allowed provided the dose has been stable, is well tolerated and there are no safety concerns. This assessment should be documented in the source document.

c. Subjects must be on stable doses of other psychotropic medication (with exclusions specified below) for at least 12 weeks prior to screening;

d. CGI-S score of ≥ 4 at screening and baseline;

e. Determined by the investigator to be medically stable at baseline/randomization as assessed by medical history, physical examination, laboratory test results, and electrocardiogram testing. Subjects must be physically able and expected to complete the trial as designed;

f. Minimum of 6 years of education or equivalent and sufficiently fluent in English to complete necessary scales and understand consent forms;

g. Subjects must have adequate hearing, vision, and language skills to perform neuropsychiatric testing and interviews as specified in the protocol;

h. 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;

i. 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);

j. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test prior to dosing at Baseline;

k. 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

5.3.1 Target Disease Exceptions

a. Subjects should be excluded with a history of more than two (2) previous failed treatment trials of SSRIs, clomipramine, venlafaxine, or desvenlafaxine, (not including the current SSRI trial) given for an adequate duration at an adequate dose as defined by the following criteria taken from the MGH-TRQ-OCD as:

   i. Treatment failure / non-response: As per the MGH-TRQ-OCD, there has been minimal or no meaningful clinical benefit as perceived by the patient despite an adequate dose and duration of treatment;

   ii. Adequate duration: At least 10 weeks of treatment with SSRI, clomipramine, venlafaxine or desvenlafaxine

   iii. Adequate dose: Defined by the USPI labeling. Refer to the table below:

Generic	Brand	Class	Dose Range[3]
Citalopram[1]	Celexa	SSRI	20-40mg
Escitalopram[1,2]	Lexapro	SSRI	10-20mg
Fluoxetine	Prozac	SSRI	20-60mg
Fluvoxamine	Luvox	SSRI	100-300mg
Paroxetine	Paxil	SSRI	40-60mg
Sertraline	Zoloft	SSRI	50-200mg
Clomipramine	Anafranil	TCA	100-250mg
Venlafaxine	Effexor XR	SNRI	75-225 mg
Desvenlafaxine	Pristiq	SNRI	50 mg

[1]Doses above 40 mg/day of citalopram are not recommended due to the risk of QT prolongation. 20 mg/day of
Citalopram is the maximum recommended dose for patients who are greater than 60 years of age, subjects with hepatic impairment, and for CYP219 poor metabolizers or those subjects taking cimetidine or another CYP2C19 inhibitor.
[2]Citalopram, escitalopram, venlafaxine, and desvenlafaxine are not FDA approved for OCD. APA guidelines for OCD include the use of citalopram, escitalopram and venlafaxine. Doses listed are for major depressive disorder.
[3] Higher doses of SSRI (except for citalopram), clomipramine, venlafaxine or desvenlafaxine are allowed provided the dose has been stable, is well tolerated and there are no safety concerns. This assessment should be documented in the source document.

b. Subjects should be excluded at screening or baseline if any medical or psychiatric condition other than OCD, as specified in the inclusion criteria, could predominantly explain or contribute significantly to the subjects' symptoms or that could confound assessment of OCD symptoms;

c. MMSE score of < 24 at Screening;

d. Current or prior history, per DSM-5 criteria, of bipolar I or II disorder, schizophrenia or other psychotic disorders, schizoaffective disorder, autism or autistic spectrum disorders, borderline personality disorder, antisocial personality disorder, body dysmorphic disorder, hoarding disorder (symptoms of hoarding disorder as part of the OCD diagnosis are allowed, but a primary diagnosis of hoarding disorder is excluded); a current diagnosis of Tourette's disorder is also excluded;

e. Any eating disorder within the last 12 months;

f. Primary active major depressive episode or primary active anxiety disorder within the past 6 months. Note: Subjects on a stable maintenance dose of a non-tricyclic, non-monoamine oxidase inhibitor (MAOI) antidepressant medication may be eligible if the subject has been treated with a stable dose for at least 3 months prior to randomization and no dose changes are expected throughout the randomization phase of the study;

g. Acute suicidality or suicide attempt or self injurious behavior in the last 12 months.

h. Score of >0 on the Sheehan Suicidality Tracking Scale for the period of 6 months prior to screening and at baseline;

i. Brown Assessment of Beliefs (BABS) score >17 at screening and baseline;

j. 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;

k. History of psychosurgery, Deep Brain Stimulation (DBS) or Electroconvulsive Therapy (ECT).

5.3.2 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;

c. Prior or current general medical condition that may confound ability to interpret safety and efficacy results as determined by the Investigator;

d. Clinical history of stroke, seizure disorder, traumatic brain injury with ongoing sequelae.

e. Body mass index >40 kg/m2;

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

g. 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;

h. 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;

i. Any unstable cardiovascular (includes uncontrolled hypertension), pulmonary, gastrointestinal, or hepatic disease 30 days prior to screening;

j. End-stage cardiovascular disease (e.g., Congestive Heart Failure New York Heart Association/CHF NYHA Class III or IV or unstable angina);

k. Positive syphilis serology including rapid plasma reagin [RPR] test and positive confirmatory testing;

l. History of chronic pulmonary disease or chronic pulmonary symptoms;

m. 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;

n. History of medically significant gastrointestinal (GI) illnesses including:

i. A current diagnosis of active, peptic ulceration or gastrointestinal bleeding within the last 6 months and/or chronic inflammatory bowel disease at screening;

ii. A history of any gastrointestinal surgery that impacts the absorption of study drug;

iii. Chronic or frequent episodes of loose stools;

o. 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.

p. Women who are pregnant or breastfeeding.

5.3.3 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/ 1.73m^2; The MDRD estimation is calculated as follows: eGFR (mL/min/1.73m^2) = 175 x (standardized Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if Black). [Scr: Standardized serum creatinine];

ii. Creatinine ≥ 2 mg/dL

g. Hematologic abnormalities at screening:

i. Hemoglobin < 10 g/dL; or

ii. WBC < 3.0 x 10^3/mm^3; or

iii. Platelet count < 100,000/mm^3.

h. Human Immunodeficiency Virus (HIV) positive at screening (indicated by positive confirmatory Western Blot);

i. HBsAg or HCV positive at screening;

j. QTcF (Fridericia) interval ≥ 470 msec during the screening or 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.

5.3.4 Prohibited Treatments and/or Therapies

a. Behavioral therapy (cognitive behavioral therapy or exposure response prevention therapy) for OCD that has been initiated within 3 months prior to screening and expected to change during the 12-week treatment period (note: Changes in behavioral therapy during the open label phase are acceptable after Extension (or Expanded Extension) week 4);

b. Previous treatment with riluzole; if subject is re-entering the study in the Expanded Extension Phase, then no use of riluzole within 12 hours of starting troriluzole.

c. Use of tricyclic antidepressants and mono-amine-oxidase (MAO) inhibitors are prohibited 30 days prior to randomization (baseline visit) and during the study (with the exception of clomipramine);

d. Use of a stimulant, neuroleptic (antipsychotic), mood stabilizer and glutamate agent (e.g. topiramate, lamotrigine, N- acetylcysteine, ketamine, memantine, sodium valproate) is prohibited within the 4 weeks prior to screening and during the study;

e. The use of a depot neuroleptic is prohibited 6 months prior to randomization (baseline visit);

f. Use of varenicline (Chantix) is prohibited 30 days prior to randomization (baseline visit) and during the randomization phase of the study;

g. Current daily anxiolytic or benzodiazepine use is prohibited Note: Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing prn are allowed as are non-benzodiazepine hypnotics for sleep if used prn, and low dose benzodiazepines (Ativan up to 1 mg/day or approximately equivalent benzodiazepine) for sleep or anxiety if used at a stable dose prn for at least 3 months prior to screening;

h. Herbal medication and herbal supplement use within 30 days of randomization and during the course of the study is prohibited;

i. Transcranial Magnetic Stimulation (TMS) is prohibited within three months prior to screening and during the study.

5.4 Prohibited Concomitant Medication

Prior use of riluzole is prohibited

The use of the following medications is prohibited 30 days prior to randomization (baseline visit) and during the ENTIRE study. Subjects should have no plans to start these medications during the study:

- Medical or recreational marijuana
- Cannabidiol (CBD) oil
- Tricyclic antidepressants (with the exception of clomipramine)
- Monoamine-oxidase (MAO) inhibitors

The use of the following medications is prohibited 4 weeks prior to screening and during the study: stimulants, neuroleptics, mood stabilizer and glutamate agents (e.g. topiramate, lamotrigine, N- acetylcysteine, ketamine, memantine, sodium valproate).

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, Section 17.2):

- 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, sulfaszalzine) which may increase the risk for hepatotoxicity

Note: fluvoxamine (CYP1A2 inhibitor) is allowed. A prior study in OCD used riluzole as adjunctive treatment to fluvoxamine [4]. Oral contraceptives which contain ethinyl estradiol (CYP1A2 inhibitor) are also allowed.

Subjects entering this study must have been on a standard of care medication, defined as an SSRI, clomipramine, venlafaxine or desvenlafaxine, for their OCD. They must have been on a stable therapeutic dose of this medication with an inadequate response for at least 8 weeks at screening and at least 10 weeks at baseline. No changes in the dose of the SSRI, clomipramine, venlafaxine or desvenlafaxine are allowed throughout the Randomization Phase of the study.

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 such as:

- 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. Ativan (up to 1 mg/day) or equivalent benzodiazepine for sleep and anxiety is allowed if used prn at a stable dose for at least 3 months prior to screening. 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.

The dose of the SOC should not be changed during the Randomization Phase of the trial. The SOC dose may be changed during the Extension (or Expanded Extension) Phase if needed but no sooner than after twelve weeks of treatment during the Extension (or Expanded Extension) phase. Subjects who enter the Extension (or Expanded Extension) Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension (or Expanded Extension) Week 4 at PI discretion.

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; and, (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 adversely affect assessment of safety or efficacy.

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

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

Any new medications initiated during the study should also be consistent with the USPI for the standard of care SSRI and other concomitant medications taken by the subject.

Lorazepam up to 1 mg/day (or equivalent benzodiazepine) can be used prn during the Extension (or Expanded Extension) Phase when clinically required per investigator judgement. Subjects should be encouraged to avoid taking these medications within 8 hours of scheduled efficacy assessments.

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

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 (140 mg and 60 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 Massachusetts General Hospital-Treatment Response Questionnaire for OCD (MGH-TRQ-OCD)

The MGH-TRQ-OCD is a clinician rated questionnaire used to assess the subject's response to standard of care treatment for OCD at screening. The subject must have an inadequate response to the standard of care treatment, as defined in the protocol, as documented on the MGH-TRQ-OCD at screening.

7.2 Mini Mental State Examination (MMSE)

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

7.3 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 OCD and assess for the presence of other major psychiatric conditions.

7.4 Borderline Personality Disorder Module (BPD)

The Borderline Personality Disorder Module is a structured interview that will be conducted at screening to confirm the diagnosis of Borderline Personality Disorder.

7.5 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 OCD severity. A SAFER pass is necessary for randomization. It 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.

7.6 Medical History

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

7.7 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.

7.7.1 Vital Signs and Physical Measurements (Height and Weight)

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

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

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

2. A subject should void just prior to being weighed;

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

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

7.7.2 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.

7.7.3 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.

7.7.4 Laboratory Assessments

Laboratory testing will include the following:

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

b) Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, BUN, uric

acid, and pregnancy testing (WOCBP). Additionally, at screening, total cholesterol, LDL, HDL, triglycerides, folate, HbA1C, P-Amylase or Lipase, TSH, and T4;

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

d) Serum pregnancy test will be conducted at screening. 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 every 3-month office visit during the Extension (and Expanded Extension) Phase;

e) HBsAg, HCV, HIV antibody detection, and RPR (reflex testing will be done for any positive RPR) will be performed at screening.

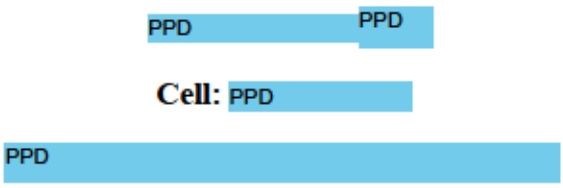
f) Urine Drug Screen for cannabis (medical and recreational), amphetamines (including

MDMA/ecstasy), cocaine, barbiturate, PCP, benzodiazepines, tricyclic antidepressants, and/or opiates at screening and baseline. Reflex confirmatory testing will be conducted on all positive urine drug screen samples.

Any lab value outside of the normal range must be brought to the attention of a physician (Investigator or Sub-Investigator) at the site. The Investigator will indicate whether or not a flagged value is of clinical significance. In addition, if warranted repeat labs can be drawn.

If a participant is unable to come in to the study site and needs to have safety labs conducted locally this is acceptable. The study site should provide the participant or local laboratory with a requisition and should collect the results. When results are obtained, in addition to entering them into the EDC, the site should redact the report of all patient identifying information and send the results directly to the Sponsor Medical Monitor.

Sponsor Medical Monitor



7.7.4.1 BDNF and proBDNF Blood Sample Collection

A biomarker sample will also be collected for plasma brain-derived neurotrophic factor (BDNF) and proBDNF. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that regulates synapse development and plasticity. It is secreted from target cells in an activity-dependent manner and is initially synthesized as a precursor (proBDNF), which is proteolytically processed

into mature factor. Measurement of both forms of neurotrophic factor may provide an assessment of potential effects of troriluzole on synaptic plasticity.

Samples should be collected via antecubital venipuncture between the hours of 10 am and 2 pm, to minimize potential diurnal variability. Serum will be collected at the admission (baseline), and Week 12 of the Randomization Phase in all subjects. If subjects enter the Extension Phase of the study, a BDNF sample will be collected at Week 48 of the Extension Phase. BDNF samples are not collected in the Expanded Extension Phase. A blood sample (5 mL) will be collected in anticoagulant-free tubes and kept at room temperature for 30 minutes, and then spun to isolate serum at 1000g Å~ 15 min at room temperature. Serum will be collected and kept at -20°C before shipping on dry ice.

7.7.4.2 Pharmacokinetics

A pharmacokinetic sample will be collected at Week 4, Week 8, and Week 12 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 visits and 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 4 and Week 8 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 that could possibly be drug-related or severe AEs that could be drug-related.

7.7.4.3 Pharmacogenetics

A pharmacogenetics blood sample will be obtained at baseline and end of study (Week 12 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.

7.7.4.4 Pregnancy Testing

Pregnancy testing should be performed on all women of childbearing potential (WOCBP) during both the Randomization Phase and Extension Phase of the study. Refer to the Schedule of Assessments/Time & Events for detailed time points in which serum pregnancy tests and urine pregnancy tests are required. Urine pregnancy testing may also be done at the discretion of the Investigator at any time during the study. Subjects should not continue in the study if the pregnancy test is positive at any time.

7.7.4.5 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 the Week 4 or Week 8 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
    - Ebstein-Barr virus serology

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

Entry into the Extension (or Expanded 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 12 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.

7.7.5 Sheehan Suicidality Tracking Scale (Sheehan STS)

The Sheehan STS (S-STS) is a prospective, patient self-reported or clinician administered rating scale that contains 16 questions to track both treatment-emergent suicidal ideation and behaviors [46,47]. 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.

7.8 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 Y-BOCS prior to other clinical / safety outcome assessments, followed by the other clinical outcome assessments.

7.8.1 Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

The Y-BOCS is a clinician-administered scale used extensively in research and clinical practice to both rate severity of OCD and to monitor improvement during treatment. It is designed to rate the severity of obsessions and compulsions as well as the type of symptoms in patients with OCD. The scale consists of 10 items, the first 5 items assess obsessions and the last 5 items assess compulsions. Subscale scores can be calculated for obsessions and compulsions, each on a scale of 0 – 20. A total score ranging from 0 – 40 can then be correlated to overall severity. The Y-BOCS Symptom Checklist will be used as an aid for identifying current symptoms.

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

7.8.2 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.

7.8.3 Clinical Global Impression – Severity Scale (CGI-S)

The CGI-S is a clinician rated assessment of the subject's current illness state on a 7 point scale. A higher score is associated with greater illness severity. The CGI-S will be conducted at screening and baseline and subsequent study visits as indicated in the Schedule of Assessments and Events.

7.8.4 Brown Assessment of Beliefs Scale (BABS)

The BABS is a semi-structured, rater-administered scale that assesses insight/delusionality both dimensionally (as a continuum of insight) and categorically (i.e., dichotomously – for example, delusional vs. nondelusional) regarding patient beliefs. These beliefs include the delusions as well as the beliefs that may underlie obsessional thinking. The *BABS* is a 7-item scale that assesses insight/delusionality during the past week.

BABS items assess the person's conviction that their belief is accurate, perception of others' views of the belief, explanation for any difference between the person's and others' views of the belief, whether the person could be convinced that the belief is wrong, attempts to disprove the belief, insight (recognition that the belief has a psychiatric/psychological cause), and ideas/delusions of reference related to the belief. The first six items are summed to create a total score that ranges from 0 to 24; higher scores indicate poorer insight. Item 7 is not included in the total score, because referential thinking is characteristic of some but not all disorders.

7.8.5 Quick Inventory of Depressive Symptomatolgy – Self Report (QIDS-SR)

The QIDS-SR is a self-report, 16 item questionnaire that subjects will use to rate symptoms of depression. Each item is rated 0-3. For symptom domains that require more than one item, the highest score of the item relevant for each domain is taken. Total scores range from 0-27 and are obtained by adding the scores for each of nine symptom domains. Higher scores indicate higher levels of depression.

7.8.6 Beck Anxiety Inventory (BAI)

The BAI is a 21 question multiple choice self-report questionnaire that subjects will use to rate symptoms of anxiety using a 4 point Likert scale. Scores on the BAI range from 0 to 63. Higher scores indicate higher levels of anxiety symptoms.

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 140 mg and 60 mg and matching placebo during the randomization phase.

During the first 4 weeks of extension phase study drug will remain blinded. Subjects who were on troriluzole during the Randomization phase will continue on their same dose during the Extension Phase. Subjects re-entering the study in the Expanded Extension Phase will continue on the same dose as the initial 48 week Extension Phase. All subjects who were on placebo

during the Randomization Phase will receive 140 mg troriluzole for the first four weeks of the Extension Phase followed by 200 mg. troriluzole will be provided as a formulated capsule.

9.1.2 Packaging, Shipment and Storage

Clinical Trial Materials should be stored at controlled temperature between 20°C and 25°C (68°F -77°F), with excursions permitted between 15°C and 20°C (59°F -68°F), 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 140 mg or placebo, QD, for the first four (4) weeks of the Randomization Phase. Subjects will then be increased to 200 mg (provided as one bottle of 140 mg and one bottle of 60 mg) or matching placebo for the duration of the Randomization Phase. Down titration back to 140 mg will only be allowed to address tolerability issues. If a subject down titrates they will need to stay on that dose for the duration of the Randomization Phase.

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

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

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 troriluzole.

In order to maintain the blind of the Randomization Phase and to safely increase all subjects to 200 mg after Extension Phase Week 4, the first 4 weeks of the Extension Phase will remain blinded.

If a subject was on active treatment in the Randomization Phase, they will start the Extension Phase on the same dose that they were taking at Week 12 of the Randomization Phase.

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

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

Subjects who complete the 48-week Extension Phase and will be continuing directly into the 48-week Expanded Extension Phase with no dose interruption will have their first visit 12 weeks after the Extension Week 48 visit. Therafter, subject will undergo visits every 12 weeks until Week 96 of the Expanded Extension Phase as outlined in Table 3 (Schedule of Assessments/Time & Events – Expanded Extension Phase).

Subjects who previously completed the Extension Week 48 visit and exited the study, will have the opportunity to return and receive an additional 48 weeks of open-label treatment with troriluzole in the Expanded Extension Phase provided it has not been more than 3 months since they completed the study and the PI believes it offers an acceptable risk-benefit profile. Returning subjects who have been off study medication for less than 4 weeks will undergo an abbreviated Baseline visit before re-entering the study. Returning subjects who have been off study medication for 4 weeks or more will be required to undergo a full Baseline visit. In addition, for returning subjects, safety laboratory assessments will be performed 4 and 8 weeks after re-starting study medication. Thereafter, study visits in the Expanded Extension Phase will be every 12 weeks until Week 48. All subject will undergo a termination visit two weeks after the last dose of study drug.

Subjects entering the Expanded Extension Phase will continue with the same dose taken at the end of the initial Extension Phase. Down titration after the first four weeks of the Expanded Extension Phase will only be allowed for tolerability purposes. Subjects who enter the Expanded Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg after the first 4 weeks at PI discretion.

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

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, in a 1:1 ratio to receive either placebo (QD) or troriluzole. Treatment assignments will be obtained by the investigator (or designee) via the IWRS system.

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

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

Subjects who complete 12 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, or the Expanded Extension Phase if the subject previously completed the initial 48-Week Extension Phase, left the study, and is re-entering the study within 3 months for an additional 48 weeks of open-label treatment with truriluzole. Investigational sites will access the IWRS at each scheduled study visit throughout the Extension Phase and Expanded Extension Phase) to track patient enrollment. If a subject has to delay the Randomization Phase Week 12 visit due to concerns about COVID-19, the subject should remain on current blinded drug until the subject is in the office. Subjects will not transition to extension phase until completing the Week 12 visit in person. If study site needs to send drug via certified and tracked courier (and this is acceptable to the institution) because an in person visit is not possible due to COVID-19 concerns, this is permissible per study. Site should contact Sponsor for IWRS instructions to dispense blinded drug that may be needed for subjects who are unable to come into the office for Week 12 visit and require drug to be shipped.

Study medication will be assigned via the IWRS system in the Extension Phase (and Expanded Extension Phase). The first 4 weeks of treatment in the Extension Phase will be blinded in order to maintain the blind in the randomization phase. From Extension Phase Week 4 on, the study will be open-label. Sites will be responsible for recording the bottle numbers dispensed to the subject on the Drug Accountability Form provided in the Regulatory Binder, as well as ensure appropriate documentation of dispensation in the subject's medical record. Once a subject completes the Extension Phase (or Expanded 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 (QD) or troriluzole (200 mg QD). Open label troriluzole will be provided during the extension (and Expanded 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 in the morning without regard to meals.

9.2.5 Dose Modifications

Randomization Phase: Subjects will receive 140 mg or Placebo for the first four (4) weeks and will then be increased to 200 mg or placebo for the duration of the study. Down titration to 140 mg will be allowed after Week 4, only in order to address tolerability issues. If a subject is down titrated they will need to remain at 140 mg for the remainder 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 140 mg for the first 4 week, and will then be

increased to 200 mg (at the Week 4 visits). Down titration to 140 mg will only be allowed to address tolerability issues. Subjects who enter the Extension Phase on 140 mg due to tolerability issues can be rechallenged to increase to 200 mg beginning at Extension Week 4 at PI discretion. All visits after week 4 will be open-label. Subjects re-entering the study in the Expanded Extension Phase will continue on the same dose as the initial 48 week Extension Phase.

For subjects who do not tolerate their study treatment (140 mg or 200 mg), the investigator may permit them to switch to night time dosing if there is reason to believe that may help tolerability. Any such changes must be documented by the investigator. If the subject is receiving 140 mg 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 randomization vendor, and pharmacovigilance role may be unblinded before data are more generally unblinded after the Randomized Phase of the study. Except as noted above, other members of the BHV research team will remain blinded.

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 Phase), discontinuation of the subject from the trial should be considered.

If the study site needs to send drug overnight via certified and tracked courier and this is acceptable to the institution because a visit is absolutely not possible to be completed due to the COVID-19 pandemic, this is permissible per study. The Sponsor should be consulted prior to shipping drug.

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

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).

- North America: PPD

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

- North America: PPD

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

SAE Telephone Contact: PPD PPD PPD (Appendix I, Section 17.1)

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 extension phase will be analyzed separately. For patients 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 226 randomized subjects. This accommodates for lost subjects, and is based on the rationale that follows.

Pittenger (2015), based on a 12 week study, concluded that riluzole produced an effect size (Cohen's d) of 0.45 in outpatients. An analysis of the Pittenger data found the correlations between baseline Y-BOCS and the Y-BOCS 8, 10 and 12 weeks, in outpatients, were 0.50, 0.45 and 0.68 respectively.

Pittenger's results are consistent with those from Emamzadehfard's (2016) study, in which riluzole produced an effect size of 0.59 at Week 10. Based on statistics presented in that 2016 paper, the correlation between baseline and Week 10, on the Y-BOCS, appears to be roughly 0.18. In both studies, more than 90% of the randomized subjects completed the study.

Assuming that no more than 10% of the subjects are lost by Week 12, a sample size of about 113 per arm will yield roughly 101subjects per arm. With an effect size of 0.45, a two-sided alpha of 0.05, and a correlation of 0.2 between baseline Y-BOCS and Week 12 this sample size provides 90% power to detect a difference between the treatment groups.

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 study therapy and provided at least one post-baseline efficacy assessment

11.4 Statistical Methods

11.4.1 Demographic and Baseline Characteristics

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

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

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 (when added to a standard of care therapy) 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 Y-BOCS total score troriluzole relative to placebo, at week 12 of the randomization phase. This treatment effect will be summarized as the difference in change from baseline in the Y-BOCS 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 Y-BOCS total score will be analyzed using Mixed Model for Repeated Measures (MMRM) analysis model. The model includes treatment, visit and the

treatment-by-visit interaction as fixed effects, and the baseline value of the Y-BOCS and baseline Y-BOCS by visit interaction as covariates. The covariance structure (SAS "R" matrix) will be initially specified as unstructured. If the model fails to converge, the analyst may try a Huynh-Feldt structure, 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: multiple imputation method using a "jump to reference" approach and a responder analysis with response defined as a 35%, or greater, improvement in the Y-BOCS and with non-completers counted as failures (NC=F). Details of these analyses are provided in the statistical analysis plan.

11.4.3 Secondary Endpoint(s)

Continuous secondary, change-from-baseline, efficacy endpoints will be analyzed using the same methodology as the primary endpoint. Further details on the secondary 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, change from baseline in the total Y-BOCS, 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

Both Pittenger (2015) and Emamzadehfard (2016), in studies similar to the randomized phase of this study, had less than 10% of the subjects fail to complete the study. Hence, we expect less than 10% of the subjects to be lost during the randomized phase of this study. As a sensitivity analysis to assess missing data assumptions of the MMRM model, the missing data will be multiply imputed for the primary endpoint using a jump to reference method. 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 are 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.

AEs are tabulated in all treated subjects. SAEs occurring in subjects enrolled but not treated are listed. Deaths are listed for enrolled subjects without regard to onset.

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

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

11.5 Schedule of Analyses

An initial analysis of the data will be conducted after the last subject completes their Week 12 visit. This will include all data from the double-blind phase of the study, but will not include efficacy data accumulated from 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 phases, and summarize all safety, laboratory and other data collected through the entire study.

Additional analyses may be conducted during the open-label phases 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 and Safety Monitoring Committee

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

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 e) 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. 215 Church Street 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 PPD Biohaven Pharmaceuticals, Inc. PPD New Haven, Connecticut 06510 PPD PPD
Clinical Research Organizations:	PPD PPD CCI PPD 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 randomized, double-blind, placebo-controlled trial of adjunctive troriluzole in Obsessive Compulsive Disorder

Study No: BHV4157-202

Draft Original Protocol Date: 09 Aug 2017

Protocol Version No: V10

Protocol Version Date: 13 Oct 2022

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		
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Medical Lead: PPD PPD PPD Biohaven Pharmaceuticals		
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