BHV4157-303 PROTOCOL V4.0 – US AND CANADA

DRUG:	Troriluzole (BHV4157)
STUDY NUMBER(S):	BHV4157-303
PROTOCOL(S) TITLE:	A Randomized, Double-Blind, Placebo-Controlled Trial of Adjunctive Troriluzole in Obsessive Compulsive Disorder
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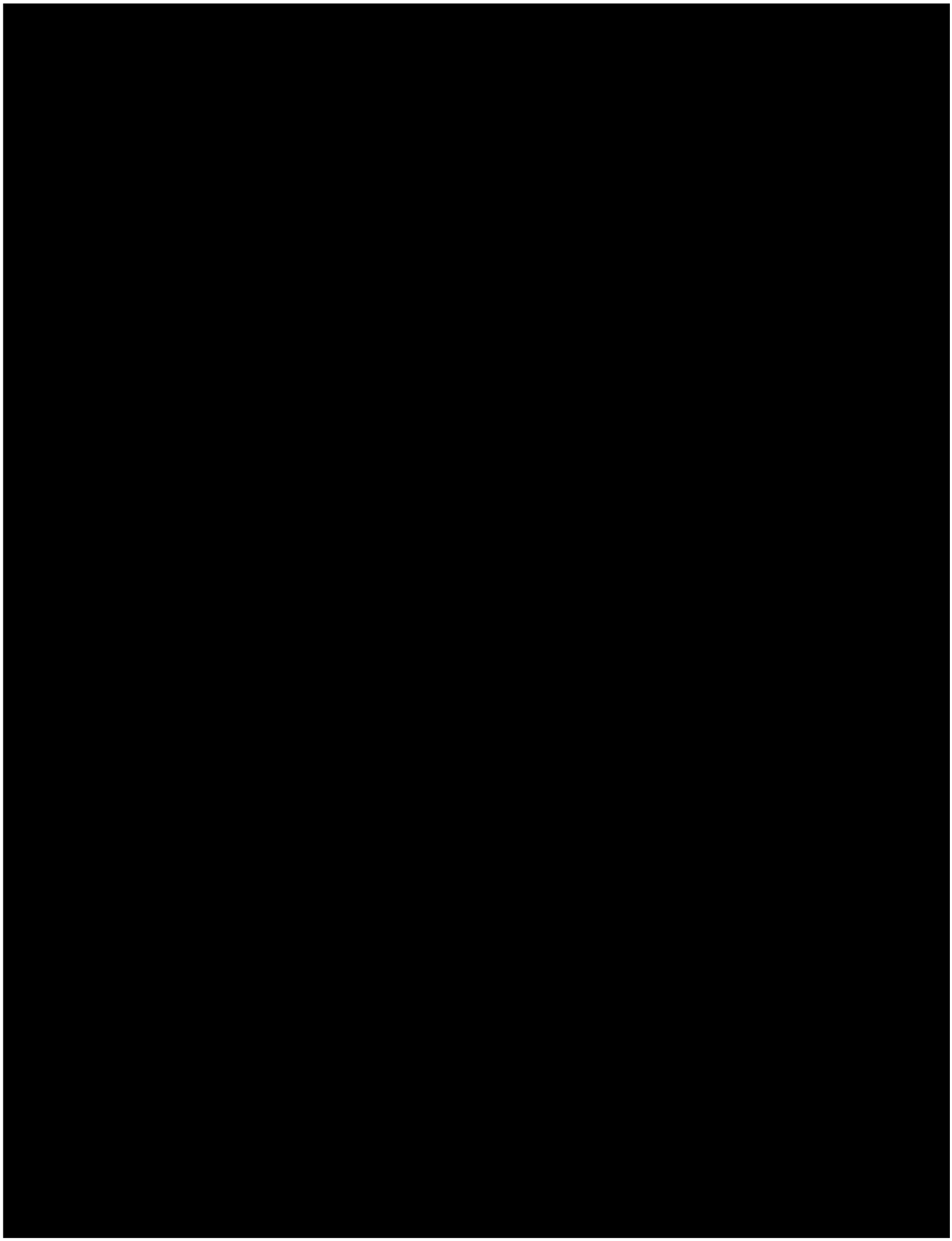

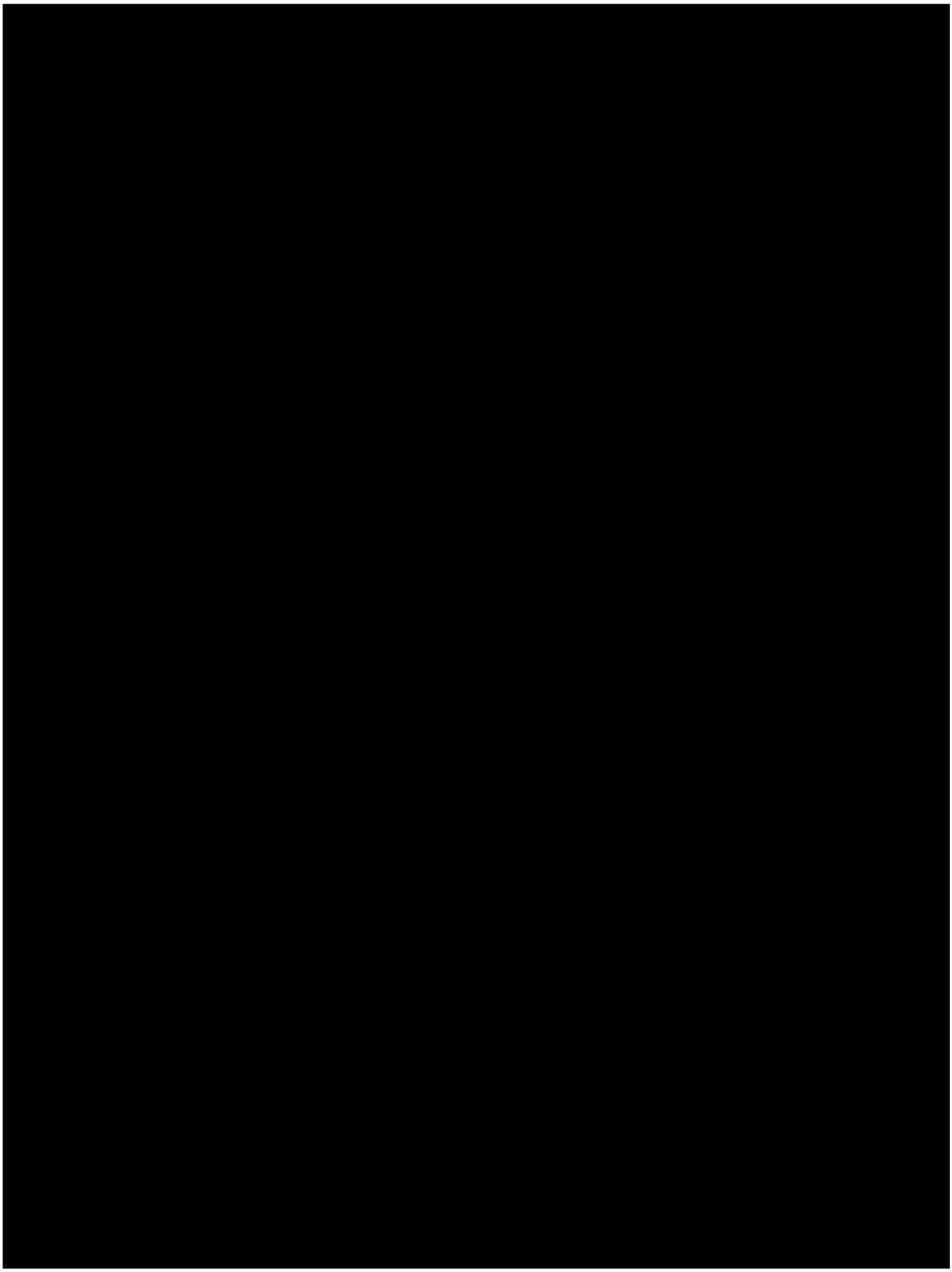

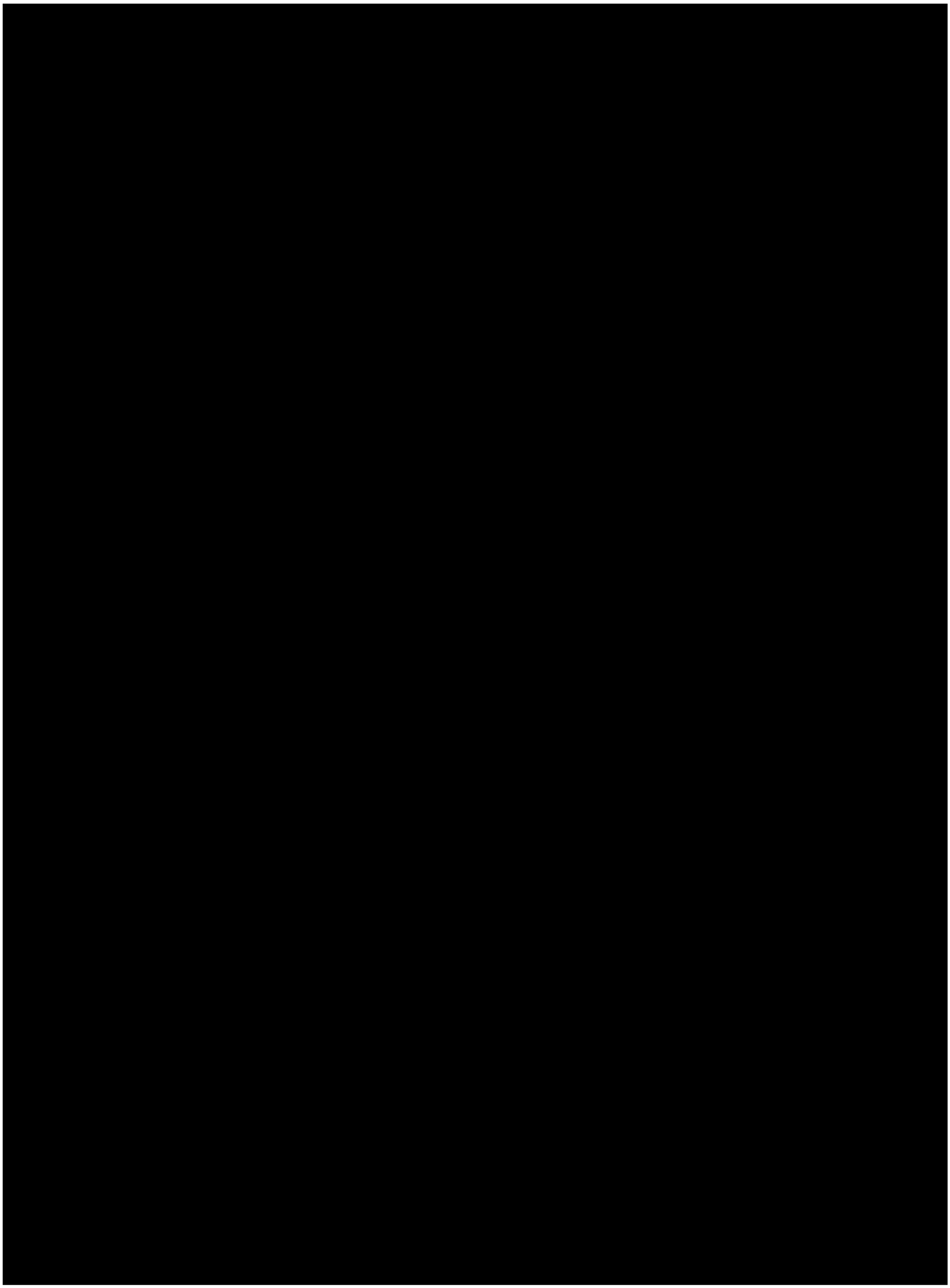

BHV4157-303 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ADJUNCTIVE TRORILUZOLE IN OBSESSIVE COMPULSIVE DISORDER

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 Pharmaceuticals, Inc., 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 Pharmaceuticals, Inc.

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

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Biohaven Pharmaceuticals, Inc. 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

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_____ _____

Date Site Number

STUDY SUMMARY (SYNOPSIS)

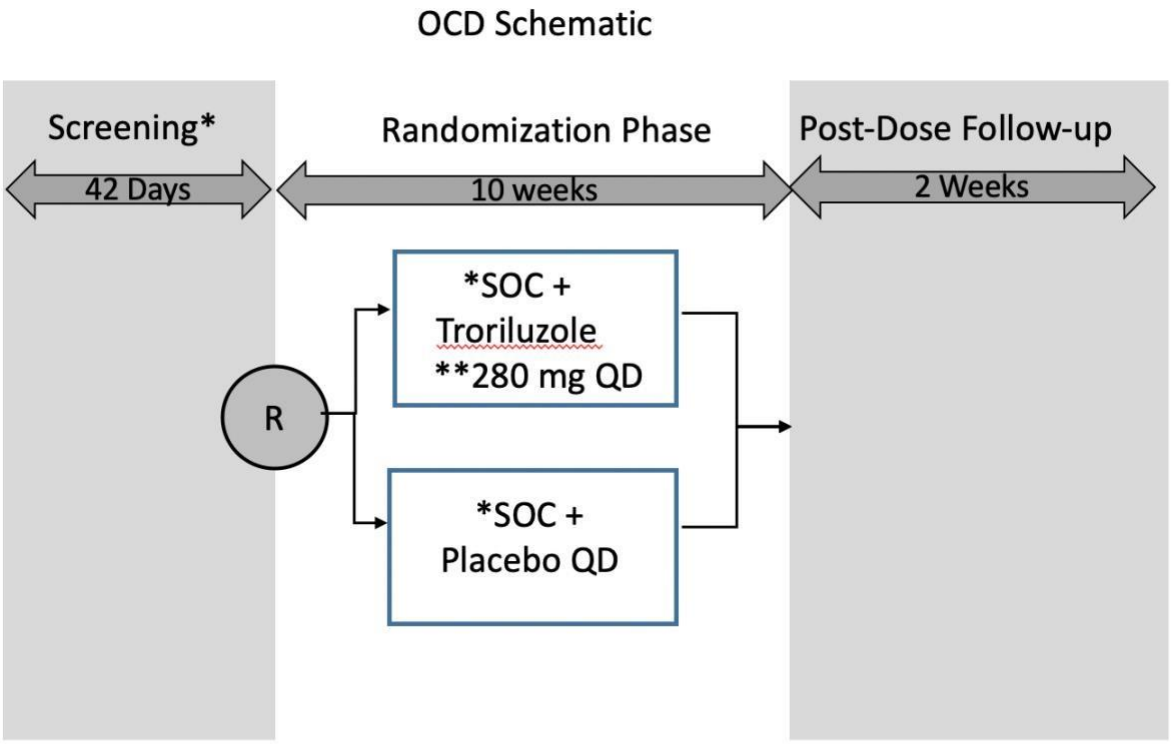
Title:	A randomized, double-blind, placebo-controlled trial of adjunctive troriluzole in Obsessive Compulsive Disorder
Rationale:	First-line treatment for Obsessive Compulsive Disorder (OCD) includes cognitive behavior therapy and selective serotonin reuptake inhibitors (SSRIs). Nonetheless, up to 60% 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.[2-7] 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 [redacted] improved bioavailability, pharmacokinetics and dosing. Riluzole is currently only indicated for Amyotrophic Lateral Sclerosis (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.

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. [2-7] 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 [redacted] for improved bioavailability, pharmacokinetics and dosing. Riluzole is currently only indicated for Amyotrophic Lateral Sclerosis (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 completed Phase 1 studies and preliminary results from recently completed studies of troriluzole, we anticipate the clinical pharmacology of troriluzole 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 [redacted] 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 OCD (confirmed by the MINI) who have had an inadequate response to standard of care (SOC) medication(s). Patients may have failed SOC in the past but must also be having an inadequate response to their current SOC. An inadequate response to their current SOC is defined by a Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 22 or greater despite at least 12 weeks of treatment at Baseline[2] at an adequate dose of their current OCD treatment. Additionally, OCD symptoms in subjects must be present for ≥ 1 year and at least of moderate severity on the Clinical Global Impression Scale severity of illness item.
Number of Subjects:	Up to approximately 700 randomized subjects

Objectives (Primary):	The primary objective of the study is to evaluate the efficacy of troriluzole as adjunctive therapy compared to placebo in subjects with OCD who have had an inadequate response to their current OCD treatment based on the change in their Y-BOCS score.
Objectives (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 Sheehan Disability Scale (SDS) • Evaluate the efficacy of troriluzole compared to placebo on global clinical condition as measured by the Clinical Global Impression Severity Scale (CGI-S);
Study Design:	BHV4157-303 is a Phase 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 SOC treatment in subjects with OCD who failed to respond adequately to their current pharmacotherapy. Current inadequate response is defined by a YBOCS score of 22 or greater despite at least 8 weeks of treatment at screening and at least 12 weeks of treatment at baseline with an adequate dose of an SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine. Subjects who are stable on SOC medication and having an inadequate response (as defined above) will be randomized to additionally receive placebo (QD) or troriluzole (280 mg QD, after two weeks at 200 mg QD). [redacted] The total treatment period will be 10 weeks, after which subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit or if eligible, will participate in the Open Label Extension Study, BHV4157-209. [redacted]

STUDY SCHEMATIC*



*Subjects should have been taking an adequate maximum tolerated dose, as defined in the study Inclusion Criteria, of an SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine for at least 8 weeks prior to Screening and 12 weeks at Baseline.
**Subjects will receive 200mg for the first 2 weeks and then will be increased to 280mg for the duration of the study. Down titration will only be allowed to address tolerability issues. Subjects will return to the clinic 2 weeks after discontinuing study medication for a follow-up safety visit or, if eligible, to enroll in the Open-Label Extension Study BHV4157-209.

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[redacted]

LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BABS	Brown Assessment of Beliefs Scale
BAI	Beck Anxiety Inventory
BCRP	Breast Cancer Resistant Protein
BID	Twice Daily
BP	Blood Pressure
BPD	Borderline Personality Disorder Module of the MINI
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression – Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
Cmax	Maximum Plasma Concentration
CNO	Certificate of Non-Objection
CONMED	Concomitant Medication
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CSTC	Cortico-Striato-Thalamo-Cortical
CYP	Cytochromes P450

DILI	Drug Induced Liver Injury
DOCS	Dimensional Obsessive Compulsive Scale
DSMC	Data and Safety Monitoring Committee
EAATS	Excitatory Amino Acid Transporters
FDA	U.S. Food and Drug Administration
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
E-R	Exposure-Response
GAD	Generalized Anxiety Disorder
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
LFTs	Liver Function Test
m^2	Meter squared
MAD	Multiple Ascending Dose
MDD	Major Depressive Disorder
mg	Milligram

MGH-TRQ-OCD	Massachusetts General Hospital Treatment Response Questionnaire for OCD
min	Minute
MINI	Mini International Neuropsychiatric Interview
mm^3	Millimeters cubed
mmHg	Millimeters Mercury
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Event Level
OAT	Organic Anion Transporter
OCD	Obsessive Compulsive Disorder
OFC	Orbitofrontal Cortex
PK	Pharmacokinetic
PCRS	Placebo-Control Reminder Script
QD	Once Daily
QIDS-SR	Quick Inventory of Depressive Symptomatology- Self Report
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SCA	Spinocerebellar Ataxia
SDS	Sheehan Disability Scale
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SRI	Serotonin Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitor
TEAE	Treatment Emergent Adverse Events
UDS	Urine Drug Screen

ULN	Upper Limit of Normal
USPI	US Package Insert
WHO	World Health Organization
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1 INTRODUCTION AND RATIONALE

1.1 Background

Biohaven Pharmaceuticals, Inc. [Biohaven] is developing a new drug, troriluzole, for the treatment of Obsessive Compulsive Disorder (OCD) as well as for other neurologic and psychiatric disorders. Troriluzole is a novel [redacted] prodrug of the glutamatergic agent riluzole. The FDA originally approved riluzole (RILUTEK®) 50 mg twice-a-day (NDA #20599) 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 [redacted] 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. [5,6,8-18] Additionally, preliminary efficacy findings from BHV4157-202, a proof of concept study, indicate, troriluzole 200 mg, administered once daily as adjunctive therapy in subjects with OCD who had an inadequate response to SOC treatment showed numerically greater improvement versus placebo in the total Y-BOCS score in the randomization phase. 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 Obsessive Compulsive Disorder (OCD).

OCD is a prevalent psychiatric disease, affecting 2-3% of the general population[19]. 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. [20] 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. [21,22] Augmentation strategies with neuroleptic medications can improve the effectiveness of serotonin reuptake inhibitors (SRIs) therapy but do not eliminate OCD symptoms [23,24]. 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.

1.1.1 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. [5,6,8-18] 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 [17]. Further genome-wide association studies have identified the glutamate related SAPAP/DLGAP proteins as additional genes of interest [25,26].

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. [27] 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 [28,29]. 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) [30,31]. Moreover, treatment with an SRI was associated with a significant decline in caudate glutamate concentration in those individuals who responded to SRI treatment. [30-33] These clinical findings are consistent with pharmacological studies demonstrating an SRI-induced inhibition of glutamate release.[34] 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 [34].

Open-label data and small clinical studies also suggest benefit from the glutamate modulator riluzole in individuals with OCD [2,35,36]. In a study by Emamzadehfard[5], 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. Findings from BHV4157-202, a multicenter, randomized, double-blind, 2-arm placebo-controlled parallel-group, proof of concept study conducted in subjects who have had an inadequate response to standard of care (SOC) treatment, showed numerically greater improvement versus placebo in the total Y-BOCS score in the randomization phase. Preliminary efficacy findings indicate, troriluzole 200 mg, administered once daily as adjunctive therapy in this study showed numerically greater improvement versus placebo in the total Y-BOCS score at Weeks, 4, 8, and 12 of the randomization phase. This difference was statistically significant at Week 8 ($p < 0.041$). At Week 12, the improvement in Y-BOCS score was numerically greater in the troriluzole group relative to placebo, but the treatment difference did not reach statistical significance ($p = 0.220$).

1.1.2 Troriluzole

1.1.2.1 Pre-Clinical Studies

Data from preclinical studies support the following findings. Please refer to the Investigator's Brochure (IB) for additional pre-clinical information.

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

[redacted]

1.1.2.2 Clinical Experience

Detailed information is available in the current version of the Investigator Brochure. Troriluzole has been observed to be well tolerated with no clinically relevant safety signals identified in the completed and ongoing clinical studies. The current troriluzole clinical program includes Phase 1 PK studies in normal healthy volunteers (BHV4157-101, BHV4157102, BHV4157-103, BHV4157-104, BHV4157-105, BHV4157-106, BHV4157-107 and

BHV4157-108), Phase 2 or 3 studies in subjects with SCA (BHV4157-201, BHV4157- 206), OCD (BHV4157-202), AD (BHV4157-203) and GAD (BHV4157-207). Overall, the PK and safety profile from the Phase 1 studies support the investigation of troriluzole at doses of 280 mg QD in Phase 2.

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

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

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

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

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

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

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

Troriluzole, will be dosed at 280 mg/day, which contains a comparable molar amount of riluzole as found in a 140 mg dose of riluzole, below the 200 mg daily dose of riluzole that has been studied in frail subjects with Amyotrophic Lateral Sclerosis (ALS) where it was found to be safely administered and generally well tolerated. [37]

1.1.2.2.1 BHV4157 Phase 2 – BHV4157-201 [Spinocerebellar Ataxia (SCA)]

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

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

1.1.2.2.2 Phase 2 - BHV4157-202 [Obsessive Compulsive Disorder (OCD)]

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

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

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

1.1.2.2.3 Phase 2 – BHV4157-203 [Alzheimer's Disease (AD)]

BHV4157-203 is an ongoing Phase 2, multi-center, randomized, double-blind, placebo controlled, parallel group study in subjects with mild to moderate AD. Subjects were randomized (1:1) to receive either troriluzole or placebo for 48 weeks. There was a 2-week fixed titration period with a starting dose of troriluzole 140 mg QD or placebo QD. If there were no issues with tolerability of the study drug during the first 2 weeks of the study, the subjects received two 140 mg capsules (total daily dose of 280 mg) for the remaining duration of the study (46 weeks). Subjects who completed the randomization phase were offered approximately 48 weeks of open-label troriluzole in an extension phase, as per investigator discretion. [38] The randomization phase is complete. The open-label extension phase is ongoing.

Results for the Week 48 co-primary endpoints indicated troriluzole 280 mg, administered once daily as adjunctive therapy on a background of AchEI and/or memantine medication for up to 48 weeks in participants with mild to moderated AD did not statistically differentiate from

placebo on the study's co-primary endpoints, the Alzheimer's Disease Assessment Scale – 11-item cognitive subscale (ADAS-Cog 11) and the Clinical Dementia Rating Sum of Boxes (CDR-Sob).

1.1.2.2.4 BHV4157-206 (SCA)

BHV4157-206 is an ongoing Phase 3, long-term, double-blind, placebo-controlled study in subjects with SCA. Subjects received either troriluzole 140 mg or matching placebo QD for the first 4 weeks, and the dose is increased to troriluzole 200 mg QD or matching placebo QD for the remaining duration of the study (44 weeks). Total study treatment duration is approximately 48 weeks.

The primary objective of this study is to compare the efficacy of troriluzole relative to placebo on ataxia symptoms after 48 weeks of treatment, as measured by the Modified Functional SARA (f-SARA). Subjects are randomized to receive either troriluzole 140 mg QD or matching placebo QD for the first 4 weeks followed by a dose increased to 200 mg QD or matching placebo QD for the remaining duration of the study (44 weeks). Total duration of the randomization phase is 48 weeks. Subjects who complete the randomization phase are offered open-label troriluzole in an extension phase, as per investigator discretion, and the open-label extension phase has been expanded from 48 weeks to 96 weeks. The total anticipated study duration is approximately 144 weeks.

BHV4157-206 is ongoing in the blinded randomization phase, and efficacy data are not available.

1.1.2.2.5 BHV4157-207 [Generalized Anxiety Disorder (GAD)]

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

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

1.1.3 Potential for Drug-Drug Interactions

Troriluzole is rapidly converted to riluzole by aminopeptidases in plasma.

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

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

Summary of CYP substrate and perpetrator potential assessment:

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

In transporter studies:

In conclusion, CYP1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when troriluzole is given concurrently with agents that affect CYP1A2 activity. Potent inhibitors of CYP1A2 (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, vemurafenib) would likely decrease the rate of riluzole elimination, while inducers of CYP1A2 (e.g., cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

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

Potential interactions may occur when troriluzole is given concurrently with other agents which are also metabolized primarily by CYP1A2 (e.g., theophylline, caffeine, and tacrine) and to a lesser extent, CYP2B6; these are however, less likely to be of clinical significance. Currently, it is not definitively known whether riluzole results in clinically significant CYP1A2 or CYP2B6

enzyme induction in humans, although lack of evidence of substantial autoinduction of riluzole metabolism after multiple dosing suggests only modest effects on CYP1A2. Additionally, although the BCRP and OAT3 transporters are inhibited by riluzole in vitro (IC_{50} > 5 µM for both), the magnitude of inhibition at the clinical dose of troriluzole is unlikely to be of clinical significance.

1.1.4 Specific Populations

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

1.1.5 Clinical Adverse Event Profile

1.1.5.1 Troriluzole

As described in the current IB, clinical experience with troriluzole derives from Phase 1 studies in healthy volunteers and a Phase 2b/3 studies in subjects with SCA, OCD, GAD and AD. Single doses up to 200 mg and multiple doses up to 280 mg daily have been well tolerated without evidence of new, clinically significant safety signals or lab abnormalities compared to the Rilutek package label. As described in the current IB, clinical experience with troriluzole during the double-blind randomization phase of study BHV4157-202 at 200 mg QD for 12 weeks was well tolerated in adult subjects with OCD. The randomization phase is complete, and the Week 48 extension phase is ongoing. Preliminary safety findings indicate that troriluzole 200 mg QD for up to 12 weeks appeared to be generally well tolerated.

1.1.5.2 Riluzole

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

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

A recent systematic review and meta-analysis of riluzole clinical trial data from other neurological disease indications showed that treatment with riluzole was well tolerated at doses of up to 200 mg daily. [39] This study analyzed safety data from 9 studies encompassing 1528 randomized patients, with Huntington’s disease, Parkinson’s disease, multiple systems atrophy, progressive supranuclear palsy, and several forms of ataxia.

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

Source: Covis USPI, 2020

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

In the 8 week placebo controlled phase of BHV4157-201 study, there were no subjects who received at least one dose of troriluzole either during the randomization phase or the open-label

extension phase (through 48 weeks) that experienced treatment emergent AST or ALT laboratory abnormalities > 3x ULN, or total bilirubin elevations > 2x ULN.

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

In the BHV4157-203 study, overall, the liver profile of troriluzole was comparable to that of placebo. For most subjects in both treatment groups, the maximum observed LFT measurements were normal at baseline and on treatment. Assessment of maximum observed abnormalities on treatment identified 4 subjects in the troriluzole group with ALT > 3x ULN on treatment (1 with ALT > 5x ULN, and all 4 with normal ALT at baseline) and 1 subject with AST > 3x

ULN on treatment (and normal AST at baseline). None of the placebo-treated subjects had ALT or AST > 3x ULN. One subject in the troriluzole group had total bilirubin > 2x ULN on treatment (with > ULN to ≤ 1.5x ULN at baseline), and 2 subjects in the placebo group had total bilirubin > 2x ULN on treatment, both with elevated total bilirubin at baseline.

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

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

Cases of drug-induced liver injury, some of which were fatal, have been reported in patients taking Rilutek. Asymptomatic elevations of hepatic transaminases have also been reported, and in some patients have recurred upon re-challenge with Rilutek. In clinical studies, the incidence of elevations in hepatic transaminases was greater in Rilutek-treated patients than placebo treated patients. The incidence of elevations of ALT above 5x ULN was 2% in Rilutek-treated patients. Maximum increases in ALT occurred within 3 months after starting Rilutek. About

50% and 8% of Rilutek-treated patients in pooled Studies 1 and 2, had at least one elevated ALT level above ULN and above 3x ULN, respectively. Monitor patients for signs and symptoms of hepatic injury, every month for the first 3 months of treatment, and periodically thereafter. The

use of Rilutek is not recommended if patients develop hepatic transaminases levels greater than 5x ULN. Discontinue Rilutek if there is evidence of liver dysfunction (e.g., elevated bilirubin).

1.1.5.2.2 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.

Cases of severe neutropenia (absolute neutrophil count less than 500 per mm^3) within the first 2 months of Rilutek treatment have been reported. Advise patients to report febrile illnesses.

1.1.5.2.3 Interstitial Lung Disease

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

Interstitial lung disease, including hypersensitivity pneumonitis, has occurred in patients taking Rilutek. Discontinue Rilutek immediately if interstitial lung disease develops.

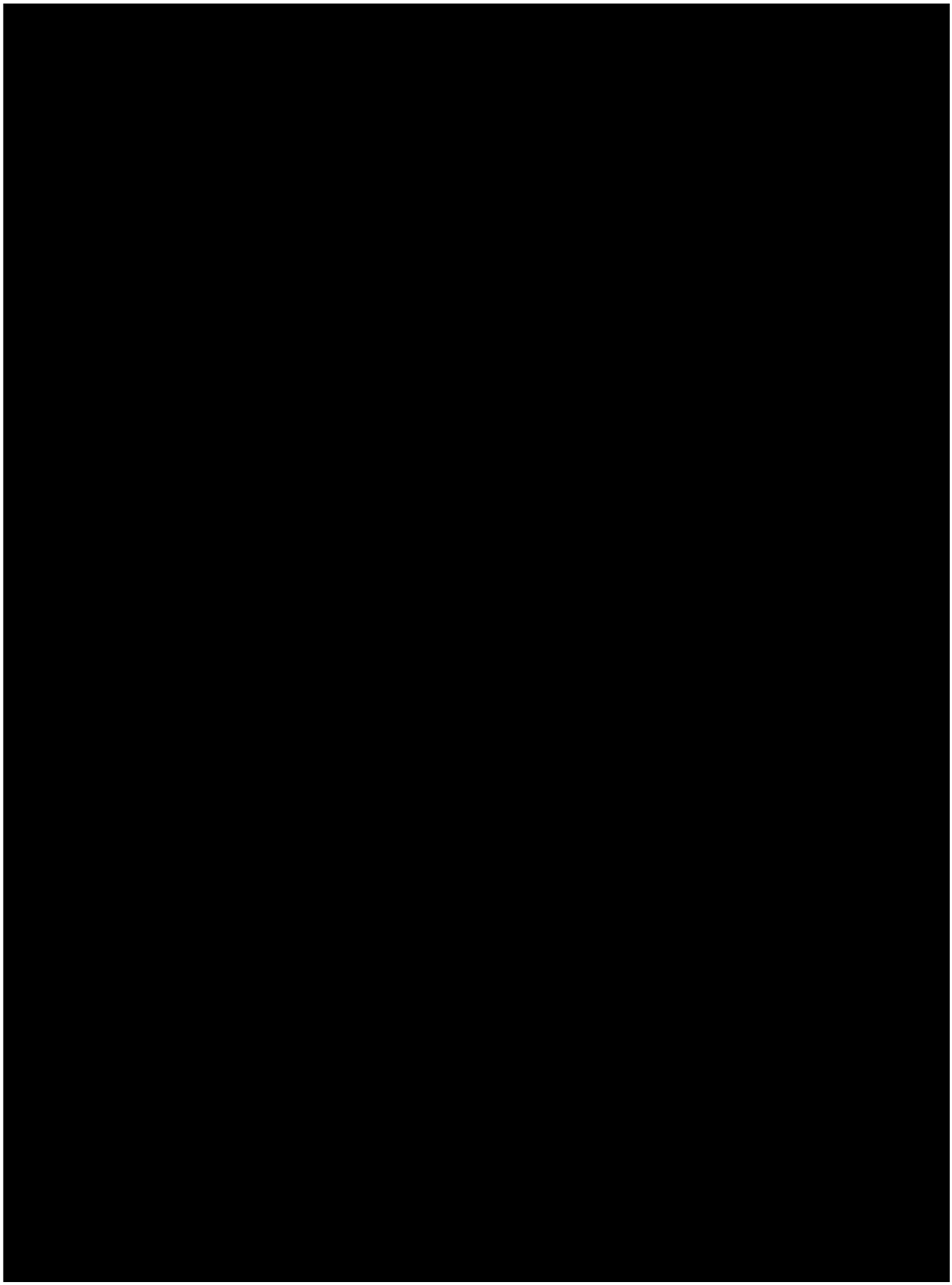
1.1.6 Potential Risk to Fetal Development

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

[redacted]



1.2.2 Standard of Care Pharmacotherapy Rationale

The planned Phase 3 protocols propose to adhere to the APA Guideline recommendations for OCD treatment which includes the use of standard of care background SSRI medications that are approved for the treatment of OCD such as fluoxetine, fluvoxamine, paroxetine, sertraline and clomipramine, as well medications used off-label for the treatment of OCD such as citalopram, escitalopram, venlafaxine and desvenlafaxine.[41] The APA Guidelines state that "although all SSRIs (including citalopram and escitalopram) appear to be equally effective, individual patients may respond well to one and not to another." In addition to the APA OCD Treatment Guidelines, non-labeled SSRI/SNRI medications are clearly noted in the literature as being commonly utilized by healthcare providers for the treatment of OCD.[42] The use of citalopram and escitalopram is also supported by guidelines from professional societies in Canada[43] U.K.[44] Germany[45], and Italy[46] Efficacy and safety of these medications in OCD is also supported by international approvals. Escitalopram is approved in Spain, the U.K., and Canada, and citalopram is approved in Spain.

Correspondingly, the use of all SSRIs, venlafaxine, and desvenlfaxine is supported by real-world evidence. A recent global study surveyed 19 researchers from specialized OCD centers in 15 countries demonstrated that a majority of sites were seeing subjects who were being treated with citalopram, escitalopram, venlafaxine, or desvenlafaxine for their OCD.[47] Of note, both centers in the US saw patients presenting on all of these medications for the treatment of OCD. Additionally, in the Phase 2 study BHV4157-202, approximately [redacted] of subjects were being treated with one of non-labeled SSRI or SNRI medications for OCD at study entrance. Inclusion of medications prescribed in the real-world clinical settings as SOC medications ensures that the Phase III trial results are generalizable to routine clinical care for OCD.

1.2.3 Dose Selection Rationale

The troriluzole dose selected for this study is 280 mg administered once daily following titration from a dose of 200 mg for the first two (2) weeks. Down titration to 200 mg will be allowed after Week 2, only if there are tolerability concerns. This dose has been selected based on safety and

pharmacokinetics as well as response in the treatment of Obsessive-Compulsive Disorder as demonstrated in Study BHV4157-202.

In two Phase 1 studies of BHV-4157 in healthy participants (BHV4157-101 and BHV4157103), doses of up to 280 mg administered once daily were well tolerated with single and multiple doses. A maximum tolerated dose was not identified. Little accumulation of BHV4157 or its active metabolite is expected with once daily dosing. In addition, a randomized, double-blind, placebo controlled study in Alzheimer's disease is currently ongoing with dosing up to 280 mg. Approximately 349 subjects have been treated in this study in a blinded fashion. No significant tolerability issues have arisen to date.

The 280 mg dose of troriluzole is equivalent to 140 mg riluzole on a molar basis. An equivalent molar dose of riluzole has previously been studied in clinical trials in frail participants with amyotrophic lateral sclerosis as well as populations with Obsessive-Compulsive Disorder and Huntington's disease. In these populations, it was found to be safely administered and generally well tolerated. Given the relatively large variability in riluzole exposures observed after riluzole administration, but not with troriluzole, previous experience with oral riluzole suggests that patients tolerate a wide range of exposures; this includes the riluzole C_{max} and AUC that are delivered by 280 mg of troriluzole. On the basis of this PK profile, troriluzole is expected to deliver therapeutic exposures of riluzole that have been demonstrated to be well tolerated and safely administered.

The target exposure of riluzole achieved with troriluzole is expected to provide a more favorable risk-benefit profile than what could be achieved with oral riluzole tablets. That is, troriluzole achieves target exposures with diminished hepatic burden (via [redacted] reduced molar drug load and diminished peak drug concentrations in the liver due to mitigated first pass metabolism). In addition, administration of troriluzole does not require fasting as is required with oral riluzole. Lastly, the delayed Tmax compared of the active metabolite of troriluzole compared to that achieved with oral riluzole tablets adds support to once daily dosing with troriluzole. These features serve both safety/tolerability and patient convenience; this will allow better treatment adherence for a medication that is anticipated to require chronic administration.

Considering the range of exposures from a single troriluzole [redacted] daily dose level in Study [redacted] an exposure-response (E-R) was not apparent in those receiving active treatment for the change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); no E-R relationship was apparent in the overall population nor in those with more severe disease at baseline. The results may suggest that within these exposure ranges, troriluzole doses are at or near maximal drug effect.

Considering the overlap in exposure between [redacted] a dose reduction, if it were to be indicated based on adverse events in the current study, is unlikely to have an effect on the primary efficacy endpoint. The overlap has been assessed by using exposures for [redacted] (for initial 4 weeks) troriluzole and the [redacted] dose studied in [redacted] along with the area under the curve during a dosing interval (AUCtau) at steady state from healthy subjects receiving troriluzole [redacted] once daily in Phase 1 studies [redacted] The percentage overlap between doses has been determined using clinical trial simulations and is demonstrated in Figure 1.

1.3 Research Hypothesis

Troriluzole is superior to placebo as adjunctive therapy when added to standard of care (SOC) treatment over a 10 week period in subjects with OCD with an inadequate response to their current OCD treatment.

1.4 Benefit/Risk

1.4.1 Benefit/Risk Assessment

The current benefit-risk analysis is based on the available data with troriluzole from in-vitro studies, preclinical studies (in rats and monkeys), and clinical studies in healthy subjects as well as patients with OCD, GAD, SCA, and AD. The analysis is supplemented by clinical studies with Rilutek tablets in ALS patients. It is considered that the benefits of evaluating troriluzole as a potential treatment for OCD outweigh the risks. Preclinical safety and toxicology studies are described in Section 1.1.2.1. Please refer to the IB for the comprehensive toxicology data package for BHV-4157.

The clinical experience with troriluzole is described in detail in Section 1.1.2.2. The adverse event profile observed in these clinical studies with troriluzole is described in Section 1.1.5. To date, approximately 1375 subjects were treated with troriluzole or placebo in the Biohaven sponsored troriluzole clinical development program. Approximately 134 healthy subjects, 186 subjects with SCA (including subjects in the extension phase), 175 subjects (including subjects in the extension phase) with OCD, 175 subjects with AD and 348 subjects with GAD or a total of 1018 subjects have been treated with troriluzole, based upon actual exposure data from

completed studies, ongoing open-label studies, and the randomization schemes for ongoing blinded clinical studies.

1.4.2 Exposure

In the 26-week toxicology study with rats, the NOAEL limits for troriluzole was 20 mg/kg for females and 6 mg/kg in males. The only adverse effect was decreased body weight gain in males at 20 mg/kg troriluzole that was considered to be secondary to sedation, a known pharmacological effect of riluzole. The increases in liver weights with no histological correlate are likely an adaptive response to increased drug metabolism, and not considered to be adverse. Doses of troriluzole caused little to no systemic troriluzole exposure. The AUC of riluzole at 20 mg/kg troriluzole in females and 6 mg/kg in males was 43,500 and 11,100 ng*hr/mL, respectively, on Day 182 (Study 73393) represents over 30- and 8-fold the projected therapeutic exposure of the active metabolite riluzole (i.e., based on target AUC exposure of as high as 1,300 ng*hr/mL). In a 9-month toxicology study with cynomolgus monkeys, once daily oral dosing was well-tolerated for 39 weeks up to 20 mg/kg troriluzole, the highest dose tested. At this dose there was little to no systemic exposure of troriluzole; in contrast, Riluzole exposure ranged from 28,500 to 37,900 ng*hr/mL (Study 31131). Pharmacokinetic models developed from in human studies of troriluzole at doses of 140mg, 200mg, and 280mg demonstrate that at of 280mg daily dosing, median expected exposure (AUCtau) is 2,400 ng*hr/mL with 10% percentile and 90% percentile expected exposures at 1,550 and 3,710 ng*hr/mL, respectively.

1.4.3 Safety and Tolerability in Clinical Studies

Overall, troriluzole was well tolerated following administration of single or multiple doses of troriluzole up to 280 mg (2 x 140 mg capsules) QD for 5 consecutive days in healthy adult subjects in Phase I studies. Administration of troriluzole 140 mg QD for up to 3 years or, in a subset of patients, 280 mg QD for up to 4 years in adult subjects with SCA was well tolerated, without any clinically significant safety signals or laboratory abnormalities. The same has been observed in subjects with OCD or SCA who received troriluzole 200 mg QD for up to 48 weeks, as well as in adult subjects with mild to moderate AD who received troriluzole 280 mg QD for 48 weeks and in adult subjects with GAD who received troriluzole 200 mg QD for up to 8 weeks.

1.4.4 Potential Benefits

The rationale for the proposed study is based on cumulative preclinical and clinical studies that implicate glutamatergic hyperactivity in the pathophysiology of OCD and suggest treatment with troriluzole has the potential to reduce OCD symptoms by modulating the glutamatergic system (see Section 1.1.1). In particular, in a Phase 2b/3 proof-of-concept study, subjects with OCD exhibited numerical, but not statistically significant, improvements in the Y-BOCS at all time points compared to the placebo with a significant difference seen at Week 8 (see Section 1.1.2.2.3). In a post-hoc analysis, treatment with troriluzole resulted in improvement in OCD symptoms that was greater both at Week 8 and Week 12 in subjects who had more severe symptoms [redacted] versus less severe symptoms [redacted] at baseline.

1.4.5 Potential Risks

Preclinical and clinical studies have demonstrated an acceptable safety and tolerability profile for troriluzole. Potential risks are those known effects that are associated with the active metabolite riluzole. The present study includes general and specific safety procedures anticipated to minimize any potential risks. General procedures will include frequent safety assessments by Investigators, thorough evaluations and review of AEs and SAEs on an ongoing basis to monitor for any safety signals or trends by the Sponsor and Medical Monitor, and DMC review of the benefit-risk of the study for subjects.

1.4.5.1 Hepatic

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

In the BHV-4157-202 study, overall, the liver profile of troriluzole was comparable to that of placebo during the randomization phase. For most subjects in both treatment groups, the maximum observed ALT abnormality was either normal or < 3x ULN both at baseline and on treatment. Assessment of maximum observed abnormalities on treatment identified 2 (1.7%) subjects in the troriluzole group with ALT > 3x ULN, and 2 (1.7%) with AST > 5x ULN, but no total bilirubin > 2x ULN during the randomization phase. None of the subjects in the placebo group had ALT or AST > 3x ULN on treatment, or total bilirubin > 2x ULN.

In the BHV-4157-207 study, most subjects in both treatment groups had normal ALT, AST and total bilirubin both at baseline and on treatment during the double-blind randomization phase. Assessment of maximum observed LFT abnormalities on treatment in the troriluzole group identified 7 (3.6%) on-treatment ALT > 3x ULN, and 2 (1%) on-treatment AST > 3x ULN in the troriluzole group. Of these, 1 (0.5%) had ALT > 5x ULN and 2 (1.0%) AST > 5 x ULN. One (0.6%) on treatment ALT > 3x ULN and 1 (0.6%) on-treatment AST > 3x ULN was observed in the placebo group. On treatment abnormalities of total bilirubin were infrequent (0 for troriluzole and 1 for the placebo group. Overall, 11 subjects (3.3%) who received at least 1 dose of troriluzole either during the randomization phase or the open-label extension experienced treatment-emergent ALT > 3x ULN and 4 (1.2%) AST > 3x ULN elevations. One subject had a total bilirubin > 2 x ULN, but this subject also had the elevation while on placebo prior to switching to troriluzole.

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.

The present study will involve monitoring of liver function and exclude subjects with elevated hepatic risk. Biohaven will adhere to the laboratory monitoring guidelines for liver function tests that are described in the Rilutek USPI. In addition, a complete baseline examination will assess predisposition for hepatic illness (e.g., hepatitis serologies, baseline abnormalities, concomitant medications, alcohol usage) and exclude subjects with underling hepatic disease and significant hepatic abnormalities (see Section 5.3). Subjects with (1) AST or ALT values >

5x ULN, or (2) AST or ALT values > 3x ULN and one of total bilirubin (TBL) > 2x ULN or INR > 1.5, or (3) AST or ALT values > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia will have study drug discontinued. Subjects with ALT or AST elevations > 3x but < 5x ULN will be evaluated medically, and additional laboratory testing may provide useful information in evaluating overall acceptability of continued treatment with troriluzole.

1.4.5.2 Hematopoietic - 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.

The present study will involve monitoring for neutropenia and exclude subjects with elevated risk of developing neutropenia (see Section 5.3). Randomized patients will be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check WBC counts. CBC will also be collected at baseline, 4-, 8-, and 10- weeks to monitor WBC counts.

1.4.5.3 Pulmonary – Interstitial Lung Disease

Troriluzole has not been associated with pulmonary findings in nonclinical toxicology studies to date, nor has interstitial lung disease has not been reported in clinical experience 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.

The present study will involve monitoring of respiratory symptoms and exclude patients with significant underlying pulmonary disease (see Section 5.3). 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.

1.4.6 Overall Benefit-Risk Assessment

OCD is a sufficiently debilitating condition with limited treatment options when patients have not responded appropriately to first-line treatment. Augmentation strategies with neuroleptic medications are associated with adverse effects including tardive dyskinesia, extrapyramidal symptoms and metabolic syndrome. Troriluzole, via its active metabolite riluzole acts on multiple targets to reduce glutamatergic hyperactivity in the cortico-striato-thalamo-cortical (CSTC) circuitry. The target exposure of riluzole achieved with troriluzole is expected to provide a more favorable risk-benefit profile than what could be achieved with oral riluzole tablets (see Section 1.2.1). The high unmet need for adjunctive treatment for OCD, together with the available preclinical and clinical data with troriluzole, provide a compelling and favorable overall benefit-risk assessment for the development of troriluzole at the 280mg daily dose as a treatment for OCD.

There is no evidence to suggest any new significant safety issues with the clinical use of troriluzole. Taking into account the measures taken to minimize the risk to subjects participating in the troriluzole clinical development program, the potential risks associated with troriluzole are justified by the anticipated benefits that may be afforded to subjects with OCD who are not responding to standard of care treatment. The safety monitoring in the planned clinical study will minimize the potential risks to study subjects.

2 STUDY OBJECTIVES

2.1 Primary

The primary objective of the study is to evaluate the efficacy of troriluzole as adjunctive therapy compared to placebo in subjects with OCD who have had an inadequate response to their current OCD treatment based on the change in their Y-BOCS score.

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 Sheehan Disability Scale (SDS);
- Evaluate the efficacy of troriluzole compared to placebo on global clinical condition as measured by the Clinical Global Impression- Severity Scale (CGI-S);

2.3 Exploratory

- Evaluate the efficacy of troriluzole compared to placebo on global functioning as measured by the Clinical Global Impression- Improvement Scale (CGI-I).
- Evaluate the efficacy of troriluzole compared to placebo on obsessive and compulsive symptomatology as measured by the change in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) obsession and compulsion subscales;
- 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);
- Evaluate the efficacy of troriluzole compared to placebo on obsessive and compulsive symptomatology as measured by the change in the Dimensional Obsessive Compulsive Scale (DOCS)
- To characterize the pharmacokinetics of troriluzole from sparse sampling, using an existing population PK modeling, and explore population PK/PD relationships.

3 STUDY ENDPOINTS

3.1 Primary

- Improvement in obsessive-compulsive symptomatology is assessed using the Y-BOCS change from baseline in the total score.

3.2 Secondary

- Safety and tolerability are assessed using the frequency of unique subjects with: SAEs; AEs leading to discontinuation; AEs 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;

- Improvement in global clinical condition is assessed using the change in the CGI-S score from baseline;

3.3 Exploratory

- Improvement in global functioning is assessed using response as defined by 'Much improved' or 'Very much improved' on the CGI-I scale;

- Improvement in obsessive and compulsive symptomatology is assessed using the change in the Y-BOCS obsession and compulsion subscale scores from baseline;

- Improvement in depressive symptomatology is measured by the change in the QIDS-SR score from baseline;

- Improvement in anxiety is assessed using the change in the BAI score from baseline;

- Improvement of insight into obsessive-compulsive beliefs is measured by the change in the BABS score from baseline;

- Improvement in obsessive and compulsive symptomatology is assessed using the change in Dimensional Obsessive Compulsive Scale (DOCS)

- The pharmacokinetic profile of troriluzole is characterized from sparse plasma concentrations observed in treated subjects using an existing population PK model. Further exploration of PK/PD relationships for both efficacy and toxicity are explored as warranted.

4 STUDY PLAN

4.1 Study Design and Duration

BHV4157-303 is a Phase 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 subjects with OCD who have had an inadequate response to standard of care treatment. Treatment failure / inadequate response on the subjects' current SOC is defined by a Y-BOCS score of 22 or greater despite at least 8 weeks of treatment at Screening and 12 weeks of treatment, at Baseline, with an adequate dose of an SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine medication.

Subjects who are stable on SOC medication and having an inadequate response (as defined above) will be randomized to additionally receive placebo (QD) or troriluzole (280 mg QD, after two weeks at 200 mg QD). [redacted]

Subjects will receive either placebo or troriluzole 200mg for the first two weeks and then will be increased to 280 mg (or matching placebo) for the duration of the study. Down titration to 200 mg (or matching placebo) after the first two weeks of the Randomization Phase will only be allowed for tolerability purposes.

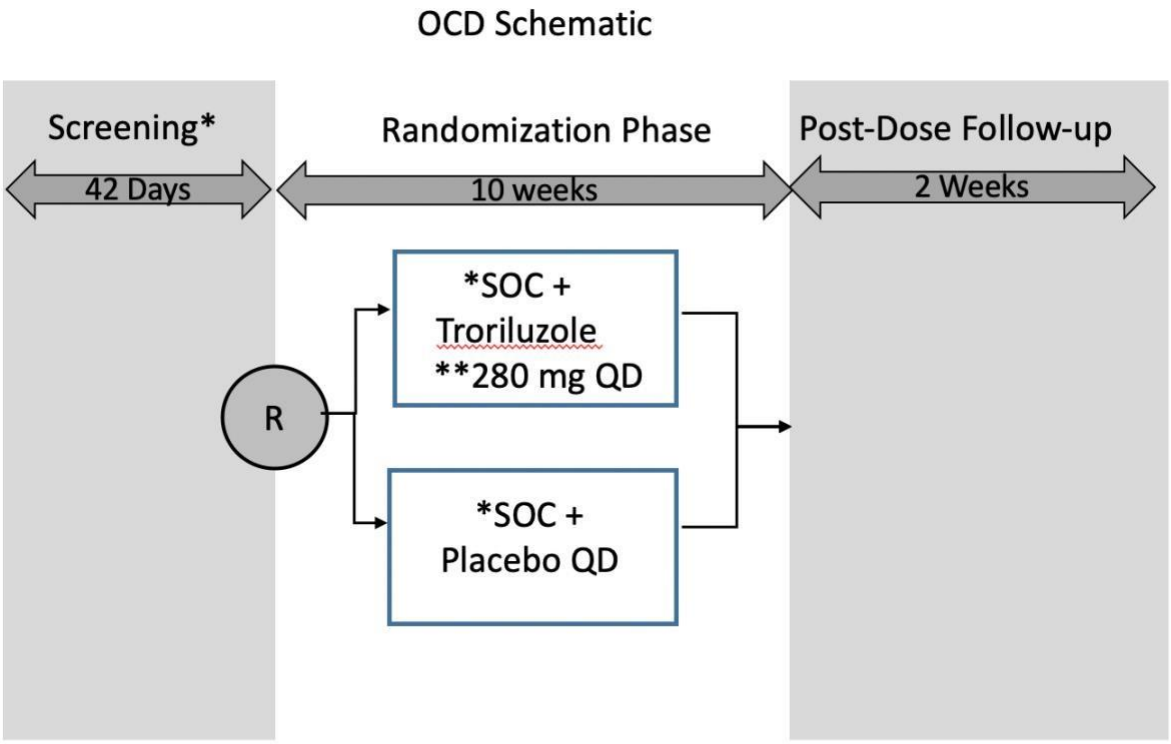
The total treatment period will be 10 weeks, after which subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit or if eligible, will participate in the Open Label Extension Study, BHV4157-209.

[redacted]

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

4.2 Study Schematic

Figure 2 Study Schematic



*Subjects should have been taking an adequate maximum tolerated dose, as defined in the study Inclusion Criteria, of an SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine for at least 8 weeks prior to Screening and 12 weeks at Baseline.
**Subjects will receive 200mg for the first 2 weeks and then will be increased to 280mg for the duration of the study. Down titration will only be allowed to address tolerability issues. Subjects will return to the clinic 2 weeks after discontinuing study medication for a follow-up safety visit or, if eligible, to enroll in the Open-Label Extension Study BHV4157-209.

4.3 Schedule of Assessments

Table 1 Schedule of Assessments and Events

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 10 or early term	Week 2 Post Last Dose	Comments
Day	**up to -42**	**0**	**14a**	**28a**	**56a**	**70a**	**84a**	
Eligibility Assessments								
Informed Consent	X							
Pharmacogenetic Informed Consent	X							
Inclusion/Exclusion	X	X						
MINI	X							
Borderline Personality Disorder Module (BPD Module)	X							
MGH-TRQ-OCD	X							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
Medical History	X							To include: smoking history, cardiovascular disease, family, OCD hx and hx of tic disorder.
Demographic Assessment	X							
Disease History	X							

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 10 or early term	Week 2 Post Last Dose	Comments
Day	**up to -42**	**0**	**14a**	**28a**	**56a**	**70a**	**84a**	
SAFER Interview	X							The SAFER Interview will be conducted remotely with the subject by a Rater at CTNI shortly after the screening visit and prior to Baseline. A SAFER pass is necessary for randomization.
Safety Assessments								
Adverse Event Assessment	X	X	X	X	X	X	X	Non-serious AEs will be collected from the initiation of study drug. SAEs will be collected from subject's written consent to within 30 days of discontinuation of dosing.
Laboratory Assessments including urinalysis	X	X		X	X	X		Laboratory assessments are not required to be fasting.
Serology	X							Serology includes HBsAg, HCV, HIV antibody and RPR testing.
Pregnancy testing (serum)	X	X		X	X	X		The site may test a subject at any time if pregnancy is suspected.
Pregnancy testing (urine)		X	X	X	X	X		WOCBP subjects must have a urine pregnancy tests performed prior to the baseline dose. The site may test a subject at any time if pregnancy is suspected.

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 10 or early term	Week 2 Post Last Dose	Comments
Day	**up to -42**	**0**	**14a**	**28a**	**56a**	**70a**	**84a**	
Urine drug test	X	X				X		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
Complete Physical Exam	X					X		To include: HEENT, neck, lymph nodes, lungs, cardi., abdomen, skin and musculoskeletal.
Physical Measurements	X					X		Height Weight: The same scale should be used for a given subject throughout their study participation. Subject should void just before being weighed. Should be recorded before a meal and at approx. the same time each day Subject should be minimally clothed (no shoes or heavy garments).
Vital Signs	X	X	X	X	X	X	X	Vital signs (Temp., BP, HR)
12-Lead ECG	X	X		X		X		
Concomitant Medication Review	X	X	X	X	X	X	X	
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	A certified clinician rated assessment.

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 10 or early term	Week 2 Post Last Dose	Comments
Day	**up to -42**	**0**	**14a**	**28a**	**56a**	**70a**	**84a**	
Clinical Outcome Assessments								
Placebo-Control Reminder Script (PCRS)		X		X	X	X		The PCRS should be read by a clinician to a subject prior to every administration of the Y-BOCS at every visit (except screening) for every subject.
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)	X	X		X	X	X		A certified clinician administered scale.
Clinical Global Impressions-Improvement Scale (CGI-I)				X	X	X		A certified clinician rated assessment.
Clinical Global Impressions-Severity Scale (CGI-S)	X	X		X	X	X		A certified clinician rated assessment.
Sheehan Disability Scale (SDS)	X	X		X	X	X		A subject-rated measure. Note on scale completion: 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. Please refer to protocol section 6.4.3.
Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR)	X	X		X	X	X		A subject "self" report. QIDS-SR should be reviewed prior to the administration of the C-SSRS.
Beck Anxiety Inventory (BAI)	X	X		X	X	X		A subject "self" report.
Brown Assessment of Beliefs (BABS)	X	X				X		A certified clinician rated assessment.
Dimensional Obsessive Compulsive Scale (DOCS)		X		X	X	X		A subject "self" report

Visit	Screening	Baseline	Week 2	Week 4	Week 8	Week 10 or early term	Week 2 Post Last Dose	Comments
Day	**up to -42**	**0**	**14a**	**28a**	**56a**	**70a**	**84a**	
Biomarker and Other Assessments								
Pharmacokinetics Blood Sample				X	X	X		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, Week 8 and Week 10 can be instructed to hold their dose of study drug that morning until after a PK trough sample is obtained, if possible and appropriate
Pharmacogenomics Blood Sample		X				X		
Clinical Drug Supply								
Randomization		X						Study Drug will be dispensed at the baseline visit. Subjects should take the first dose in the morning the day after the baseline visit
Dispense Study Drug		X	X	X	X			The first dose should be taken the day after the baseline visit. Study medication should be administered in the morning.
Drug Accountability			X	X	X	X		

a Visit window +/- 3 days

4.3.1 Screening Phase

The purpose of the Screening Visit is to ensure that the appropriate subjects are entered into the trial. The maximum duration of the Screening Phase is 42 days; however subjects must have been on at least 8 weeks of their current SOC OCD therapy [SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine] at an adequate dose at Screening and at least 12 weeks by the Baseline visit. The investigator will determine that the subject meets eligibility criteria and will collect demographic and medical data presenting a full characterization of the subject. All attempts should be made to obtain medical and pharmacy records to confirm the subject's medical and medication treatment history. It is estimated approximately 1200 subjects will enter the screening phase of the trial.

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

After sponsor approval, a subject may be re-screened.

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 who are randomized will be dispensed troriluzole (280 mg QD) or placebo (QD) (in a

1:1 ratio). This troriluzole should be taken in addition to the subjects SOC medications

Subjects will receive 200mg or placebo for the first two (2) weeks and will then be increased to

280mg or placebo for the duration of the study. Down titration to 200 mg will be allowed after Week 2, only in order to address tolerability issues. If a subject is down titrated the subject will need to remain at 200 mg for the remainder of the Randomization Phase.

The total treatment period will be 10 weeks, after which subjects will return to the clinic two weeks after discontinuing study medication for a follow-up safety visit or if eligible, will participate in the Open Label Extension Study, BHV4157-209.

- Subjects should take their medication in the mornings. If tolerability issues arise, please refer to Section 7.2.4.

Please refer to the Schedule of Assessments/Time & Events for details on procedures during the Randomization Phase. There is a visit window of +/- 3 day visit window during the Randomization Phase of the study. It is estimated that up to approximately 700 subjects will enter this phase of the trial.

4.3.3 COVID-19 Contingencies

Please note as the treatment period of this study is only 10 weeks, ***all visits should be in person and subjects should expect to have to come in for all study visits***. The study visits in this study are relatively close together due to dose increases and for the necessary data to be collected. Therefore, there will be minimal flexibility with the COVID -19 pandemic and subjects will be expected to come in for all visits whenever possible or may need to be discontinued. Remote safety visits may be allowed on a case by case basis; however, the investigator should contact the sponsor medical monitor (or designee) to discuss the most appropriate course of action. If the remote visit requires laboratory testing, local labs should be obtained and reviewed by the investigator. A redacted version of the local lab report should be forwarded to Biohaven when available for review. With sponsor approval, shipping of study drug directly to the subject via overnight tracked and certified courier will also be allowed. Sponsor contact below:

Sponsor Medical Monitor

[redacted]

4.4 Post Study Access to Therapy (if applicable)

An Open Label extension study will be made available for eligible subjects. Subjects that qualify for participation in the open label extension study will receive 48 weeks of troriluzole treatment.

No other post study drug access is available.

5 POPULATION

5.1 Number of Subjects

Up to approximately 700 subjects are expected to be randomized in this study.

5.2 Inclusion Criteria

Informed Consent

1. Subjects must provide a written signed informed consent form/forms (IRB/EC specific) prior to the initiation of any protocol required procedures.

Age and Sex

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

Target Population

3. Primary diagnosis of 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;

4. Subjects must be currently experiencing non-response or inadequate response to their current SOC medication defined as:

    a. Subjects Y-BOCS total score must be ≥ 22 at Screening **and** Baseline, reflecting moderate or severe OCD symptoms.

5. Subjects must currently be on an SSRI (with the exception of fluvoxamine, see Section 1.1.3), 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 12 weeks at Baseline of SSRI (with the exception of fluvoxamine, see Section 1.1.3), clomipramine, venlafaxine or desvenlafaxine;

   b. Adequate Dose: Defined by the table below:

Refer to table below:

Generic	Class	Dose Range3
Citalopram[1,2]	SSRI	20-40mg
Escitalopram[2]	SSRI	10-20mg
Fluoxetine	SSRI	20-60mg
Paroxetine	SSRI	40-60mg
Sertraline	SSRI	50-200mg
Clomipramine	TCA	100-250mg
Venlafaxine[2]	SNRI	75-225 mg
Desvenlafaxine[2]	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 subjects 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's (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.

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

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

8. Subjects must "pass" the SAFER interview performed by CTNI (Rater Training vendor) prior to randomization;

9. 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;

10. Minimum of 6 years of education or equivalent to complete necessary scales and understand consent forms;

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

12. 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 AEs and concomitant medications;

13. 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:

    a. one barrier method (e.g. diaphragm with spermicide, condom with spermicidal gel, intrauterine devices, cervical cap);

    b. 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);

14. WOCBP must have a negative serum pregnancy test at screening and a negative urine pregnancy test within approximately 24 hours prior to dosing at Baseline;

15. 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

Target Disease Exceptions

1. Subjects with a history of more than two (2) previous failed or inadequate treatment classes[3,4] given for an adequate duration at an adequate dose as defined by the following criteria taken from the MGH-TRQ-OCD as:

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

   a. Adequate duration: At least 12 weeks of treatment

Adequate dose: Defined by the USPI labeling.

Refer to the table below:

Generic	Class	Dose Range[3]
Citalopram[1]	SSRI	20-40mg
Escitalopram[1,2]	SSRI	10-20mg
Fluoxetine	SSRI	20-60mg
Fluvoxamine[4]	SSRI	100-300mg
Paroxetine	SSRI	40-60mg
Sertraline	SSRI	50-200mg
Clomipramine	TCA	100-250mg
Venlafaxine	SNRI	75-225 mg
Desvenlafaxine	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 subjects 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's, (except for citalopram), clomipramine, venlafaxine or desvenlafaxine that are outside of the range above would still be considered an adequate dose.
[4] Fluvoxamine is allowed to be evaluated as a historical treatment but is not allowed to be the subject's current standard of care treatment.
[5] For the purposes of this study, pharmacologic classes may be defined as including, but not limited to:

- SSRIs and clomipramine (considered as one class)
- SNRIs

[6] Two (2) failed trials of medications within a class will be considered a class failure

2. 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;

3. 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;

4. Any eating disorder within the last 12 months;

5. 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;

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

7. **Any positive ("yes") C-SSRS response to questions 1-5 in last 6 months** at screening and/or Since the Last Visit (before dosing) at the Baseline visit;

8. Total BABS score >17 at screening and baseline;

9. Subjects 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;

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

Medical History Exclusions

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

12. 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 during screening (subjects with a positive result for cannabis, that agree to refrain from use during the period of the study and test negative upon retest during the screening phase may participate);

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

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

15. Subjects with a history of Type I or Type II insulin-dependent diabetes mellitus (IDDM);

16. Body mass index >40 kg/m^2;

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

18. 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;

19. 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;

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

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

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

23. History of chronic pulmonary disease or chronic pulmonary symptoms. Well controlled asthma is allowed per investigator's clinical judgement;

24. 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;

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

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

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

    c. Chronic or frequent episodes of loose stools;

26. History or evidence of any medical, neurological or psychological condition that would expose the subject to an undue risk of a significant AE or interfere with assessments of safety and efficacy during the course of the trial as determined by the clinical judgment of the investigator or the sponsor.

27. Women who are pregnant or breastfeeding.

Physical and Laboratory Test Findings

28. Uncontrolled hypertension is exclusionary. Per investigator judgement, subjects may be enrolled who have stable hypertension for at least 3 months (12 weeks) prior to screening. A blood pressure measurement of greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is an absolute exclusion. If a technical issue is suspected, the reading may be repeated once, and the subject may be enrolled if blood pressure is not greater than 150 mm Hg systolic or 100 mm Hg diastolic per investigator judgement.

29. 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;

30. Hepatic test abnormalities at screening (may be repeated one time for confirmation in screening prior to baseline):

    a. Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) or GGT > 1.5 times the upper limit of normal; or

    b. Total bilirubin > the upper limit of normal

31. Lipase value greater than 3 times the upper limit of normal (ULN) accompanied by abdominal pain at screening;

32. HbA1C ≥ 7.0% at screening;

33. Pathologic renal findings at screening as defined by the presence of either of the following criteria:

    a. 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];

    b. Creatinine ≥ 2 mg/dL

34. Hematologic abnormalities at screening:

    a. Hemoglobin < 10 g/dL; or

    b. WBC < 3.0 x 103/mm^3; or

    c. Platelet count < 100,000/mm^3; or

    d. Neutrophils, Absolute < 1500/mm^3

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

36. HBsAg or HCV positive at screening;

37. 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.

Prohibited Treatments and/or Therapies

38. 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 10-week treatment period;

39. Previous treatment with riluzole. Subjects with known hypersensitivity to riluzole, placebo or any of the excipients;

40. Previous participation in a study with troriluzole (screen-failed subjects from

41. BHVN4157-202 may be considered for this trial with approval from the medical monitor); Subjects who are participating in any other clinical research study;

42. Subjects who would likely require prohibited concomitant therapy (see Section 5.4) after randomization;

43. 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);

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

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

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

47. Current daily anxiolytic (except buspirone and hydroxyzine) or benzodiazepine use is prohibited Note: Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing as needed are allowed as are non-benzodiazepine hypnotics for sleep if used as needed, and low dose benzodiazepines (lorazepam 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;

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

49. 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:

1. Medical or recreational marijuana;

2. Cannabidiol (CBD) oil;

3. Tricyclic antidepressants (with the exception of clomipramine);

4. 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. gabapentin, pregabalin, topiramate, lamotrigine, N- acetylcysteine, ketamine, memantine, sodium valproate, lithium).

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, and be avoided with strong CYP1A2 inhibitors (e.g., fluvoxamine, ciprofloxacin). 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 III, Section 17.2):

1. Strong to moderate CYP1A2 inhibitors which may increase the risk of riluzole associated AEs, including the SSRI fluvoxamine; strong inhibitors are prohibited (See Appendix III, Section 17.2);

2. Strong to moderate CYP1A2 inducers which may result in decreased efficacy (See Appendix III, Section 17.2);

3. Hepatotoxic drugs (e.g. allopurinol, methyldopa, sulfasalazine) which may increase the risk for hepatotoxicity.

Note: Fluvoxamine is a strong CYP1A2 inhibitor and is therefore prohibited. A prior study in OCD used riluzole as adjunctive treatment to fluvoxamine [5] and preliminary results from a drug-drug interaction study with troriluzole demonstrated that riluzole concentrations were increased up to 3-fold. Oral contraceptives which contain ethinyl estradiol (moderate CYP1A2 inhibitor) are allowed.

Hypnotic Use: New use of hypnotics should be avoided. For the management of persistent sleeping difficulties or insomnia, subjects may receive the following medications at no higher than the indicated doses such as:

1. Zolpidem tartrate: up to 10 mg at bedtime (HS) as needed (prn);

2. Zolpidem tartrate extended release: up to 12.5 mg at HS prn;

3. Zaleplon: up to 20 mg at HS prn

4. Eszopiclone: up to 3 mg at HS prn.

Low dose anxiolytic pre-medications prior to necessary medical diagnostic testing prn are allowed. Lorazepam (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 study.

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

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

The generic name (where possible), start date, end date and dosing information for any medication (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.

Subjects 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. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

> 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.

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:

1. 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;

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

5.6 Justification for obtaining Ethnicity Data

It is important to collect the ethnicity of the subjects enrolled in this study in order to advance the scientific knowledge and potential treatment of Obsessive Compulsive Disorder by defining and analyzing potential differences in responses and metabolism to BHV-4157 compared to placebo across the various ethnicities.

5.7 Gender Distribution

Both males and females will be enrolled into this study. Until now, there is no indication for gender- specific differences related to treatment with the investigational product, BHV4157.

5.8 Deviation from Inclusion/Exclusion Criteria

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

6 STUDY CONDUCT AND DESCRIPTION OF STUDY PROCEDURES

6.1 Study Materials

The sponsor will provide investigational product which will include troriluzole (100 mg and 140 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.

6.2 Eligibility Assessments

6.2.1 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-TRQOCD at screening.

6.2.2 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.

6.2.3 Borderline Personality Disorder Module (BPD)

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

6.2.4 SAFER Interview

The SAFER Interview is a structured interview conducted remotely by the Rater Training 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.

6.2.5 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 and subject history of OCD, and history of tic disorder if available.

6.3 Safety Assessments

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

6.3.1 Vital Signs and Physical Measurements (Height and Weight)

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

Blood pressure will be recorded at scheduled visits. The following recommended guidelines will aid delegated site staff in taking accurate blood pressure assessments:

1. Subjects should:
    a. be sitting quietly in a room by themselves for ten (10) minutes,
    b. have their feet on the floor,
    c. have their legs uncrossed,
    d. not have had caffeine nor tobacco right before the study visit, and
    e. have their arm straight and at heart level.
2. A calibrated, reliable blood pressure monitor should be used;
3. The same calibrated, reliable blood pressure monitor should be used for repeat values;
4. Please ensure the correct cuff size is used;

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, if possible, 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).

6.3.2 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.

6.3.3 Physical Exam

Subjects will undergo a complete physical exam as outlined by the Schedule of Assessments/Time & Events. 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. A physical exam may be conducted at any time based on investigator judgement.

6.3.4 Laboratory Assessments

Laboratory testing will include the following:

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

2. Serum Chemistry: sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK (fractionated as defined by the vendor plan), total protein, albumin, total bilirubin (if greater than 2 mg/dl bilirubin will be fractionated), glucose, creatinine, (eGFR) according to the re- expressed abbreviated (fourvariable) Modification of Diet in Renal Disease (MDRD) Study equation < 30 ml/min/

3. $1.73m^2$; 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), BUN, and uric acid.

4. Additionally, at Screening, total cholesterol, LDL, HDL, triglycerides, B12, folate, HbA1C, Lipase, TSH, and free T4;

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

6. Central Lab, serum pregnancy test will be conducted at screening, baseline and at scheduled visits, as specified in the Schedule of Assessments/Time & Events. On site, urine pregnancy tests will be performed prior to dosing, at baseline and at subsequently scheduled visits, as specified in the Schedule of Assessments/Time & Events or at the discretion of the Investigator;

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

8. On site urine drug screen (UDS) for cannabis (medical and recreational), amphetamines (including MDMA/ecstasy), cocaine, barbiturate, tricyclic antidepressants, PCP, benzodiazepines, tricyclic antidepressants and opiates at screening and baseline. Central Lab, 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 into 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 subject identifying information and send the results directly to the Sponsor Medical Monitor.

Sponsor Medical Monitor

[redacted]

6.3.4.1 Pharmacokinetics

A pharmacokinetic (PK) sample will be collected at Week 4, Week 8, and Week 10 of the Randomization Phase. Subjects should be instructed to take their dose at their routine time on the days for the next visit, unless the visit is scheduled in the morning, in which case subject will be instructed to hold their dose and only take the dose after the blood sample is collected at the clinical site.

Each time PK is requested the sites should collect (1) time of last dose, and (2) whether they ate a meal within 2 hours of the last dose.

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.

6.3.4.2 Pharmacogenetics

A pharmacogenetics blood sample will be obtained at baseline and at the Week 10 visit 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.

6.3.4.3 Pregnancy Testing

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

6.3.4.4 Evaluation of Laboratory Assessments

The management of abnormal LFTs are described herein. Review of LFTs (ALT, AST, bilirubin, alkaline phosphatase) will be evaluated by a physician or other qualified medical personnel.

If AST or ALT values are between 3x ULN and <5x ULN at any time after randomization, the investigator will medically evaluate the subject. Medical assessment of the subject can include the following:

- Must include, but not limited to, repeat LFT and Abnormal Liver Panel assessments (Chemistry: Sodium, Potassium, Chloride, Calcium ALT "Alanine aminotransferase", AST "Asparate aminotransferase", LDH "Lactate dehydrogenase", Alkaline Phosphatase, GGT"Gamma glutamyl transferase", Phosphorus "Phosphate", Bicarbonate, Total Protein, Albumin, Total Bilirubin, "Bilirubin, Total" (with reflex to Direct and Indirect), Random Glucose, Creatinine, BUN "Blood Urea Nitrogen", Uric Acid, Total Creatinine Kinase with reflex to Isoenzymes, Coagulation- PT, INR, aPTT, Hepatitis, A IgM "HAV IgM", Hepatitis B Surface Antigen "HBsAg", Hepatitis B IgM Core Antibody "HBc IgM", HCV Screen, Epstein-Barr Viral (EBV), Capsid Antigen IgG, Epstein-Barr Viral (EBV), Capsid Antigen IgM, Cytomegalovirus (CMV) IgM, Cytomegalovirus (CMV) IgG within 1 week and follow until resolution. All reasonable efforts should be made to obtain these repeat LFT assessments within 48 to 72 hours if possible, per the FDA Guidance for Industry[1]. 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 ALT or AST values are above >5x ULN at any time after randomization, the investigator will assess and manage the subject as appropriate, including:

- Study medication must be discontinued immediately;

- Bring subject in for physical exam and evaluation:

    1. Assess for right heart failure, hypotension, and signs/symptoms of alcohol use disorder;

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

    3. Assess for potential exposure to environmental toxins;

    4. Evaluate for abdominal pain, splenomegaly, hepatomegaly.

- Obtain the Abnormal Liver Panel as outlined above as soon as possible, with either a local lab or preferably central lab; and, follow to resolution;

- Assess AEs;

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

6.3.5 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. [48] This tool, through a series of simple, plain-language questions that anyone can ask supports in the assessment of an individual's suicide risk. The answers to this series of questions help users identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs.

There are two versions that will be used for the trial: Screening (to include lifetime assessment and within the last six (6) months) and Since last visit. The C-SSRS is administered by a certified rater. The C-SSRS will be completed on a paper form at the site. Subjects who have any positive ("yes") C-SSRS response to suicidal ideations in the last 6 months at Screening and/or since the last visit (before dosing) at the Baseline visit will be excluded from participation in the trial.

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.

6.4 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.

6.4.1 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. [49,50] It is designed to rate the severity of obsessions and compulsions as well as the type of symptoms in subjects 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.

6.4.2 Placebo-Control Reminder Script (PCRS)

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

6.4.3 Sheehan Disability Scale (SDS)

The SDS is a subject-rated measure of functional disability in domains of work, social and family life. [51] The SDS has demonstrated sensitivity to treatment effects in numerous randomized controlled trials in populations with varied diagnoses. 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 range 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 subject's 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.

6.4.4 Clinical Global Impression – Improvement Scale (CGI-I)

The CGI-I is a clinician rated assessment of the subject's improvement in global functioning on a 7 point scale. The CGI-I will be conducted at study visits as indicated in the Schedule of Assessments and Events and the subject's improvement will be compared to baseline.

6.4.5 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. The higher the score indicates a more severe illness. The CGI-S will be conducted at screening and baseline and subsequent study visits as indicated in the Schedule of Assessments and Events.

6.4.6 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. non-delusional) regarding subject beliefs. [52] 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.

6.4.7 Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR)

The QIDS-SR should be reviewed prior to the administration of the C-SSRS.

The QIDS-SR is a self-report, 16 item questionnaire that subjects will use to rate symptoms of depression. [53] 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.

6.4.8 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. [54] Scores on the BAI range from 0 to 63. Higher scores indicate higher levels of anxiety symptoms.

6.4.9 Dimensional Obsessive Compulsive Scale (DOCS)

The DOCS is a self-report assessment based on 4 different dimensions. These dimensions are based on contamination, responsibility for harm and mistakes, incompleteness/symmetry and unacceptable thoughts. [55]

6.5 Early Discontinuation of Study

All subjects who discontinue study treatment early should complete the 2-Week Post Dose Visit unless they would like to stay in the study. 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). A subject may discontinue from treatment and continue in the study. If a subject is willing to stay in the study off of treatment, they will continue their study visits as noted in the time and events table.

6.5.1 Early Discontinuation from the Study

Subjects MUST discontinue the IP (and non-investigational product at the discretion of the Investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), ECG, and laboratory abnormalities (confirmed by repeat testing if appropriate) or intercurrent illness which, in the opinion of the Investigator or

sponsor indicates that continued participation in the study is not in the best interest of the subject.

This may include the following:

- Treatment-emergent ECG abnormalities (1) QTcF values that exceed an absolute QTcF value of 500 msec, or (2) QTcF prolongation that exceeds the baseline QTcF values by > 60 msec.

- Treatment-emergent hepatic laboratory abnormalities (1) AST or ALT values > 5x ULN, or (2) AST or ALT values > 3x ULN and one of total bilirubin (TBL) > 2x ULN or INR > 1.5, or (3) AST or ALT values > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia.

- Treatment-emergent renal laboratory abnormalities (1) Serum creatinine values > 3x ULN, if SCr was normal at baseline, or (2) Serum creatinine increase > 3x from baseline values, if SCr was not normal at baseline.

- Absolute neutrophils of $\leq 1500/mm^3$

- Treatment-emergent elevated blood pressure noted as (1) systolic value $\geq$ 180 mm/Hg or (2) diastolic blood pressure >110 mm/Hg and these elevations cannot be otherwise explained by another cause. Confirmation of these values should be collected by following the blood pressure collection guidelines found in section 6.3.1 of this protocol. Three measurements should be taken fifteen (15) minutes apart. If the mean value (average of all three collections) are confirmed to be systolic value $\geq$ 180 mm/Hg or diastolic value is > 110 mm/Hg at any study visit the subject should be discontinued from the study.

- Occurrence of interstitial lung disease.

Additional scenarios which may lead to Early Discontinuation from the study include:

- Disease progression, which, in the opinion of the Investigator or sponsor indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy

- Termination of the study by Biohaven Pharmaceuticals

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness

6.5.2 Lost to Follow Up

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

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

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

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

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7 STUDY DRUG MANAGEMENT

7.1 Description of Study Drug

7.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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 subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, the investigational products are: troriluzole capsules 100 mg and 140 mg and matching placebo.

7.1.2 Packaging, Shipment and Storage

Clinical Trial Materials should be stored at controlled temperature between 20^0C and 25^0 C

(68^0F -77^0F), with excursions permitted between 15^0C and 30^0 C (59^0F -86^0F), 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.

7.2 Dose and Administration

7.2.1 Randomization Phase

Subjects will be randomized at the baseline visit to troriluzole 280mg or placebo. All subjects will receive 200 mg (2 x 100 mg capsules) or matching placebo, QD, for the first two (2) weeks and will be increased to 280 mg (2 x 140 mg capsules) or matching placebo for the duration of the Randomization Phase. Down titration to 200 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 subjects 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 nighttime dosing if there is reason to believe that may help tolerability. Any such changes must be documented in the subject's records by the investigator. If the subject is receiving 200 mg and this switch in dosing time does not result in acceptable tolerability, then dosing should be discontinued.

7.2.2 Method of Assigning Subject Identification

The investigator or designee will need to access an Interactive Response Technology (IRT) to enroll subjects into the trial, randomize subjects, and manage study drug supplies. Initially the investigator or designee will enter the subject during the Screening Visit after informed consent is obtained and a subject number will be assigned. After completion of all screening evaluations, all eligible subjects will be randomized, in a 1:1 ratio to receive either placebo (QD) or troriluzole. Treatment assignments will be obtained by the investigator (or designee) via the IRT system. [redacted]

Investigational sites will access the IRT at each scheduled study visit throughout the study. The IRT 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 IRT to discontinue the subject from participation in the study.

7.2.3 Selection and Timing of Dose and Administration

Subjects will be randomized to receive placebo (QD) or troriluzole (280 mg QD). Study Drug will be dispensed at the baseline visit and subsequent visits throughout the study. Subjects should take the first dose the day after the baseline visit. Study medication should be administered in the morning without regard to meals.

7.2.4 Dose Modifications

Subjects will receive 200 mg or Placebo for the first two (2) weeks and will then be increased to 280 mg or placebo for the duration of the study. Down titration to 200 mg will be allowed after Week 2, only in order to address tolerability issues. If a subject is down titrated, they will need to remain at 200 mg for the remainder of the Randomization Phase.

For subjects who do not tolerate their study treatment (200 mg or 280 mg), the investigator may permit them to switch to nighttime 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 200 mg and this switch in dosing time does not result in acceptable tolerability, then dosing should be discontinued.

7.3 Blinding and Unblinding

Blinding is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject 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 bioanalytical scientist, Biohaven Drug Supply Coordinator, IWRS randomization vendor, and pharmacovigilance role may be unblinded before data are more generally unblinded after the Randomized Phase of the study. The bioanalytical analyst will be unblinded in order to minimize unnecessary analysis of placebo blood PK sample. Results of the blood concentration assay will be kept secure until database lock and unblinding for the primary endpoint. [redacted] Except as noted above, other members of the Biohaven research team will remain blinded.

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

7.4 Treatment Compliance

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

7.5 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 Biohaven 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 Biohaven Study monitor or the sponsor's designee.

8 ADVERSE EVENTS

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject 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.

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

8.1 Serious Adverse Events

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

8.1.1 Definition of Serious Adverse Event (SAE)

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

- Death;
- Life-threatening;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;

- Congenital anomaly/birth defect in the offspring of a subject who received 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):

    1. Intensive treatment in an emergency room or at home for allergic bronchospasm;

    2. Blood dyscrasias or convulsions that do not result in inpatient hospitalization;

    3. Development of drug dependency or drug abuse;

    4. Potential drug induced liver injury (see section 8.4).

8.1.2 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 Biohaven 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.

8.1.3 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.

8.1.4 Collection and Reporting Serious Adverse Events

Following the subject'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 PPD immediately via telephone, upon observing or learning of the event. PPD will then immediately notify the Biohaven Medical Monitor of the event. The SAE form must then be submitted to PPD within one working day. The Investigator is responsible for submitting all applicable events to the Independent Review Board (IRB) as per the IRB's reporting requirements. Additionally, the Investigator, or designated staff, is responsible for entering the

SAE information in the Electronic Data Capture (EDC) system (i.e.: event term, start stop dates, causality, severity).

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

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

- North America: 1-888-488-9697

Sites may instead, if needed, scan/email to report an SAE/Pregnancy (subject line must include

"Biohaven Protocol BHVxxxx-xxx") wilsafety@ppd.com

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

- North America: 1-800-201-8725

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

SAE Telephone Contact: [redacted] (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.

8.2 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.

8.3 Pregnancy

If following initiation of the investigational product, it is subsequently discovered that a study subject 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 subject safety). Protocol-required procedures for the study will be

discontinued and the follow up must be performed on the subject unless contraindicated by the pregnancy (i.e., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

8.4 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of the initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs as per Section 8.1.

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 subject must discontinue from the trial and appropriate follow up requirements.

8.5 Non-serious Adverse Events

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

8.5.1 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 subject to have the study drug discontinued or interrupted;
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

9 STATISTICS

Detailed plans for analysis will be summarized in a separate Statistical Analysis Plan document, [redacted] A summary of statistical aspects of the design and intended analysis is provided here.

9.1 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; AEs; and vital sign, ECG and laboratory abnormalities. Thus, for these endpoints, multiple occurrences of the same event are counted only once per subject.

9.2 Sample Size

The sample size for this study will be up to approximately 700 randomized subjects. This accommodates for lost subjects [redacted] and is based on the rationale that follows.

Assuming that no more than 20% of the subjects are lost by the end of the double-blind phase, a sample size of about 300 per arm will yield roughly 240 subjects per arm. Assuming a standard deviation of 5.8, a 2-sided alpha of 0.05, this sample size provides 90% power to detect a difference on the Y-BOCS total score change from baseline of 1.72 between the treatment groups. Under similar assumptions, a sample size of 250 subjects randomized per arm in one of the randomized cohorts will yield roughly 200 subject per arm which provides at least 90% power to detect a difference of 1.9 between treatment groups.

9.3 Populations for Analysis

The following analysis sets are defined for this protocol:

- Enrolled subjects: Subjects who signed an informed consent form and were assigned a Subject Identification number (SID)

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

[redacted]

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

[redacted]

- Modified Intent to Treat (mITT) Subjects (randomization phase): randomized subjects that received at least one dose of study therapy and provided a non-missing baseline assessment and at least one non-missing post-baseline on-treatment efficacy assessment in the randomization phase

[redacted]

9.4 Statistical Methods

9.4.1 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.

9.4.2 Primary Endpoint(s)

As the primary objective of this study is based on the evaluation of severity of subjects' 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) as taken, a treatment policy 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. This treatment effect will be summarized as the difference in change from baseline in the YBOCS between the groups receiving troriluzole and placebo.

Since the primary intent of this trial is to evaluate the effect of the drug as taken, a treatment policy strategy will be employed. All available assessments on the subject will be used regardless of treatment discontinuation, treatment non-compliance, protocol allowed dose adjustments, or initiation or adjustment of concomitant medications related to other symptoms.

The data will be analyzed based on the combined randomization strata as well as individual randomization strata (for baseline Y-BOCS strata). The change from baseline in the Y-BOCS total score will be analyzed using Mixed Model for Repeated Measures (MMRM) analysis model. The model with all mITT subjects [redacted] The covariance structure (SAS "R" matrix) will be initially specified as unstructured. If the model fails to converge, the analyst may try a HuynhFeldt structure, followed by an AR(1) structure. [redacted] The troriluzole and placebo groups will be compared at each week 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 [redacted] Sensitivity analyses will include, but not limited to, multiple imputation methods using a "jump to reference" or a "tipping point" approach. In addition, a responder analysis with response defined as a 25%, or greater improvement in the Y-BOCS and with non-completers counted as failures (NC=F) will be conducted using the Cochran-Mantel-Haenszel method [redacted] Additional details of these analyses are provided in the statistical analysis plan.

9.4.3 Secondary Endpoint(s)

The change from baseline on the SDS total score and the CGI Severity score will be analyzed using the same methodology as the primary endpoint. Further details on the secondary and exploratory analyses are provided in the SAP.

9.4.4 Adjustment for Multiplicity

Type 1 error will be controlled for the primary and secondary efficacy endpoints by testing them with a gate-keeping procedure. [redacted] 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.

9.4.5 Missing Data

Based on the recently completed study BHV4157-202, no more than 20% of the subjects failed to complete the study. Hence a similar rate for this study will be assumed. 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, for example, “jump to reference” and "tipping point" methods. Further details on the handling of missing data, including for the SDS, are provided in the statistical analysis plan.

9.4.6 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 AE 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 tabular displays of on-treatment liver function test results are provided. Safety summaries will be provided for the overall treated sample as well as within each randomized stratum separately.

[redacted]

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP),

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

This study will be conducted in compliance with the protocol. The protocol and any amendments and the subject 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 subjects 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).

[redacted]

10.3 Institutional Review Board/Independent Ethics Committee

The Investigators agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favorable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the Investigator site and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

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

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

10.4 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Biohaven (or designee) will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

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

the form will be entered in his or her CRF. The subject will be provided with a copy of his or her signed and dated informed consent form.

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

The rights, safety, and well-being of study subjects 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 subject'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 where 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.

10.5 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation of each study subject. 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 subjects 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.

11 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 subject;
- 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 IP dispensing and accountability.

11.1 Source Documentation

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

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

11.2 Study Files and Record Retention

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

12 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.

13 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.

14 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.

15 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.

16 CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A randomized, double-blind, placebo-controlled trial of adjunctive troriluzole in Obsessive Compulsive Disorder

Study No: BHV4157-303

Original Protocol Date: 18 Dec 2020

Protocol Version No: V4.0

Protocol Version Date: 05NOV2024

- 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: [redacted] Biohaven Pharmaceuticals, Inc.	Refer to last page for esignature	
Clinical Operations: [redacted] Biohaven Pharmaceuticals, Inc.	Refer to last page for esignature	
Biometrics: [redacted] Biohaven Pharmaceuticals, Inc.	Refer to last page for esignature	
Medical Lead: [redacted] Biohaven Pharmaceuticals, Inc.	Refer to last page for esignature	
Regulatory Affairs: [redacted] Biohaven Pharmaceuticals, Inc.	Refer to last page for esignature	

17 APPENDICES

17.1 APPENDIX I - Names of Study Personnel

Sponsor:	Biohaven Pharmaceuticals, Inc. Refer to contact list in study binder for contact information
Medical Monitor:	[redacted] [redacted] Biohaven Pharmaceuticals, Inc. 215 Church Street New Haven, Connecticut 06510 [redacted] Back Up: [redacted] Biohaven Pharmaceuticals, Inc. 215 Church Street New Haven, Connecticut 06510 [redacted]
Clinical Research Organizations:	Catalyst Clinical Research 2528 Independence Blvd, Suite 100 NC 28412 Accelsiors Headquarter Bahnhof-Par 2 Ch-6340 Baar, Switzerland Accelsiors Haros St. 103 1222 Budapest Hungary Refer to contact list in study binder for contact information

Central Laboratory:	ACM Global Laboratories 160 Elmgrove Park Rochester, NY 14624 Refer to contact list in study binder for contact information
Central ECG:	ERT 1818 Market Street, 10th floor Philadelphia, PA 19103 Refer to contact list in study binder for contact information
Integrated Trial Technology (IRT)	4G Clinical 370 Washington Street Wellesley, MA 02481 Refer to contact list in study binder for contact information
Data Management and Biostatistics	Rho 2635 E. NC Hwy. 54 Durham, NC 27713 Refer to contact list in study binder for contact information
Rater Training	Massachusetts General Hospital (MGH) through Clinical Trials Network and Institute (CTNI) 55 Fruit Street Boston, MA 02114 Refer to contact list in study binder for contact information
Pharmacovigilance:	PPD Refer to SAE, Pregnancy Surveillance Forms and study binder for contact information.

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

Enzyme System*

CYP1A2 Potent and Moderate Inhibitors

Amiodarone
Ciprofloxacin
Efavirenz
Enoxacin
Furafylline
Fluvoxamine
Genistein
Idrocilamide
Interferon
Methoxsalen
Mexiletine
Osilodrostat
Phenylpropanolamine
Pipemidic Acid
Propranolol
Rofecoxib
Rucaparib
Ticlopidine
Troleandomycin
Vemurafenib
Zafirlukast

CYP1A2 Potent and Moderate Inducers

Beta-napththoflavone
Carbamazepine
Insulin
Methylcholanthrene
Modafinil
Nafcillin
Phenytoin
Primidone
Rifampin
Ritonavir
Teriflunomide

*This list is not exhaustive

REFERENCES CITED

1. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62(6):617-27. (In eng). DOI: 10.1001/archpsyc.62.6.617.

2. Pittenger C, Bloch MH, Wasylink S, et al. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial. J Clin Psychiatry 2015;76(8):1075-84. DOI: 10.4088/JCP.14m09123.

3. Ghaleiha A, Entezari N, Modabbernia A, et al. Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study. J Psychiatr Res 2013;47(2):175-80. DOI: 10.1016/j.jpsychires.2012.09.015.

4. Arabzadeh S, Shahhossenie M, Mesgarpour B, et al. L-carnosine as an adjuvant to fluvoxamine in treatment of obsessive compulsive disorder: A randomized double-blind study. Hum Psychopharmacol 2017. DOI: 10.1002/hup.2584.

5. Emamzadehfard S, Kamaloo A, Paydary K, et al. Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study. Psychiatry Clin Neurosci 2016;70(8):332-41. DOI: 10.1111/pcn.12394.

6. Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther 2016;41(2):214-9. DOI: 10.1111/jcpt.12370.

7. Coric V, Milanovic S, Wasylink S, Patel P, Malison R, Krystal JH. Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. Psychopharmacology 2003;167:219-220.

8. Monaghan DT, Yao D, Cotman CW. L-[3H]Glutamate binds to kainate-, NMDA- and AMPA-sensitive binding sites: an autoradiographic analysis. Brain Res 1985;340(2):378-83. DOI: 10.1016/0006-8993(85)90936-9.

9. Egashira N, Shirakawa A, Abe M, et al. N-acetyl-L-cysteine inhibits marble-burying behavior in mice. J Pharmacol Sci 2012;119(1):97-101. (http://www.ncbi.nlm.nih.gov/pubmed/22510519).

10. Iijima M, Kurosu S, Chaki S. Effects of agents targeting glutamatergic systems on marble-burying behavior. Neurosci Lett 2010;471(2):63-5. DOI: 10.1016/j.neulet.2009.12.048.

11. Pittenger C. Glutamatergic agents for OCD and related disorders. Current treatment options in psychiatry 2015;2(3):271-283. DOI: 10.1007/s40501-015-0051-8.

12. Pittenger C. Glutamate modulators in the treatment of obsessive-compulsive disorder. Psychiatr Ann 2015;45(6):308-315. DOI: 10.3928/00485713-20150602-06.

13. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol Ther 2011;132(3):314-32. (In eng). DOI: 10.1016/j.pharmthera.2011.09.006.

14. Rodriguez CI, Kegeles LS, Levinson A, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology 2013;38(12):2475-83. DOI: 10.1038/npp.2013.150.

15. Stewart SE, Fagerness JA, Platko J, et al. Association of the SLC1A1 glutamate transporter gene and obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet 2007;144B(8):1027-33. DOI: 10.1002/ajmg.b.30533.

16. Carlsson ML. On the role of cortical glutamate in obsessive-compulsive disorder and attention-deficit hyperactivity disorder, two phenomenologically antithetical conditions. Acta Psychiatr Scand 2000;102(6):401-13. DOI: 10.1034/j.1600-0447.2000.102006401.x.

17. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. Arch Gen Psychiatry 2006;63(7):769-76. DOI: 10.1001/archpsyc.63.7.769.

18. Bloch MH, Wasylink S, Landeros-Weisenberger A, et al. Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry 2012;72(11):964-70. DOI: 10.1016/j.biopsych.2012.05.028.

19. Jenike MA. Clinical practice. Obsessive-compulsive disorder. N Engl J Med 2004;350(3):259-65. DOI: 10.1056/NEJMcp031002.

20. Pallanti S, Quercioli L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. Prog Neuropsychopharmacol Biol Psychiatry 2006;30(3):400-12. DOI: 10.1016/j.pnpbp.2005.11.028.

21. Husted DS, Shapira NA. A review of the treatment for refractory obsessive-compulsive disorder: from medicine to deep brain stimulation. CNS spectrums 2004;9(11):833-47. (http://www.ncbi.nlm.nih.gov/pubmed/15520607).

22. Pallanti S, Hollander E, Goodman WK. A qualitative analysis of nonresponse: management of treatment-refractory obsessive-compulsive disorder. J Clin Psychiatry 2004;65 Suppl 14:6-10. (http://www.ncbi.nlm.nih.gov/pubmed/15554782).

23. McDougle CJ, Fleischmann RL, Epperson CN, Wasylink S, Leckman JF, Price LH. Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 1995;56(11):526-8. (http://www.ncbi.nlm.nih.gov/pubmed/7592506).

24. Saxena S, Wang D, Bystritsky A, Baxter LR, Jr. Risperidone augmentation of SRI treatment for refractory obsessive-compulsive disorder. J Clin Psychiatry 1996;57(7):303-6. (http://www.ncbi.nlm.nih.gov/pubmed/8666572).

25. Mattheisen M, Samuels JF, Wang Y, et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry 2015;20(3):337-44. DOI: 10.1038/mp.2014.43.

26. Stewart SE, Yu D, Scharf JM, et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry 2013;18(7):788-98. DOI: 10.1038/mp.2012.85.

27. Naaijen J, Zwiers MP, Amiri H, et al. Fronto-Striatal Glutamate in Autism Spectrum Disorder and Obsessive Compulsive Disorder. Neuropsychopharmacology 2016. DOI: 10.1038/npp.2016.260.

28. Baxter LR. Brain imaging as a tool in establishing a theory of brain pathology in obsessive compulsive disorder. J Clin Psychiatry 1990;51 Suppl:22-5; discussion 26. (In eng) (https://www.ncbi.nlm.nih.gov/pubmed/2298713).

29. Baxter LR, Saxena S, Brody AL, et al. Brain Mediation of Obsessive-Compulsive Disorder Symptoms: Evidence From Functional Brain Imaging Studies in the Human and Nonhuman Primate. Semin Clin Neuropsychiatry 1996;1(1):32-47. (In eng). DOI: 10.1053/SCNP00100032.

30. Bolton J, Moore GJ, MacMillan S, Stewart CM, Rosenberg DR. Case study: caudate glutamatergic changes with paroxetine persist after medication discontinuation in pediatric OCD. J Am Acad Child Adolesc Psychiatry 2001;40(8):903-6. (In eng). DOI: 10.1097/00004583-200108000-00011.

31. Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J Am Acad Child Adolesc Psychiatry 2000;39(9):1096-103. (In eng). DOI: 10.1097/00004583-200009000-00008.

32. Bhattacharyya S, Khanna S, Chakrabarty K, Mahadevan A, Christopher R, Shankar SK. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. Neuropsychopharmacology 2009;34(12):2489-96. (In eng). DOI: 10.1038/npp.2009.77.

33. Chakrabarty K, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. Neuropsychopharmacology 2005;30(9):1735-40. (In eng). DOI: 10.1038/sj.npp.1300733.

34. Maura G, Roccatagliata E, Ulivi M, Raiteri M. Serotonin-glutamate interaction in rat cerebellum: involvement of 5-HT1 and 5-HT2 receptors. Eur J Pharmacol 1988;145(1):31-8. (In eng). DOI: 10.1016/0014-2999(88)90345-7.

35. Coric V, Taskiran S, Pittenger C, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. Biological Psychiatry 2005;58:424-428.

36. Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. Journal of Child and Adolescent Psychopharmacology 2007;17(6):761-767.

37. Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 2008;32(3):525-49. DOI: 10.1016/j.neubiorev.2007.09.005.

38. BHV4157-203-protocol. A Phase 2 Randomized Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of BHV-4157 in Patients with Mild to Moderate Alzheimer's Disease. Biohaven Pharmaceuticals, Inc., 2018.

39. Liu J, Wang LN. The efficacy and safety of riluzole for neurodegenerative movement disorders: a systematic review with meta-analysis. Drug Deliv 2018;25(1):43-48. DOI: 10.1080/10717544.2017.1413446.

40. Pittenger C, Coric V, Banasr M, Bloch MH, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. CNS Drugs 2008;22(9):761-786.

41. Koran L SH. Guideline Watch (March 2013): Practice Guideline for the Treatment of Patients with Obsessive Compulsive Disorder. APA Practice Guidelines 2013.

42. Del Casale A, Sorice S, Padovano A, et al. Psychopharmacological Treatment of Obsessive-Compulsive Disorder (OCD). Curr Neuropharmacol 2019;17(8):710-736. DOI: 10.2174/1570159X16666180813155017.

43. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry 2014;14 Suppl 1:S1. (In eng). DOI: 10.1186/1471-244X-14-S1-S1.

44. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014;28(5):403-39. DOI: 10.1177/0269881114525674.

45. AWMF. S3-Guideline/National Disease Management Guideline Unipolar Depression - Short Version. 2012.

46. Albert U DOB, Maina G. Evidence based Psychiatric Care - Towards Italian guidelines for the pharmacological treatment of Obsessive-Compulsive Disorder (OCD) in adults: a preliminary draft. Journal of the Italian Society of Psychiatry 2019;5:21-9.

47. Brakoulias V, Stockings E. A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder. Expert Opin Pharmacother 2019;20(1):47-53. (In eng). DOI: 10.1080/14656566.2018.1540590.

48. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266-77. DOI: 10.1176/appi.ajp.2011.10111704.

49. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989;46(11):1006-11. (In eng). DOI: 10.1001/archpsyc.1989.01810110048007.

50. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. II. Validity. Arch Gen Psychiatry 1989;46(11):1012-6. DOI: 10.1001/archpsyc.1989.01810110054008.

51. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int Clin Psychopharmacol 2008;23(2):70-83. (In eng). DOI: 10.1097/YIC.0b013e3282f2b4d6.

52. Eisen JL, Phillips KA, Baer L, Beer DA, Atala KD, Rasmussen SA. The Brown Assessment of Beliefs Scale: reliability and validity. Am J Psychiatry 1998;155(1):102-8. (In eng). DOI: 10.1176/ajp.155.1.102.

53. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry 2003;54(5):573-83. (In eng). DOI: 10.1016/s0006-3223(02)01866-8.

54. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988;56(6):893-7. (In eng). DOI: 10.1037//0022-006x.56.6.893.

55. Abramowitz JS, Deacon BJ, Olatunji BO, et al. Assessment of obsessive-compulsive symptom dimensions: development and evaluation of the Dimensional Obsessive-Compulsive Scale. Psychol Assess 2010;22(1):180-98. DOI: 10.1037/a0018260.

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