Title Research Project: **Double-Blind, Placebo-Controlled, Single-Dose Crossover Study Examining the Effects of Sublingual Riluzole (BHV-0223) on Public Speaking in Social Anxiety Disorder**
Principal Investigator: Michael H. Bloch, MD
HIC# 1605017768
Date of Approval: 6/28/2017 VALID THROUGH 7/26/2018
NTC03017508

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: **Double-Blind, Placebo-Controlled, Single-Dose Crossover Study Examining the Effects of Sublingual Riluzole (BHV-0223) on Public Speaking in Social Anxiety Disorder**			
Principal Investigator: Michael Bloch MD, MS		**Yale Academic Appointment:** Assistant Professor	
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Protocol Correspondent Name & Address (*if different than PI*): Angeli Landeros-Weisenberger			
Campus Phone: (203)785-7683	**Fax:** (203)737-5104	**E-mail:** Angeli.landeros@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**			**tment:**
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and

degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI

Yes • No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

Yes • No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☒ Specify Other Yale Location: Yale Child Study Center
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

☐ APT Foundation, Inc.	☐ Haskins Laboratories
☐ Connecticut Mental Health Center	☐ John B. Pierce Laboratory, Inc.
☒ Clinical Neuroscience Research Unit (CNRU)	☐ Veterans Affairs Hospital, West Haven
☐ Other Locations, Specify:	☐ International Research Site (Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC)	Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Yale University RSC (YU-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ *Nursing Research Committee	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form

☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. Two years.

3. **Research Type/Phase: (Check all that apply)**

   a. **Study Type**

   ☒ Single Center Study
   ☐ Multi-Center Study

   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐

   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**

   ☒ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.*

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes____No _X__ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	unding	unding Mechanism
Michael H. Bloch, MD MS	Sublingual Riluzole for the Social Anxiety Disorder	Biohaven Pharmaceuticals	Federal ☐ State ☐ Non Profit ☒ Industry ☐ Other For I rofit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:

			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit Other	Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name: Kimberly Gentile VP, Clinical Operations
Company: Biohaven Pharmaceuticals Inc.
Address: 234 Church Street, Suite #304
New Haven CT 06510
Tel. 860-690-9543

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Michael H Bloch	Yale	Mhb32
Role:Co-Investigator	Christopher Pittenger	Yale	PITT
Role:Co-Investigator	Angeli Landeros-W.	Yale	Al495
Role:Co-Investigator	Jerome Taylor		Jht28
Role: Study Personnel	Baris Olten, MD	Yale	BO222
Role:Study Personnel	Jessica A. Johnson	Yale	Jaj62

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested. The goal of the current proposal is to examine the acute anxiolytic effects of BHV-0223 on subjects with social anxiety disorder performing an anxiety-provoking speech task.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

- Social Anxiety Disorder is common and causes significant impairment.
- First-line treatments for Social Anxiety Disorder are only partially effective. Many SAD patients experience little or inadequate symptom relief with available treatments.
- Riluzole is a glutamate modulating agent that would potentially target a new mechanism to treat anxiety.
- Riluzole has been shown to reduce anxiety in adults Major Depression, Generalized Anxiety Disorder and Obsessive Compulsive Disorder.

Social anxiety disorder (SAD) affects approximately 12.1% of all Americans and is defined as a "marked and persistent fear of one or more social situations," causing impairment and distress (1). SAD typically impairs academic achievement, work productivity, social relationships, and results in a significantly poorer quality of life(2). SAD is associated with subsequent development of depression, alcoholism, and cardiovascular disease (1-3).

Roughly one-third to one-half of patients with generalized SAD do not experience significant clinical benefit from current evidence-based treatments, such as pharmacotherapy with selective serotonin reuptake inhibitors (SSRI) or venlafaxine and cognitive behavioral therapy (CBT) (4-7). Failure of anxiety relief in patients with SAD is a source of substantial morbidity, distress, and decreases in quality of life.

Several pharmacological treatments are utilized on an as-needed basis because of their short-term, potent anti-anxiolytic effects. These pharmacological agents include benzodiazepines (which target the gamma-aminobutyric acid-A receptor (GABA-A) and beta-blockers (beta adrenergic receptor antagonists) (8, 9). Although, benzodiazepines are quite effective at reducing anxiety over the short term (10) in specific situations (e.g. flying on an airplane), their side-effects and tolerability currently limit their usefulness in many situations (e.g. performance or public-speaking anxiety) (8, 9). Benzodiazepine use is associated with impaired short-term concentration, decreased alertness and psychomotor impairment (9, 11). Chronic benzodiazepine use is further associated with physiologic dependence, rebound anxiety on discontinuation and, possibly even interference with the efficacy of CBT (one of the first-line treatments for anxiety) (9, 11). Beta-blockers, on the other hand, are effective at acutely reducing the peripheral physical symptoms of anxiety (e.g. heart palpitations, tremors etc.) but have no effect on

the cognitive or emotional symptoms of anxiety (9, 10, 12-15). Novel pharmacological treatments are needed to improve patient outcomes with SAD, both chronically to reduce symptoms and acutely to reduce impairment during situations where symptoms are most likely to be impairing (e.g. public speaking or performance anxiety).

Riluzole is a glutamate-modulating agent that is FDA-approved for the treatment of amyotrophic lateral sclerosis. Riluzole has been documented at physiologically realistic drug concentrations to (1) inhibit certain voltage-gated sodium channels reducing glutamate release and (2) enhance astrocytic uptake of extracellular glutamate. Several uncontrolled trials have suggested the efficacy of riluzole for reducing anxiety symptoms in adults with Generalized Anxiety Disorder, Obsessive-Compulsive Disorder and Major Depression (16-20). An 8-week, open-label, fixed-dose, trial of 18 adults with GAD given riluzole (100mg/day) demonstrated a significant improvement over time with riluzole treatment (17). Sixty-seven percent of adults with GAD responded to riluzole treatment (defined as a greater than 50% decrease in HAM-A) and 44% of subjects had a remission of anxiety symptoms after riluzole treatment (HAM-A<8) (17). No double-blind, placebo-controlled trials of riluzole have been conducted in the treatment of patients with primary anxiety disorders. Riluzole is quite well tolerated in psychiatric and ALS population, with nausea and sedation being the most common side effects. Elevation of liver function tests is a common occurrence with chronic riluzole administration and necessitates periodic monitoring but has been without clinical consequences in psychiatric trials with riluzole to date.

Biohaven Pharmaceuticals recently developed BHV-0223, which is a sublingual form of riluzole, being investigated for the treatment of ALS. BHV-0223 has several advantages over the currently available riluzole formulation in that it (1) avoids first-pass metabolism, thereby reducing overall drug burden to the liver and (2) has produced subjective reports of relaxing effects when administered to healthy subjects.

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

    - We are proposing a crossover trial in which 20 adults with Social Anxiety Disorder with the primary outcome being anxiety on the impromptu speech task.
    - Each subject will be given BHV-0223 (or placebo) under double-blind conditions 1-hour before performing the impromptu speech task on 2 separate study days.
    - There will be a 2 to 10 day washout period between study days.
    - There will be a final Follow-up visit 2 to 10 days later to do blood work and complete physical exam.

Overview:

We propose conducting a double-blind, placebo controlled crossover study examining the effects of BHV-0223 on public speaking anxiety. Twenty subjects with DSM-5 defined social anxiety disorder and clinically significant public speaking anxiety on the Impromptu Speech Task will be enrolled in a challenge study. Subjects will be given BHV-0223 (or placebo) under double-blind crossover conditions 1 hour prior to performing each of 2 impromptu speech tasks. The two study days involving BHV-0223 (or placebo) administration and impromptu speech task will be separated by 2 to 10 days to allow for medication washout. There will be a final follow-up visit 2 to 10 days later to perform a complete Physical exam and do follow-up liver function testing and a Complete Blood Count. Our primary outcome will examine BHV-0223's effects (compared to placebo) on self-rated anxiety during the impromptu speech task. We will also collect physiological measures of anxiety, clinician-rated measures of anxiety, and measures of speech performance as secondary outcomes.

Screening:

A baseline screening assessment to determine study eligibility, clinical ratings, and physical health will be conducted at least one week prior to the challenge study.

Medical Assessments

During the screening visit, vital signs (BP, HR: supine, standing X 2-3 min), physical exam (including a comprehensive exam of the oral cavity see Appendix 1), and clinical laboratory tests (i.e. CBC with differential, complete metabolic panel (CMP) (including electrolytes, LFTs, BUN, creatinine and glucose), TFTs, urine drug screen, and routine urinalysis) will be completed. A pregnancy test will be given to all females of childbearing age enrolled in the study prior to participating in the study sessions. We will also perform a visual inspection of the mouth cavity to assess local tolerability before and 1 hour after administering study medication on each study day (please see appendix document for further details).

Psychiatric Assessments

The SCID (Structured Clinical Interview for DSM disorders) on the screening day to verify presence of social anxiety disorder and the absence of other psychiatric conditions (psychotic disorders, current substance abuse/dependence etc.). The *Liebowitz Social Anxiety Scale (LSAS)* will be administered to determine that public speaking anxiety symptoms are significant enough for inclusion in the trial. The LSAS is a rating scale that assesses SAD severity (21) and a 5-item subscale rates public speaking fear (22). Psychiatric rating scales examining the severity of anxiety (*Hamilton Anxiety Rating Scale (HAM-A* (23)) and depressive symptoms *Hamilton Depression Rating Scale (HAM-D*) (24) will also be administered. Per FDA guidelines, suicidal ideation and behavior will be monitored using the C-SSRS(25) at screening and on every visit day.

Intervention:

Subjects will be given BHV-0223 35mg or placebo in a random order as assigned through the CMHC pharmacy with a 2 to 10 day separation between task days. Randomization will be performed by the CMHC pharmacy. The identity of the treatments will be concealed by the use of study drugs that are identical in packaging, labeling, schedule of administration and appearance. Placebo and study drug will be prepared in a like fashion in the CMHC pharmacy. Unblinding of a specific patient's randomization assignment will only occur during the study in the case of specific patient emergencies.

BHV-0223 is a sublingual, oral-disintegrating tablet containing 35mg of riluzole drug substance. BHV-0223 35mg tablets have shown bioequivalence to riluzole 50mg administered orally (please see PIND 128411 for further details). The half-life of BHV-0223 is just under 8 hours. Riluzole is a member of the benzothiazole class of medications. Chemically, its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. The efficacy of riluzole in the treatment of ALS was established in two well-controlled studies. Patients randomized to treatment with riluzole showed longer time to tracheoctomy or death compared to those treated with placebo. The recommended dose of riluzole in the treatment of ALS is 50mg taken every 12 hours (at least an hour before, or two hours after, a meal to avoid food-related decreases in bioavailability). Riluzole's mechanism of action in the treatment of ALS is unknown but thought to be due to its down-modulation of glutamatergic neurotransmission.

The most commonly observed adverse reactions of riluzole, dosed at 100mg/day, in placebo-controlled trials were asthenia (19.2%), nausea (16.3%), dizziness (3.9%), decreased lung function (10.2%), diarrhea (2.9%), abdominal pain (5.1%), pneumonia, vomiting (4.2%), vertigo (1.9%), oral paresthesia, anorexia (3.2%), and somnolence (1.9%). In a study with approximately 4,000 patients given riluzole for ALS, three cases of neutropenia were reported within the first two months of treatment.

Rarely, jaundice is a side effect as well. Riluzole has also been found to cause elevations in serum aminotransferase even in patients without a history of liver disease. Experience with riluzole in 800 patients with ALS demonstrated that approximately 50% of riluzole treated patients experienced at least one ALT/SGPT level above the upper limit of normal, 8% had elevations >3x upper limit of normal (ULN), and 2% >5x ULN. BHV-0223 may have reduced overall drug burden on the liver as the sublingual formulation avoids first-pass metabolism.

Subjects will be asked to come back 2 to 10 days after the second task day to perform a complete Physical Exam, Visual examination of the oral cavity, Vital signs (BP, HR: supine, standing X 2-3 min), Complete Blood count and Liver function test.

Assessments

Impromptu Speech Behavioral Assessment Test

The impromptu speech BAT will be performed 1 hour after the subject receives study medication as outlined in the table below (26-28). Participants will be asked to speak about pre-determined topics for 10 minutes to a small audience of research staff

(27). Patients with more severe social anxiety symptoms are often not able to speak for the full 10 minutes and have shorter speech lengths when compared to those with less severe social anxiety symptoms (26-28). VAS-anxiety, State-Trait Anxiety Inventory and the Self-Statement during Speech Test (SSPS) (28) will be assessed before and after the speech. The Local Tolerability Assessment (Appendix 1) will be performed at screening, baseline, 1 hour after receiving the study medication and before discharge.

The Table below shows the assessment schedule for participants enrolling in the trial.

		Challenge DAY 1					2-10 day washout period	Challenge DAY 2					2-10 days	
Measure	Screening	Baseline	0	1h	2h	3h		Baseline	0	1h	2h	3h		Follow up visit
Local Tolerability Assessment	X	X		X		X		X		X		X		
Impromptu Speech Task				X						X				
VAS-anxiety	X	X	X	X	X	X		X	X	X	X	X		
VAS-speech performance				X						X				
SSPS		X		X				X		X				
STAI		X		X				X		X				
DSST		X		X				X		X				
Immediate and Delayed Word Recall		X		X				X		X				
Clinicial-rated VAS-anxiety				X						X				
Clinician rated VAS-speech performance				X						X				
LSAS	X	X						X						
SCID	X													
C-SSRS	X					X						X		
Physical Exam with Vital signs (BP, HR: supine, standing X 2-3 min) and Visual exam of the oral cavity	X	X				X		X				X		X
Blood test	X													X
Urine Test	X	X						X						
EKG	X													
STUDY MEDICATION ADMINISTRATION			X						X					

The rating scales utilized in the trial are detailed in the table below. Ratings will be conducted by raters that are blinded to treatment assignment and will not be present during medication administration.

RATING SCALES:

1) *Visual Analog Scale (VAS) of Anxiety States:* The VAS includes scales for anxiety, drowsiness, high, irritability, anger, and sadness. These scales are 100 mm lines marked by participants at a point corresponding to the apparent intensity of the feeling state (0=none, to 100=most ever) (29). We will also use clinician-rated visual analogue scales to measure subject anxiety and speech performance during the Impromptu Speech Task.
2) *Self-Statement During Public Speaking Scale (SSPS):* The SSPS is a rating scale used to measure cognitions that occurred during a speech (28).
3) *State-Trait Anxiety Inventory (STAI):* The STAI is a standardized rating scale of trait and state anxiety (30).
4) Digit Symbol Substitution Task (DSST): Digit Symbol Substitution Tasks requires the subject to match symbols with their corresponding digit. It consists of 9 digit symbols matched with their corresponding numerical digit. Subjects are asked to match as many number-symbol pairs within a 90 second time limit. Performance

of the DSST has been demonstrated to be impaired by acute treatment with benzodiazepines (31).
5) Immediate and Delayed Word Recall Test – In this task, a list of 10 words will be repeated 3 times to subjects at a pace of 1 word every 2 seconds. Immediately after presentation of the list and 5 minutes later subjects will be asked to recite as many of the words as they can from memory. Performance on this task has been demonstrated to be impaired by acute treatment with benzodiazepines (31).
6) Local Tolerability Assessment: Systematized oral cavity inspection checklist (Appendix 1).
7) Columbia-Suicide Severity Rating Scale (C-SSRS) – Assessment of suicidal ideation and behavior in clinical and research settings(25)

Statistical Analyses

Assuming that there are no ordering or period effects in the trial, we will use a paired t-test to compare ratings of anxiety during the impromptu speech task after BHV-0223 vs. placebo treatment. Given a sample size of 20 subjects, assuming a one-sided α=0.1, we would have 80% power to detect a treatment effect size=0.5 or greater. As a comparison previous studies of benzodiazepines have demonstrated an effect size of at least 0.9 on similar speech paradigms (32). Our primary measure will be the VAS-anxiety after the impromptu speech task (BHV-0223 compared to placebo). As additional secondary measures we will collect (1) subject ratings of speech performance, self-statements during public speaking (SSPS) and specific anxiety symptoms during speech (STAI); (2) clinical ratings of speech performance; (3) duration of speech; (4) assessments of cognition – (DSST and 15 word recall) and 5) side-effects.

4. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
   ii. the plan for the collection of material or the conditions under which material will be received
   iii. the types of information about the donor/individual contributors that will be entered into a database
   iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
    i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

20 subjects who meet DSM-5 criteria for Social Anxiety Disorder and have a baseline LSAS public speaking subscale score>6 will be recruited through the Yale Child Study Center. We have experience recruiting subjects with social anxiety disorder through a trial examining the effects of ketamine for social anxiety disorder.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

PATIENTS WITH SOCIAL ANXIETY DISORDER:

Inclusion Criteria:

1) Male or female (post-menopausal, surgically sterile, or negative pregnancy test at screening and agreement to utilize an established birth control, including complete abstinence, during the testing period) between the age of 18 and 65 yrs.
2) Meet DSM-5 criteria for social anxiety disorder by structured clinical interview (SCID) and have a LSAS public speaking subscale score >6.
3) Stable psychiatric medications. Patients must have had stable doses of all psychiatric medications for the month prior to treatment and have been on stable doses of SSRI and antidepressants for at least 1 month prior to study enrollment. As needed benzodiazepine use will be permitted as long as subjects refrain from using benzodiazepines for the 48 hours prior to the study.
4) Medically and neurologically healthy on the basis of physical examination, SMAC-20 (including LFT's, TFT's), VDRL, CBC w/ diff, urinalysis, urine toxicology, EKG, and medical history. Individuals with stable medical problems that do not have CNS effects or interfere with medications administered (e.g., oral hypoglycemics) may be included if their medications have not been adjusted in the month prior to entry;
5) Urine toxicology screen negative for drug of abuse.
6) Able to provide written informed consent according to the Yale Human Investigation Committee (HIC) guidelines.

Exclusion Criteria:

1. Positive pregnancy test
2. Breastfeeding females
3. History of substance abuse disorder (ETOH, cocaine, opiates, PCP) within the last 6 months or positive urine toxicology on screening (within the previous 6 months).
4. History of pervasive developmental disorder or psychotic disorder by DSM-IV-TR criteria.
5. Presence of dentures, braces, piercings at the time of dosing, or any physical findings in the mouth or tongue that, in the opinion of the Principal Investigator, would be likely to interfere with successful completion of the dosing procedure.
6. Subjects with a medical condition that might interfere with the physiological absorption and motility (*ie*, gastric bypass, duodenectomy) or gastric bands.
7. Subjects with any clinically significant abnormality or abnormal laboratory test results.
8. Subject has a current diagnosis of viral hepatitis (HBsAG or HVC) or a history of liver disease.
9. Subject has significant history of seizure disorder other than a single childhood febrile seizure (eg. Epilepsy)
10. Subjects using any drugs known to induce or inhibit CYP 1A2 metabolism (examples of inducers: rifampin, carbamazepine, etc.; examples of inhibitors: fluvoxamine, ciprofloxacin, fluoroquinolones, etc.) within 30 days prior to the first study drug administration.
11. Subject with a history of allergic reactions to riluzole or other related drugs.
12. Subject has a history of anaphylaxis, a documented hypersensitivity reaction, or a clinically important reaction to any drug.
13. Subject has received another investigational drug or device within the 30 days (90 days for biologics) prior to the first dosing or is currently participating in an investigational study involving no drug administration.
14. Subject with clinically significant electrocardiogram (ECG) abnormalities (QTcF >450 msec) or vital sign abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at Screening or Baseline (Day -1).
15. Any reason which, in the opinion of the Principal Investigator, would prevent the subject from participating in the study.

8. How will **eligibility** be determined, and by whom?

Screening: After an initial telephone contact to rule out obvious exclusions from the study protocol, potential participants will be scheduled for a screening visit at the Yale Child Study Center. A member of our research team will discuss all aspects of this research: its purpose, the procedures that will be performed, any/all risks of the procedures, possible benefits, and possible alternative treatments. All patients will also

be informed that the standard of care for patients with SAD who have failed the first line treatments [SSRI, SNRI (or alternative SSRI), and CBT] is a trial of a monoamine oxidase inhibitor (MAOI), not Riluzole (National Institute for Health and Care Excellence 2013). The research team will discuss the inclusion and exclusion criteria for the study. If patients are considered eligible according to study criteria and if they agree to enroll in the study, they will sign the consent forms and schedule a time to go to the CNRU for screening visit 2.

Screening visit 2 will occur on the CNRU (may be done directly after Screening Visit 1 if convenient for the participant), and medical assessments (physical exam, EKG, blood draw, and urinalysis), and a battery of psychiatric rating scales will be performed, as indicated in Table1 (excluding the SCID which is done during screening visit 1). We will also contact the subject's primary care provider or treating provider to confirm their psychiatric history and SAD diagnosis after receiving a signed release form from the subject.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The risks in this study include:

1) drug side effects of riluzole
2) worsening of symptoms
3) blood sampling
4) ratings
5) unanticipated side effects

Drug side effects

BHV-0223 (riluzole) is a member of the benzothiazole class of medications. Chemically, its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. The efficacy of riluzole in the treatment of ALS was established in two, well-controlled studies. Patients randomized to treatment with riluzole showed longer delay to tracheostomy or death compared to those treated with placebo. The recommended dose of riluzole in the treatment of ALS is 50mg taken every 12 hours (at least an hour before, or two hours after, a meal to avoid food-related decreases in bioavailability). Riluzole's mechanism of action in the treatment of ALS is unknown but thought to be due to its blockade of glutamatergic neurotransmission.

The most commonly observed adverse reactions of riluzole, dosed at 100mg/day, in placebo-controlled trials were asthenia (19.2%), nausea (16.3%), dizziness (3.9%), decreased lung function (10.2%), diarrhea (2.9%), abdominal pain (5.1%), pneumonia, vomiting (4.2%), vertigo (1.9%), oral paresthesia, anorexia (3.2%), and somnolence (1.9%). In a study with approximately 4,000 patients given riluzole for ALS, three cases of neutropenia were reported within the first two months of treatment.

Rarely, jaundice is a side effect as well. Riluzole has also been found to cause elevations in serum aminotransferase even in patients without a history of liver disease. Experience with riluzole in 800 patients with ALS demonstrated that approximately 50% of riluzole treated patients experienced at least one ALT/SGPT level above the upper limit of normal, 8% had elevations >3x upper limit of normal (ULN), and 2% >5x ULN.

A single non-ALS patient with epilepsy treated with concomitant carbamazepine and Phenobarbital experienced marked, rapid elevations of liver enzyme with jaundice four months after starting riluzole that returned to normal seven weeks after treatment discontinuation.

Riluzole's effect on liver functioning warrants monitoring of serum LFT levels every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter (PDR). Serum LFT levels should be evaluated more frequently in patients who develop elevations. Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when <5x ULN. In trials, if ALT levels were <5 x ULN, treatment continued and ALT levels usually returned to below 2X ULN within 2-6 months. Treatment in studies was discontinued if ALT levels exceeded 5x ULN.

Riluzole is contraindicated in patients with a history of severe hypersensitivity reactions to riluzole or any of the tablet components. Riluzole should be prescribed with caution in patients with current evidence or history of abnormal liver function. Baseline elevations of several LFTs (especially bilirubin) should preclude the use of riluzole. Riluzole should be used with caution in elderly patients whose hepatic or renal functions may be compromised due to age. Females and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian populations. BHV-0223 may have reduced overall drug burden on the liver as the sublingual formulation avoids first-pass metabolism.

Patients should be instructed to report any febrile illness to their physicians. Patients should also be warned about the potential for dizziness, vertigo, or somnolence and advised not to drive or operate machinery until they have gained sufficient experience on riluzole to gauge whether or not it effects their mental or motor abilities. Patients treated with riluzole should be discouraged from drinking excessive amounts of alcohol as it may increase the risk of serious hepatotoxicity.

Worsening of symptoms

Since Riluzole or placebo is added to the patients' current medications, the risk of symptoms worsening in this study is not significantly greater in this clinical trial than it would be if the patient's medications were changed as part of standard clinical care. Furthermore, the acute effects of study medications should dissipate within 8 hours of taking the single dose of medication. The only additional risks in this study are potential adverse effects of riluzole.

Blood sampling

As a result of their participation in these studies, subjects will have more blood drawn than would be the case in usual clinical practice. Approximately three (3) tablespoons of blood will be drawn during the study. Subjects will be instructed to refrain from donating blood or participating in research involving blood donation during the study and for the 8 weeks following the study. Blood sampling may cause pain, bruising and infection. Some subjects may faint during blood sampling.

Ratings and Speech Task

Patients may find the battery of behavioral ratings tedious. Additionally, the subjects are likely to find the speech task anxiety provoking. Subjects may (and often do) discontinue the speech task at any point if they feel excessively uncomfortable. We have used this speech tasks in previous task without significant adverse events.

Unanticipated side effects

Although riluzole is an approved drug for the treatment of ALS, its use in patients with SAD might be associated with unforeseen risks such as worsening of existing symptoms or emergence of new symptoms. All medications can be associated with allergic reactions. Any clinical trial involves risks and side effects that cannot be predicted. Subjects will be told of any important new information that might affect their decision to continue in the study. In addition, the HIC will be notified regularly of any new information about the safety of the study medication.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Conducting the medication administration under supervision of research staff will allow closer monitoring for detecting symptom changes or adverse effects. A psychiatrist on site will be always emergently available to subjects participating in the study to deal with any unanticipated issues that arise. Records will be maintained according to FDA Good Clinical Practice guidelines to insure protection of confidentiality and security of records.

Drug Side Effects:

Subjects will be closely monitored for any side effects by a study doctor and research assistant throughout the medication challenges. Additionally, subjects will be screened using physical exam and laboratory assessments to identify any medical conditions that

may put subjects at increased risk. All female subjects of child bearing age will be tested for pregnancy prior to enrollment and if positive excluded from the study.

Blood Sampling:

Experienced clinical research staff will perform blood draws using good clinical technique to minimize associated risks.

Ratings and Speech Tasks:

There is minimal risk associated with the questionnaires, clinical assessments and speech task. Clinical research staff will exercise sensitivity when conducting ratings and assessments. A study specific MD will be emergently available on site on testing days, should unanticipated issues arise.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal

Moderate Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

1. We do not view the risks associated with the sublingual riluzole as minimal.

2. Given the now established safety and validity of the current dose of riluzole in our prior work, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Michael H. Bloch, MD) according to the following categories:

a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening OR
2. results in in-patient hospitalization or prolongation of existing hospitalization OR
3. results in persistent or significant disability or incapacity OR
4. results in a congenital anomaly or birth defect OR
5. results in death OR

6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

6. Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), and funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X Food and Drug Administration

The principal investigator (Michael H. Bloch, MD) will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?

ii. What provisions are in place for management of interim results?
iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Assuming that there are no ordering or period effects in the trial, we will use a paired t-test to compare ratings of anxiety during the impromptu speech task after BHV-0223 vs. placebo treatment. Given a sample size of 20 subjects, assuming α=0.05, we would have 80% power to detect a treatment effect size=0.58 or greater. As a comparison previous studies of benzodiazepines have demonstrated an effect size of at least 0.9 on similar speech paradigms (32). Our primary measure will be the VAS-anxiety after the impromptu speech task (BHV-0223 compared to placebo). As additional secondary measures we will collect (1) subject ratings of speech performance, self-statements during public speaking (SSPS) and specific anxiety symptoms during speech (STAI); (2) clinical ratings of speech performance; (3) duration of speech; (4) assessments of cognition – (DSST and 15 word recall) and 5) side-effects.

We additionally take an interim examination of the efficacy data at the trial after 10 subjects to evaluate the initial side-effects of the compound and to examine initial efficacy. We would consider a treatment effect size of less than 0 (BHV-0223 worsen anxiety during the impromptu speech task compared to placebo) as a rationale to stop the trial early.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

BHV-0223 (riluzole) is a member of the benzothiazole class of medications. Chemically, its molecular formula is C 8 H 5 F 3 N 2 OS and its molecular weight is 234.2. Riluzole is FDA approved for the treatment of amyotrophic lateral sclerosis (ALS). The mode of action of this compound is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA? **IND # 130224**
b. Who holds the IND? **Michael H. Bloch, MD MS**
c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☐ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☐ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☐ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☐ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☐ Yes ☐ No

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

The clinical safety profile of riluzole has been described in the US Prescribing Information on its use in ALS. This safety information is excerpted herein. Additionally,

literature reports on the use of riluzole in ALS, psychiatric disorders and other indications are summarized.

While the majority of this data is based on chronic administration of riluzole tablets at a total oral dose of 100 mg/day, the proposed development plan for BHV-0223 targets a sublingual dose that is approximately 30% lower (70 mg/day) but is expected to achieve exposures bioequivalent to that associated with the RILUTEK dose approved for use in ALS. The available safety data on chronic administration of riluzole at a total daily dose of 50 mg shows a more favorable safety profile than the recommended daily dose of 100 mg (i.e., 50 mg PO BID) – particularly with respect to impact on liver enzyme tests. Therefore, with a lessened overall drug burden for BHV-0223 (70 mg per day) compared to RILUTEK (100 mg per day), safety is expected similar or better for BHV-0223 compared to RILUTEK.

Overall, riluzole tablets have been well tolerated in populations with ALS and diverse neuropsychiatric conditions that include Major Depressive Disorder (MDD), Obsessive- Compulsive Disorder (OCD) and Generalized Anxiety Disorder (GAD). In randomized controlled trials (RCTs) comparing a 100 mg daily dose of riluzole with placebo, no AEs occurred at rates greater than 5% and twice that of placebo. The AEs occurring greater than 5% and at least 2% more than placebo included asthenia (18% vs 12% placebo) and nausea (14% vs 9%). These two AEs showed trends for a dose response(33).

The published literature on the use of riluzole tablets in psychiatric disorders, while generally comprising of case-series, is consistent with this tolerability profile. Lab abnormalities associated with riluzole consist of elevated transaminases that typically are below 5x upper limit of normal (ULN) and often resolve while on treatment (Bensimon and Doble 2004). Experience with incidents of alanine aminotransferase (ALT) increasing >5xULN are limited, insofar as the USPI recommends immediate drug discontinuation. Effects on transaminases show a dose response (33). Importantly, total daily doses of 50 mg were not associated with increased rates of marked ALT elevations (>5xULN) compared to placebo (1.3% vs 2.1%, respectively) and such occurrences had a later onset than placebo (median 254 vs 219 days). Total daily doses of 100 mg and 200 mg had greater rates of marked ALT elevations than placebo and the median occurrence was within 60 days.

Experience from Published Reports

The PubMed database was searched for available reports on clinical use of riluzole in patients (e.g., case-series, randomized trials). The search strategy included crossing riluzole (as a title or abstract word) with either report type (clinical trial) or “trial” (abstract). The publications are summarized in Appendix B. The cumulative data are consistent with the current USPI and are described in the following sections.

Clinical reports document the use of riluzole in populations with ALS, Huntington Disease, Spinal Cord Injury (SCI), ataxias, Fragile X Syndrome, Spinal Muscular Atrophy, Multiple Sclerosis, neuropathic pain, Multiple System Atrophy, Parkinson Disease and Irritable Bowel Syndrome. With regards to ALS studies that are not reflected in the USPI, the Early Access Programme (34) described the open-label experience of 7,916 patients with ALS who were prescribed riluzole tablets for an average duration of 202 days. Tolerability was consistent with the USPI. The rate of

ALT increases of > 3xULN and >5xULN was 3.7% and 0.7% respectively – rates that were lower than observed in the randomized controlled trials. The lab abnormalities in studies on other disorders revealed no novel signals compared to the studies described in the USPI; elevations in LFTs were noted. In the study on Huntington Disease (35), one subject demonstrated a reversible elevation of

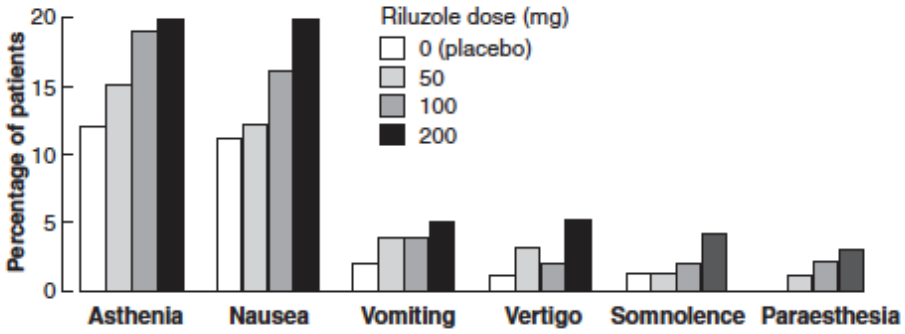
ALT >5xULN after being dosed with 200 mg/day. In the population with acute SCI (treated with riluzole within 12 hours of traumatic injury and on a back-drop of other common interventions like high-dose steroids), higher reversible elevations in LFTs were also observed; however, higher rates of abnormalities were noted prior to intervention (9 – 37%) and many of these patients were on medication regimens with hepatotoxic potential– thus complicating interpretation of the safety reports from this study.

As is suggested from the summary of published data (Appendix B) on the safety profile of riluzole to treat not only ALS, but also certain mood, anxiety and behavioral conditions, the adverse event profile recorded in these patients does not appear to be different either in nature, severity or frequency, to those listed in the currently FDA approved USPI for RILUTEK.

Dose Relationship to Safety and Tolerability

Study 301 described in (33) is the only randomized controlled trial that included doses of riluzole less than 100 mg/day and, hence, provides data relevant to exposures expected for the BHV-0223 program. In this study, 959 patients with ALS were randomized to up to 18 months of treatment with either placebo, 50 mg/day riluzole (dosed 25 mg PO BID), 100 mg/day riluzole (dosed 50 mg PO BID) and 200 mg/day riluzole (dosed 100 mg PO BID). Tolerability as reflected in the most common AEs were dose dependent for asthenia, nausea, vomiting, vertigo, somnolence and paresthesias.

Rate of selected AEs by dose

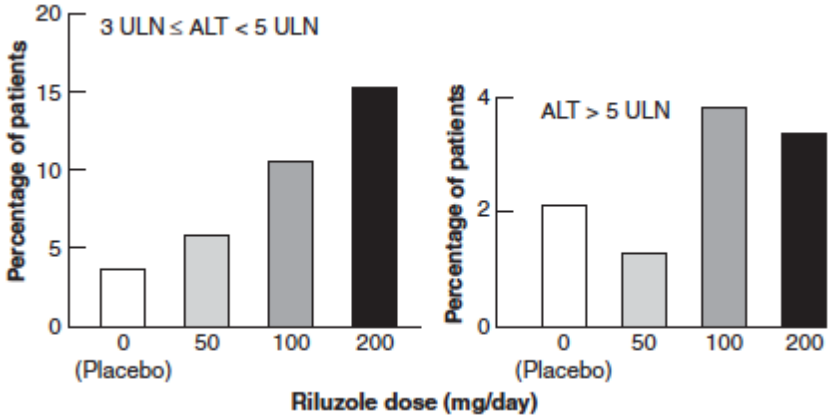


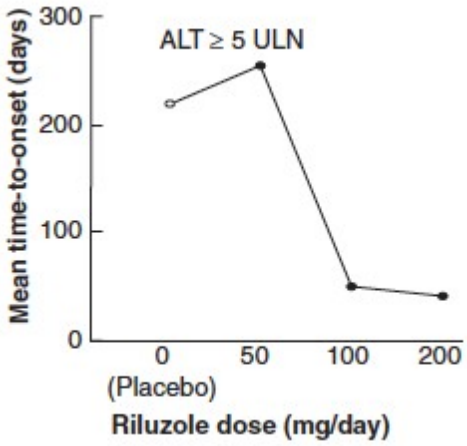
Summary graphic from Bensimon & Doble 2004 (Bensimon and Doble 2004)

Effects on hepatic lab parameters also demonstrate a dose dependent pattern. The rate of marked ALT elevations (≥5xULN) were lower in the 50 mg daily dose group (1.3%) than the placebo (2.1%), 100 mg daily dose group (3.8%) or 200 mg daily dose group (3.3%). Mean time to onset of marked ALT elevation distinguished placebo (219

days) and the 50 mg daily dose group (255 days) from the 100 mg (51 days) and 200 mg (42 days) daily dose groups. This pattern suggests a potential threshold phenomenon for impact on transaminases.

Dose relationship of rate of ALT effects





Summary graphics from Bensimon & Doble 2004 (36). The left panel indicates the proportion of study subjects demonstrating ALT elevations by dose. The right panel indicates the mean time to first observation of any ALT ≥ 5xULN.

The USPI provides a warning on Liver Injury for riluzole and proscribes specific monitoring of liver chemistries. Lab abnormalities associated with riluzole consist of elevated transaminases. These elevations are typically below 5xULN and often resolve while on treatment (36). Experience with incidents of ALT increasing >5xULN are limited, insofar as the USPI recommends immediate drug discontinuation. A dose-response is seen for elevations in transaminases within the available documentation on riluzole (33). Total daily doses of 50 mg were not associated with increased rates of marked ALT elevations (>5xULN) compared to placebo (1.3% vs 2.1%, respectively) and such occurrences had a later onset than placebo (median 254 vs 219 days). Total daily doses of 100 mg and 200 mg had greater rates of marked ALT elevations than placebo and the median occurrence was within 60 days. This pattern of adverse hepatic effects is consistent with observations that drugs associated with doses of at least 50

mg per day have a significantly greater propensity for liver injury and the associated incidents of liver injury are more serious (37).

While few cases of markedly elevated transaminases have been cited in the literature in association with elevated total bilirubin (38-40) (as well as the USPI), the outcomes in these cases were non-fatal and noted to be readily resolving. Further, interpretation of these cases is confounded by limited details and complicating factors. For example, the case cited in the USPI involves a subject with epilepsy treated with riluzole at doses up to 250 mg/day and who was on multiple concomitant medications (e.g., phenobarbital and carbamazepine) and who also had mildly elevated alkaline phosphatase and gamma-GT levels at baseline (Details noted in RILUTEK SBA).

In the course of the clinical development program for BHV-0223, the Sponsor intends to adhere to laboratory monitoring guidelines for LFTs that are described in the USPI for all subjects on chronic dosing. In addition, a complete baseline examination will assess predisposition for hepatic illness (e.g., hepatitis serologies, baseline abnormalities, concomitant medications, alcohol usage). We would welcome any advice that the Review Division would be prepared to offer in regard to additional assessments.

Safety Data from the Phase 1 Study BHV223-101

There were no drug-related SAEs reported in BHV-223-001. Additionally, no patients discontinued treatment due to drug-related AEs. BHV-0223 had good mouth palatability with expected mild and transient oral paresthesias. The vast majority of subjects rated the oral parathesias as mild and not bothersome, with few patients considering the numbness to be “somewhat” bothersome. The PI deemed all cases of paresthesias as mild. All cases of oral parathesias were transient and resolved. Overall, the preliminary results suggest that the SL formulation of riluzole is well tolerated and associated with mild, transient and not bothersome oral paresthesias. The Sponsor believes that the potential safety benefits on hepatic function, ease of administration for patients with dysphagia and potential to avoid the negative food effect associated with the generic tablet formulation outweigh any mild and transient oral numbness associated with the API.

FDA-approved Labeling

The current FDA-approved labeling for riluzole includes three Warnings:

- Liver injury (causing elevated levels of liver enzymes serum transaminase [ALT/SGPT]; [AST/SGOT], bilirubin, and/or gamma-glutamate transferase [GGT] levels). 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 × ULN, and about 2% of patients will have elevations > 5 × ULN.
- Neutropenia (causing one portion of your white blood cell test results are considered abnormal, and this can make you more prone to infections). Among approximately 4000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm3), all seen within the first 2 months of riluzole treatment.
- Interstitial lung disease (causing dry cough and/or difficulty breathing). Cases of interstitial lung disease (see ADVERSE REACTIONS) have been reported in patients

treated with riluzole, some of them severe; upon further investigation, many of these cases were hypersensitivity pneumonitis.

Additionally, per the Riluzole label, Riluzole has been shown to impaired fertility when administered to male and female rats prior to and during mating at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m2 basis.

3. **Source:** a) Identify the source of the drug or biologic to be used.

BHV-0223 will be obtained from the CMHC pharmacy and supplied by Biohaven Pharmaceutical Inc.

b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
If yes, by whom?

Biohaven Pharmaceutical Inc.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS**	☐ **Yale Cancer Center**
☒ **CMHC Pharmacy**	☐ **West Haven VA**
☐ **PET Center**	☐ **None**
☐ **Other:**	

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☐ **Not applicable to this research project**

If use of a placebo is planned, provide a justification which addresses the following:

a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

Several pharmacological treatments are utilized on an as-needed basis because of their short-term, potent anti-anxiolytic effects. These pharmacological agents include benzodiazepines (which target the gamma-aminobutyric acid-A receptor (GABA-A) and beta-blockers (beta adrenergic receptor antagonists)(8, 9). Although, benzodiazepines are quite effective at reducing anxiety over the short term (12) in specific situations (e.g. flying on an airplane), their side-effects and tolerability currently limit their usefulness in many situations (e.g. performance or public-speaking anxiety)(9, 10). Benzodiazepine use is associated with impaired short-term concentration, decreased alertness and psychomotor impairment (9, 11). Chronic benzodiazepine use is further associated with physiologic dependence, rebound anxiety on discontinuation and, possibly even interference with the efficacy of CBT (one of the first-line treatments for anxiety) (9, 11). Beta-blockers, on the other hand, are effective at acutely reducing the peripheral

physical symptoms of anxiety (e.g. heart palpitations, tremors etc.) but have no effect on the cognitive or emotional symptoms of anxiety (9, 10, 12-15). Novel pharmacological treatments are needed to improve patient outcomes with SAD, both chronically to reduce symptoms and acutely to reduce impairment during situations where symptoms are most likely to be impairing (e.g. public speaking or performance anxiety). A placebo is given on a single-study day in addition to the subject's regular medications in order to provide an adequate comparison condition to assess BHV-0223's efficacy.

b. State the maximum total length of time a participant may receive placebo while on the study.

Placebo will be given for 1 dose.

c. Address the greatest potential harm that may come to a participant as a result of receiving placebo.

Since Placebo is added to the patients' current medications, the risk of symptoms worsening when patients are receiving placebo in this study is not significantly greater in this clinical trial than it would be if the patients had not received the placebo and continued their current medication.

d. Describe the procedures that are in place to safeguard participants receiving placebo.

If a patient has worsening of symptoms, the patient will be offered inpatient or outpatient therapy and/or additional pharmacological treatments as clinically indicated.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?
☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No If no, explain why this is acceptable.

Study participants cannot be given study drug at study completion in the absence of an approved open-label study as recommend by the FDA in response to an initial IND request. This is a proof-of-concept study to determine if sublingual riluzole is helpful on a single time basis for speech anxiety.

B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary, " and attach any other pertinent documents. Then select "save and submit" to submit your request**; and

e. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents

impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

      Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable):

Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number):

Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations:

Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements:

Distributes the investigational device to subjects enrolled in the IRB-approved protocol:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol___20

b. If this is a multi-site study, give the total number of subjects targeted across all sites___

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☒ Letter	☒ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☒ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Patients with Social Anxiety Disorder in the Yale Center for Anxiety and Mood Disorders Clinic will be recruited for this study. Additionally, some subjects will respond to the contact phone number on the clinicaltrials.gov trial listing, flyers, or postings on the departmental website/YCCI recruitment database. We will also reach out to local providers and leaders of local social anxiety groups by letter to inform them of our study. Lastly, we will recruit subjects from a list of subjects who expressed interest and/or participated in a trial examining ketamine for Social Anxiety Disorder.

b. Describe how potential subjects are contacted.

Clinicians will be informed about the opportunity and asked to inform their patients about the opportunity if appropriate. Potential subjects interested in the trial will initiate first contact with the study recruitment coordinator or another member of the research team.

c. Who is recruiting potential subjects?

Co-investigators Angeli Landeros-Weisenberger and Jerome Taylor, MD will inform clinicians at the clinic about the opportunity and may ask patients directly if they are seeing the patients clinically.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

A brief psychiatric and medical history will be collected during telephone screening including Axis I diagnoses, medical and neurologic diagnoses, as well as recent medication and psychotherapy changes. All information will be stored in locked cabinets/password protected computer in an office that is locked. Information that will

breach subject confidentiality will not be shared. Rather, data will only be released upon written consent of the subject and will be available for review by the Yale human Investigation Committee. We will hold paper files for seven years at which point they will be destroyed.

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☐ Fax numbers

☒ E-mail addresses

☐ Social Security numbers

☐ Medical record numbers

☐ Health plan beneficiary numbers

☐ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

☐ Vehicle identifiers and serial numbers, including license plate numbers

☐ Device identifiers and serial numbers

☐ Web Universal Resource Locators (URLs)

☐ Internet Protocol (IP) address numbers

☐ Biometric identifiers, including finger and voice prints

☐ Full face photographic images and any comparable images

☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects

☒ Yes, some of the subjects

☐ No

If yes, describe the nature of this relationship.

Some of the subjects might be recruited from the outpatient service at the Yale Child Study Center. Dr. Bloch and Dr. Taylor currently work as providers in the clinic. Subjects will be informed that participation or lack of participation in this study will not affect the clinical care they receive at the clinic.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment purposes only

☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

We are requesting a waiver of HIPAA authorization for recruitment purposes only. Subjects will be initially recruited through clinicians at Yale Child Study Center and the clinicaltrials.gov registry. We will need to use PHI such as name, telephone number and email addresses to schedule initial screening interviews. It would be impractical to coordinate initial subject enrollment and recruitment without this data.

Signed authorization is impractical because initial screening of patients recruited through clinicaltrials.gov or clinician referral may occur over the telephone or email.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

   ☐ Compound Consent and Authorization form

   ☒ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.

Michael H. Bloch MD, MS
Christopher Pittenger MD, PhD
Jerome Taylor MD
Angeli Landeros-Weisenberger MD
Jessica A. Johnson, BS
Baris Olten, MD

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

•The research team (PI, his designee or research coordinator) will explain the study to the patient.
•Understanding of the study will be tested using a brief questionnaire (see consent form) of the key elements of the study.
•Every attempt will be made to include spouses, significant others, and family in the consent process.
•The research team will discuss the patient's participation in the study with the patient's psychiatric primary clinician. The clinician's opinion about the patient's participation and ability to provide informed consent will be documented.

- Subject will be given a copy of the signed consent form

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Protocol does not involve subjects with limited decision making capacity

11. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Adult consent form.

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Protocol does not involve non-English speaking subjects.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not Requesting a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No

b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. Full waiver of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

PHI about subjects will include name, age, diagnosis, medical record data, results of physical examination including EKG information, laboratory tests, psychiatric rating scores, and performance on psychiatric tests (impromptu speech and attention bias tests). The urine toxicology results will be placed in the research study record. The subject

will have a medical record at CMHC. Since the baseline urine toxicology and lab results will be collected during a visit at CMHC, the results of this test will become part of the CMHC medical record. This will be disclosed to the subject in the consent form and the investigator has obtained a Certificate of Confidentiality to protect all sensitive information connected with this study.

b. How will the research data be collected, recorded and stored?

All study ratings completed during study visits, histories obtained at screening and medical records pertaining to study procedures are secured in locked files and stored on password-protected computers. Since this is an investigator-initiated study, the PI and study team will develop Clinical Research Forms (CRFs) for this study. These forms will be labeled with a unique random study code that cannot identify the patient. The key linking the code to the subject's identifiable information will be kept in an electronic excel file which is kept in a password protected file, on a password protected computer on the secure Yale server. A paper copy of this "master file" will be kept in a locked file cabinet as noted above. This master file will be kept separately from any coded data so that the identity of the participant will not be disclosed. Information which is required to be part of the medical record will be filed into the CMHC medical record. If a medical record has not been created, one will be created with this visit. The results of the medical and psychiatric evaluations conducted as part of this research will be available to clinicians caring for the subject unless the participant requests otherwise. The Yale Human Investigation Committee may review records of this research. In the case of published reports of this study, the identities of all participants will be protected.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☒ Portable Hard Drive ☒ Secured Server ☐ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

All of the information obtained from subjects in this research study will be locked clinic files or on a password protected server to insure confidentiality. Also, the methods utilized include storing identified data separately from that which need not be identified, storing medical records according to CMHC policy, and utilizing a secure server.

Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Data will be kept in a locked filing cabinet whose access is only obtainable by study personnel and electronic clinical data will be kept on a password protected server. The PI will also conduct periodic assessments to ensure that confidentiality provisions

established at the onset of the study are maintained throughout the study and during data analysis. Additionally, all staff involved in the handling of subject data are/or will be trained on the requirements of HIPAA Privacy Rule and Human Subject Protection. If the PI should leave Yale, the PI will collaborate with his Department Chair and Faculty Advisor to ensure that proper and continued protection of individually identifiable information and protected health information continues.

After a period of five years these files will be destroyed by ITS approved methods or de-identified to protect subject confidentiality. All identifiable data will be destroyed by Dr. Bloch when the research is completed. Paper will be shredded via the confidential CMHC bins and all electronic files will be deleted or edited so that there is no identifiable information.

Impromptu speeches will be videotaped during the study. The subject has the right to request a copy of the video after the whole trial is completed, however, they will not have the right to edit the videos. The videotapes can be destroyed at any point in time upon request by the subject, otherwise, they will be kept for 5 years. After that time they will be destroyed or de-identified.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

In addition to study investigators, members of the HIC, the study sponsor, and the FDA may have access to study data.

g. If appropriate, has a Certificate of Confidentiality been obtained?

A Certificate of Confidentiality has been obtained to protect the drug toxicology results. Where possible, information will be destroyed that may link the subject to illicit drug use. Since a CMHC chart will need to be created for these subjects by virtue of their visit to the site, there is a concern that these results could be traced back to the subject. Subjects who test positive on the toxicology test will not be able to participate in this protocol. Subjects will be encouraged to seek treatment for their substance use, as appropriate.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

Although considered unlikely to be encountered, limits to confidentiality such as mandatory reporting requirements for abuse of children or the elderly will be complied with.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There may be no direct benefit from a subject's participation in this study. The potential benefits to society of these investigations are considerable. SAD continues to be a major public health problem with tragic cost to the individual, the family, and the community. The present study may improve our understanding of SAD by providing a pharmacologic rationale for developing novel treatments.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   The subject may discuss other non-research treatments for SAD with their practitioner or remain on their current standard of care regiment. This will include a discussion of pharmacologic, psychosocial, and somatic treatments.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants will be paid $50.00 for the screening visit; $100 for each of the study challenge days and $50 for the follow-up visit; for a total of $300.00 cash upon completion of the study. We will be able to reimburse up to $200.00 in travel and lodging if you are traveling from greater than 50 miles distance, receipts will be required to issue reimbursement checks.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   The study drugs and all medical procedures in this research study will be provided free of charge to the participants. There are no charges for the study visits, including the cost of parking on challenge days and transportation and lodging up to $200 for subjects traveling from a greater than 50 miles distance.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? If a physical injury or illness occurs as a direct result of participation in this study, study physicians and nursing personnel will be provided emergency medical care and ensure that research participants receive prompt evaluation and medical treatment as necessary. In severe cases this may involve a transfer to Yale-New Haven Hospital emergency room. The cost of treatment for any such injury

or illness will not be paid for through the study and will be the responsibility of the research participant.

a. Where and from whom may treatment be obtained?

In the event of a significant medical emergency the participant will be transported to Yale New Haven Hospital. Should there be adverse psychiatric effects as a result of the study they will receive either inpatient treatment on the CNRU at CMHC or as an outpatient from the Yale Child Study Center.

b. Are there any limits to the treatment being provided?

In the unlikely event that any psychiatric care more intensive than regular clinic visits and a couple of nights of observation on the CNRU is required as a direct result of participation in this study, study personnel will provide emergent care and stabilization. Longer observation on the CNRU and more frequent clinic visits, if necessary in the short term may also be provided. If longer-term psychiatric care is required, beyond what is normally provided by a research clinic, then study personnel will provide referrals and otherwise endeavor to assist participants in arranging such care.

c. Who will pay for this treatment?

Since this is an investigator initiated study, the study's investigators will provide additional short-term inpatient hospitalization that is needed to provide emergent care and stabilization following any adverse psychiatric events. Longer-term psychiatric care to alleviate a participant's symptoms below their severity when entering the study or medical treatments provided at other facilities will be billed to the participant or the participant's insurance company. Participants do not give up any of their legal rights by signing the consent forms.

d. How will the medical treatment be accessed by subjects?

As part of the study protocol, participants will be systematically asked about any adverse events they experience and their SAD symptom severity by study personnel. They will also be instructed to inform study personnel if they believe they have suffered an adverse event or worsening of their SAD symptoms as a result of the protocol.

APPENDIX 1

Local Tolerability Assessment

A local tolerability assessment will be performed at baseline and 1 hour after study medication administration on study days 1 and 2. Any alteration of the appearance of the tongue, palate and buccal mucosa space will be recorded. Oral tolerability assessment will include:

Any history of dysphagia (difficulty swallowing), dysgeusia (the distortion of the sense of taste) or burning, stinging or tingling sensation of the mouth.

Systematic examination of the oral cavity for any signs of erythema, swelling or ulceration (ulcers which are white, small, punched out lesions of epithelial surfaces of the mouth) of the mucosa.

Also check for stomatitis (inflammation and infection of the oral mucosa), gingivitis (inflammation of the gums leading to erythema, swelling and bleeding), xerostomia (a dry mouth) or staining of mucosa.

• **Areas to be inspected:**

- Right palate area

- Left palate area

- Right sublingual area

- Left sublingual area

- Right upper buccal area

- Right lower buccal area

- Left upper buccal area

- Left lower buccal area

• **Severity Grading Scale**:

Grade 0: Normal mucosa

Grade 1: Localized mucosal erythema and/or irritation without ulceration

Grade 2: Generalized erythema and/or irritation and induration without ulceration

Grade 3: Ulceration, with or without any other combination of signs.

ORAL CAVITY INSPECTION

☐ **Not Done**

Time of Assessment
(24 hour clock) _____:_____

Right Palate Area	☐	**Right Upper Buccal Area**	☐
Left Palate Area	☐	**Right Lower Buccal Area**	☐
Right Sublingual Area	☐	**Left Upper Buccal Area**	☐
Left Sublingual Area	☐	**Left Lower Buccal Area**	☐

Severity Grading Scale:
Grade 0: Normal mucosa
Grade 1: Localized mucosal erythema and/or irritation without ulceration
Grade 2: Generalized erythema and/or irritation and induration without ulceration
Grade 3: Ulceration, with or without any other combination of signs.

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