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Evaluation of the Efficacy of Vortioxetine for Posttraumatic Stress Disorder

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I. PROJECT ABSTRACT

Posttraumatic stress disorder (PTSD) is a chronic and common anxiety disorder that follows exposure to an overwhelming traumatic event. The majority of patients with PTSD also meet criteria for other psychiatric disorders and many attempt suicide. Despite its impact on society, little is known about the etiology or pathophysiology of this disorder. PTSD is responsive to pharmacological treatments such as selective serotonin reuptake inhibitors (SSRIs), but response rates rarely exceed 60%, and even fewer patients (20-30%) achieve clinical remission. Thus, there is a clear need to develop novel and improved therapeutics for PTSD.

We will assess the efficacy of vortioxetine using a 12-week, double-blind, parallel-group, placebo-controlled trial of adults with PTSD. Although Vortioxetine has not been approved by the Food and Drug Administration for the treatment of PTSD, it has been approved for the treatment of major depressive disorder and its safety profile is well characterized. In addition to measures of symptomatic improvement in PTSD, we will also assess changes in cognitive function and quality of life. Furthermore, we propose to investigate longitudinally whether certain biological surrogate markers (neurophysiology, genotyping, mRNA) are predictive of treatment response.

II. SPECIFIC AIMS

1. Specific Aim 1 (Primary Aim): To determine the efficacy of Vortioxetine compared with placebo in improving PTSD symptoms.
Hypothesis: PTSD patients randomized to acute therapy (12 weeks) with Vortioxetine will show more improvement in PTSD symptoms compared to patients randomized to placebo, as determined by mean changes in the Clinician-Administered PTSD scale (CAPS-5) score over the course of 12 weeks.

2. Specific Aim 2 (Secondary Aim): To determine the efficacy of Vortioxetine in treating PTSD in terms of overall response rate.
Hypothesis: PTSD patients randomized to acute therapy (12 weeks) with Vortioxetine will have a greater rate of treatment response compared to subjects randomized to placebo, as determined by at least 30% improvement from baseline in CAPS-5 total score and a Clinical Global Impression of Improvement (CGI-I) score of 1 or 2.

3. Specific Aim 3 (Secondary Aim): To determine the efficacy of Vortioxetine in reducing depressive symptoms in PTSD patients.
Hypothesis: PTSD patients randomized to acute therapy with Vortioxetine will show more improvement in depressive symptoms compared to subjects randomized to placebo, as determined by mean changes in the Montgomery-Asberg Depression Rating Scale (MADRS) score over the course of 12 weeks.

4. Exploratory Aim 1: Startle: To assess fear potentiation, conditional discrimination (AX+/BX-), and fear inhibition using acoustic startle methodology in a classical conditioning paradigm in PTSD patients before and after treatment with Vortioxetine.
Hypothesis: PTSD subjects randomized to 12 weeks of Vortioxetine will have improved fear inhibition as measured by the AX+/BX- paradigm compared to baseline, while placebo subjects will not show improvement.
5. Exploratory Aim 2: Cognition, Functional Capacity, and Quality-of-Life: To assess neurocognitive performance (pre- and post-treatment) with tests shown to be sensitive to PTSD (e.g. learning and memory, concentration and attention, and executive functioning). In addition, to explore performance-based measures of everyday living skills, and measure quality-of-life as indexed by subjective reports.
Hypothesis: Statistically significant changes detected for these variables will be correlated across domains.
6. Exploratory Aim 3: Genotyping and Gene Expression: To explore whether response to Vortioxetine is associated with certain candidate gene polymorphisms previously associated with PTSD, and whether treatment with Vortioxetine alters gene expression patterns differentially in treatment responders and non-responders.
Hypothesis: Polymorphisms of specific candidate genes previously identified as relevant to PTSD will be differentially distributed between responders and non-responders to vortioxetine.

III. SIGNIFICANCE/BACKGROUND

Significance of PTSD and Limitations of Current Pharmacotherapies

PTSD is a common chronic anxiety disorder that is often debilitating and follows exposure to an overwhelming traumatic event. PTSD occurs in approximately 8%-14% of the U.S. population (Breslau et al 1998; Davidson et al 1991; Kessler et al 1995). Rates of PTSD among women in the US are higher than in men being approximately twice that of men 12%-18% (Breslau et al 1998; Resnick et al 1993).
The burden of PTSD on individuals and society is significant. First, the majority of PTSD sufferers also meet the diagnostic criteria for several other psychiatric disorders (Breslau et al 1991; Resnick et al 1993), especially major depression (Koenen et al 2003; Neria and Bromet 2000) and many also attempt suicide (Davidson et al 1991). Significant health problems are more likely to occur in individuals with PTSD than in those without PTSD, particularly hypertension, bronchial asthma, peptic ulcer (Davidson et al 1991), gastrointestinal problems (Leserman et al 1996), increased rates of surgery, and visits to the physician (Solomon and Davidson 1997; Zoellner et al 1999). Despite the devastating impact of PTSD on the lives of millions worldwide, little is known about the etiology or pathophysiology of this disorder. Although disruptions in the hypothalamic-pituitary adrenal (HPA) Axis, noradrenergic, and serotonergic systems have been proposed as neurobiological substrates in the development of PTSD, the exact underpinnings of the neurobiology of PTSD remain to be fully elucidated.

U.S.-based practice guidelines for PTSD have recommended cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) as first-line treatments (APA, 2004;

VA/DoD 2003). However, the 2 FDA-approved SSRIs paroxetine and sertraline have modest effects, limited efficacy in all 3 clusters of illness (avoidance/numbing, reexperiencing, and hyperarousal), and few patients develop remission (Davidson 2006a). Many placebo-controlled trials of other medications in PTSD have failed, and even recent studies of approved medications (e.g. sertraline) have failed to show efficacy in specific subgroups of PTSD patients such as combat veterans treated in Department of Veterans affairs clinics (Friedman et al. 2007). There is therefore a tremendous need to identify new medications that are efficacious for PTSD. Vortioxetine, with its muti-modal action at multiple serotonin receptor subtypes in addition to serotonin transporter inhibition, offers a novel approach to the treatment of this recalcitrant disorder.

Progress in treating PTSD will also require better understanding of the biological characteristics associated with improvement during treatment. As detailed below, this proposal will use state-of-the-art biological and psychological phenotype measurements to identify moderators and mediators of outcomes with vortioxetine treatment. Through this proposal we are seeking to enhance treatment approaches for PTSD by evaluating the novel compound, vortioxetine, and to apply biological signatures to identify treatment prediction and response. The combined expertise across these sites makes for a unique and complementary research approach. We are not aware of any other research team using these state-of-the-art biological approaches along with expertise in prospective treatment prediction to address these seminal questions in PTSD.

IV. DRUG INFORMATION

A. Investigational Drug: Vortioxetine

Vortioxetine is a newly approved antidepressant with a unique pharmacological profile. It is a potent SSRI and, in addition, has a high affinity for the $5HT_{1D}$, $5HTT_3$, and $5HT_7$ receptors where it acts as an antagonist. It is also a $5HT_{1A}$ agonist and $5HT_{1B}$ partial agonist. Of particular interest to this PTSD study is the finding that vortioxetine exhibits considerable positive effects on attention, memory, and executive function in patients with major depression, as well as improving performance-based measures of disability.

V. RESEARCH DESIGN AND METHODS

A. Overview of Study

The study design is a 2-site, 12-week, randomized, double-blind, placebo-controlled, parallel-arm, flexible dose trial evaluating the efficacy, safety, and tolerability of Vortioxetine for male and female adult outpatients with PTSD. The primary outcome assessment will occur at 12 weeks. A total of 60 patients will be randomized across the 2 study sites. Subjects must have PTSD symptoms for at least 3 months prior to randomization, and have at least moderate PTSD symptom severity as measured by a score ≥ 28 on the CAPS-5 Past-month version at the screening and baseline visits for inclusion in the study. The study population will be comprised of men and women with PTSD resulting from any form of DSM-5-defined trauma. Combat-related PTSD will not be an exclusion, but no cases with pending litigation or disability claims associated with PTSD will be enrolled.

The 4 study phases consist of the following:

(1) Screening Phase and (if necessary) Medication-Washout: Informed consent will be signed at the initiation of the screening phase. As part of the informed consent process, participants will be asked whether they are willing to have their research assessments videotaped, and to indicate their authorization for Audio/Video/Photography Recording on the

consent form. Patients refusing to consent to videorecording will still be permitted to participate in the study. Recordings of study visits will be used by the study team for interrater reliability training and assessment. Screening for psychiatric and medical eligibility will involve vital signs, weight, blood tests, pregnancy test, drug screen, psychiatric interviews, medical and psychiatric history, physical exam and electrocardiogram (EKG). We will also draw the genotype sample at this visit for consenting subjects.

If a patient is already taking medication for PTSD and has achieved therapeutic response, s/he will not be tapered off the effective medication(s) to participate in this study, and will not be eligible for the study. Patients who are taking a psychotropic medication that has proven ineffective for their PTSD symptoms will be tapered off the medication prior to randomization. Whenever possible, decisions to taper a patient's medication for the purpose of study participation will be made in conjunction with the patients' prescribing physician. Patients will be tapered off ineffective psychotropic medications over 7-21 days, though patients on fluoxetine or protriptyline will be required to be off those medications for 5 weeks prior to baseline. Risks associated with medication tapering will be discussed with the patient. This washout process will be conducted and monitored by the study physician.

(2) Study Period I – Pretreatment Testing (Days –7 to –1): Visit 1. During this study period, subjects will undergo surrogate marker testing (psychophysiology, and neuropsychological testing). These visits will be conducted over a 7-day period prior to the day of randomization, following the successful completion of all the screening procedures in Phase 1 above. We anticipate that these procedures can be completed in 1 study visit; however, we will be flexible to allow additional visits if required due to subject fatigue or time constraints.

3) Study period II Treatment (Day 0 to 84): Visits 2 through 9. This is the 12-week period of double-blind placebo-controlled acute treatment. At day 0, EKG for safety monitoring will be conducted. The baseline mRNA sample will be collected. All subjects who continue to meet eligibility criteria will be randomized to one of two groups: Vortioxetine or placebo. Randomization will be performed at a 1:1 ratio into two treatment groups, and both vortioxetine and placebo will be distributed to the patient in blister packs. If a participant is taking 10mg of vortioxetine they will be provided with 2 blister packs at each visit. If a participant is taking 20mg, they will be provided with 4 blister packs. Surrogate marker testing for psychophysiology, mRNA, and neuropsychological testing will be repeated at the completion of the double-blind treatment. Due to the amount of study procedures for certain study visits, we will allow study visits to be done over two days.

4) Follow-Up (Day 84 to 98): Visit 10. Patients will return to the clinic two weeks after the last dose of study medication for assessment of psychiatric status, sucidality, follow-up of any abnormal laboratory or EKG results, and to assist with transition of psychiatric care, if indicated.

See the **Schedule of Events** chart at the end of this section for details of the procedures performed during each visit.

B. Justification of Sample Size
Power Analysis:

Samples of n=60 (2 groups) are associated with reduced but adequate power. Between group differences in change scores of d=.70 are detectable with .80 power at p<.05. Correlations of

.33 between two variables are detectable with power=.80 in the full sample of 60. Within treatment conditions (n=30) correlations of r=.50 are detectable with the same level of power.

C. Informed Consent, Regulatory and Ethical Considerations

The study will be conducted in accordance with Good Clinical Practices (GCP), 21CFR Parts 50 and 56 and all applicable regulatory requirements. Approval for conduct of the study will be obtained from the institutional review boards at both sites.

Written informed consent will be obtained from each subject prior to any study procedures. All potential subjects will be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected. The subjects' understanding of the study procedures will be tested in the form of oral questioning or written testing. Investigators at each site will retain the original copy of the Informed Consent Form and HIPAA documents signed by the patient, and duplicates will be provided to the patient.

D. Screening Phase

The screening procedure includes an extensive phone interview and, if eligible, a screening visit. Clinical staff members (bachelor's or masters-level research assistant, Ph.D., or M.D.) trained in DSM diagnostic interviewing will conduct an initial phone interview to determine likely diagnostic suitability. If the patient is deemed preliminarily eligible for participation, s/he will then be invited for an in-person screening visit. If the potential participant is deemed ineligible after the brief phone interview or expresses interest in alternatives to study participation, the phone interviewer will give appropriate referrals. Upon arrival at the research clinic, the principal investigator or a trained delegate will briefly describe the details of the study procedures, risks and benefits, alternative treatments, and confidentiality of information. Potential participants will independently read and review the consent and HIPAA forms, and then the researcher obtaining consent will address any questions that the participant may have. Once the participant communicates his or her thorough understanding of the study and decides that s/he wishes to participate, he/she will be asked to sign and date the form. No study procedures will occur prior to the conclusion of the informed consent process.

After patients consent to participate, they will undergo several procedures, which will occur over 1-2 visits. These include: (1) psychiatric interview by a research psychiatrist or psychologist; (2) a structured clinical interview (the Mini International Neuropsychiatric Interview, "MINI," Modules A and C through P); (3) administration of the CAPS-5, Columbia Suicide Severity Rating Scale (CSSRS), and Clinical Global Impression of Severity (CGI-S); (4) completion of several self-report instruments; (5) collection of blood samples for safety testing and genotype analysis, pregnancy testing (if indicated), urine sample [urinalysis, toxicological screen]; (6) EKG; and (7) physical examination.

A clinical researcher with specialized training in diagnostic assessment will perform the specified modules of the MINI and the rating scales. Appropriately trained study staff will conduct all medical tests and obtain biological samples for the following laboratories: blood samples for serum chemistries, liver function panel, free T4, thyroid stimulating hormone, hepatitis B surface antigen, hepatitis C antibody, serum pregnancy, gamma-glutamyl transferase (GGT), and complete blood count (CBC), urinalysis and urine drug screen. At the conclusion of the screening process, the patient will be contacted within several days regarding preliminary eligibility. All patients who are eligible will be scheduled for an in-person visit approximately one week after the initial evaluation. The participant will continue into Study

Period I at that time. If deemed ineligible for the protocol, a study physician will explain the reasons for disqualification, and these patients will receive appropriate research or treatment referrals. If symptoms worsen significantly during this period, as determined by the study physician's assessment, subjects will be removed from the study and given appropriate referrals after meeting with the study investigators. Options would include referral to the resident psychopharmacology clinic or referral back to their treating physician.

E. Study period I: Pre-Treatment Testing

During this testing phase, which will be scheduled within one week of the day of randomization**,** we will examine neurobiological surrogate markers involving psychophysiology (startle) and neuropsychological testing.

F. Study period II: 12-Week Randomized, Double-Blind, Placebo-Controlled Trial

Study Period II is the 12-week double-blind treatment period. On the day of randomization, an EKG and laboratory tests (blood samples for CPK and a urine sample for pregnancy testing will be collected.

Patients will be assessed in-person weekly or every other week from Visit 2 through Visit 9, using self-report and clinician-administered measures to gauge changes in symptomatology (see Schedule of Events chart below). In order to maximize patient retention and account for unpredictable schedules, the treatment window will consist of the target visit date plus/minus 2 days for Visit 2 through Visit 4 and plus/minus 3 days for Visit 5 through Visit 10. Patients will be randomized at a ratio of 1:1 to receive either Vortioxetine at a starting dose of 10 mg /day or placebo. Concurrent treatment with other psychotropic medication will NOT be permitted during the study with the exceptions of the hypnotics zolpidem, eszopiclone, zaleplon, and diphenyhdramine. Patients taking diphenydramine will be instructed not to take any doses of this medication for three days prior to the visits that involve Neuropsychological testing or the Startle Task. These hypnotics will be allowed up to 3 doses per week during the trial. The CBC, blood chemistries, serum pregnancy, thyroid function measures and urinalysis will also be repeated at week 12. At the end of this study period, the neurophysiology, neuropsychological, and mRNA measures will be repeated. Patients will be outpatients for the duration of the study. Due to the amount of study procedures for certain study visits, we will allow study visits to be done over two days.

Dosing of Study Medication: All patients will be started on 10 mg vortioxetine/day (or placebo equivalent) dosed in the morning with food. Patients experiencing sedation from the medication may be switched to evening dosing at the discretion of the study psychiatrist. If by Week 4 the patient has demonstrated inadequate benefit from the medication, the dose will be increased to 20 mg/day. Patients unable to tolerate the 20 mg/d dose may be reduced to 10 mg/day between weeks 4 and 8. Patients unable to tolerate 10 mg will be discontinued from the trial. The dose of study medication should remain stable for weeks 8-12.
Medication compliance will be monitored by pill counts conducted at every visit during study period II. The patient will also maintain a medication diary to mark the date and time they took their medication. Women of child bearing potential will also use the diary to indicate the start date of their menstural cycles, as this information will inform analysis of the startle testing data.

G. Follow-up

After participants completing the 12 week randomized treatment phase, they will return to the clinic 14 days later (Visit 10) for a follow-up evaluation. All subjects who complete the trial or discontinue the study because of lack of response or side effects will receive assistance in transitioning to another care provider as clinically appropriate at the research site (if they choose to do so), or will be referred back to their referring physician. Patients with clinically significant abnormal laboratory tests at Visit 9 will have those tests repeated at the follow-up visit.

H. Early Termination from Protocol

Medical or Administrative Reasons: Subjects will be terminated early if any of the following occur: (1) Intolerance to study drug in the dose range required by the study; (2) worsening of PTSD or depressive symptoms such that the subject's safety is endangered (e.g. suicidality); (3) If patient becomes manic or psychotic; (4) a serious adverse event (SAE) that is either: i) considered by the investigator to be possibly, probably, or definitely related to the study medication, or ii) places the subject at increased risk of harm if s/he were to continue in the study.

Suicidal ideation is assessed at each study visit with the Columbia Suicide Severity Rating Scale (CSSRS), an instrument endorsed by the FDA for clinical trials. This brief instrument systematically tracks suicidal ideation and behavior (e.g., suicide attempts, wish to die, thoughts of suicide, and plan and intent), and classifies events according to the following categories*:* ***Suicidal events*** *– completed suicide, suicide attempt, preparatory acts toward imminent suicidal behavior and suicidal ideation.* ***Non-suicidal events*** *– self-injurious behavior, no suicidal intent and other, no deliberate self-harm.* ***Indeterminate or potentially suicidal events*** *– self-injurious behavior, suicidal intent unknown.* Subjects who are considered by the study psychiatrist to be at high risk for suicide are discontinued from the study and referred for hospitalization and further treatment as clinically indicated.

Poor Adherence***:*** Every effort will be made to encourage subject compliance with the dosage regimen as per the protocol. A record of the supplies dispensed, taken and returned will be recorded at each visit. Compliance will be monitored by pill counts. Subjects who miss three or more consecutive days of Vortioxetine during the study are considered non-compliant and will be counseled about need for adherence. Patients found to miss three consecutive doses of study medication twice will be withdrawn from the study. Non-adherent patients are classified as dropouts in the analysis.

Drop-outs: Drop-outs will be defined as randomized subjects lost to follow-up who do not complete the 12-week double-blind treatment period. Randomized subjects who drop out prior to completing one post-randomization efficacy assessment will not be included in the primary efficacy analysis.

SCHEDULE OF EVENTS											
Visit Number	**S1**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Week (± 2 days for V2-V4, ± 3 days for V5-10)		**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**
Day		**-7**	**0**	**7**	**14**	**28**	**42**	**56**	**70**	**84**	**98**
Informed consent	X										
Demographics/Hollingshead	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Weight	X		X			X		X		X	X
Psych/Medical eval. by MD	X									X	
Physical examination	X									X	
12-lead EKG	X		X							X	
MINI modules A, C-P	X										
Dispense Study Drug & Diary			X	X	X	X	X	X	X		
Laboratory Tests											
CBC	X									X	
Blood Chemistry	X									X	
Liver Function Tests	X									X	
GGT	X										
Urinalysis	X									X	
Urine drug screen	X										
Serum Pregnancy	X									X	
Urine Pregnancy			X								
CPK			X							X	
TSH, Free T4	X									X	
Hepatitis B and C	X										
Pharmacokinetics						X		X		X	
Psychiatric Measures											
CAPS and CGI	X		X		X	X		X		X	
MADRS			X		X	X		X		X	
CSSRS	X		X	X	X	X	X	X	X	X	X
E-TRIP	X										
PCL-5/QIDS-SR			X		X	X		X		X	
CTQ & PDS Screen	X										
PSQI			X			X		X		X	
SDS	X		X				X			X	
Life Experiences Survey			X							X	
Safety Measures											
PRISE/Con meds			X	X	X	X	X	X	X	X	X
FIBSER				X	X	X	X	X	X	X	
Exploratory Aim Testing											
Startle Paradigm		X								X	
Genotype/Methylation			X							X	
Neuropsychological Testing: BACS + UPSAB		X								X	
mRNA			X							X	

Abbreviations: CAPS = Clinician-Administered PTSD scale; CBC = Complete blood count; CGI I/S = Clinical Global Impression Scale (improvement and severity); CSSRS = Columbia Suicide Severity Rating Scale; CTQ = Childhood Trauma Questionnaire; EKG = Electrocardiogram; ETRIP = The Emory Treatment Resistant Interview for PTSD; FIBSER = Frequency, Intensity and Burden of Side Effects Rating; GGT = Gamma glutamyl transpeptidase; Hollingshead= Hollingshead 4 Factors of Social Status Scale; MADRS= Montgomery Asberg Depression Rating Scale; PCL-5 =The Posttraumatic Stress Disorder Checklist for DSM-5; PRISE = Patient Rated Inventory of Side Effects; PSQI = Pittsburgh Sleep Quality Index; PDS = Post-traumatic stress Diagnostic Scale; PSSR = PTSD Symptom Scale Self Report; QIDS-SR = Quick Inventory of Depressive Symptoms; SDS = Sheehan Disability Scale; T4 = Thyroxine; TSH = Thyroid stimulating hormone;
Notes: Patients who terminate early will complete the Visit 9 safety and efficacy procedures.

I. Efficacy and Safety Tests and Procedures

1. Measures and Questionnaires

See **Appendix B** for a brief description of the rating scales.

2. Blood and Urine Tests for Safety

2a. At the start of the study, participants will undergo specific laboratory tests, as outlined in the Schedule of Events above. Blood tests include: complete blood cell count (CBC) with differential, thyroid functioning (TSH), and free thyroxine, fasting blood sugar, liver function tests (LFTs), including total bilirubin, a hepatitis panel, and a serum pregnancy test in women of child-bearing potential. Participants also undergo a urine toxicology screen, urine pregnancy test and urinalysis testing**.** Additional blood or urine tests for disallowed medications or drugs of abuse may be performed during the randomization phase at the discretion of the investigator.

3. Pharmacokinetics Testing

3a. As outlined in the schedule of events, participants will undergo confirmatory laboratory testing at visits 5, 7, and 9. Blood will be drawn and tested to confirm the level of Vortioxitine in the participant's system at the time of their study visit.

J. Exploratory Biological and Neuropsychological Assessments

In addition to the treatment outcome goals, we will examine previously identified genetic risk factors for predictors of treatment response. We will also examine SNPs associated with PTSD which meet genome-wide significance within an ongoing cross-sectional n=8000 Genome Wide Association Study.

Hypothesis 1: Based on our extensive prior experience in examining physiological markers of fear responding, we hypothesize that trauma-exposed individuals with PTSD will exhibit a higher likelihood of responding to PTSD treatment if they display differential physiological signatures of PTSD (e.g. increased dark-enhanced startle and decreased extinction of fear), compared to those without these physiological signatures of PTSD.

Hypothesis 2: Based on our previous work in PTSD identifying significant cognitive and functional capacity deficits, we hypothesize that treatment of with vortioxetine will improve cognitive and functional capacity.

Hypothesis 3: Based on our pilot data that interventions for PTSD can ameliorate genetic predisposition, we hypothesize that trauma-exposed individuals with PTSD will exhibit a higher likelihood of responding to PTSD treatment if they are carriers of risk alleles of the FKBP5, the ADCYAP1R1 gene and other genes (e.g., DAT, BDNF, COMT, CRHR1, 5-HTTLPR, RGS2, GABRA2), compared to non-carriers of risk alleles. We will also examine gene expression and epigenetic risk factors associated with PTSD as predictors of treatment response. These will

include differential mRNA expression and epigenetic (methylation) marks identified pretreatment, previously associated with differential PTSD risk to identify how modulators of gene function relate to treatment response.

1. DNA

We will draw DNA on all consenting subjects to evaluate whether carriers of identified risk alleles are associated with response or non-response to voritoxetine.

2. mRNA

We will draw 12 mls of blood at baseline and at week 12 to evaluate the expression of HPA-related mRNA expression.

3. Neurophysiology: Startle Testing

3a. Conditioning sessions. The following methods will allow us to assess fear acquisition, and conditional discrimination (learned safety), as well as the subjects' awareness of reinforcement contingencies in the experiment. The aversive stimulus (US) in these studies will be a 250 ms airblast with an intensity of 80 p.s.i. directed to the larynx as described in similar human fear conditioning studies (Grillon & Davis, 1997; Jovanovic et al. 2005). A compressed air tank connected to polyethylene tubing and controlled by a solenoid switch will emit the airblasts. The conditioned stimuli (CS's) used in the AX+/BX- session (A, B, C and X) will be different colored shapes; in the fear acquisition and extinction sessions the CS's will be neutral pictures. The CS's will be presented on a computer monitor. The pictures and colored shapes will be counterbalanced across subjects. The stimuli will be presented using SuperLab 3.0 for Windows (Cedrus, Inc.) and synchronized with the psychophysiological data acquisition using a DIO card (Measurements Computing, Inc). The psychophysiological data will be collected with Biopac MP150 (Biopac Systems, Inc.). Skin conductance will be acquired concurrently with acoustic startle.

3b. Acoustic startle. The acoustic startle response (eyeblink component) will be measured via electromyography (EMG) of the right *orbicularis oculi* muscle. Two 5 mm Ag/AgCl pre-gelled disposable electrodes will be positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus. All resistances will be less than 6 kilo-ohms. EMG activity is acquired at a sampling rate of 1kHz, amplified and digitized. The startle probe (noise burst) will be a 108-dB [A] SPL, 40-ms burst of broadband noise with a near instantaneous rise time.

3c. Response keypad. To assess subject awareness and US expectancy during each experimental session subjects will respond on a response keypad (SuperLab, Cedrus Corp.) in coordination with the EMG startle response monitoring system (SR-LAB, San Diego Instruments). During the fear conditioning sessions subjects will press a button marked "+" if they expect a CS to be followed by the US, a button marked "-" if they do not expect a CS to be followed by the US, and a button marked "0" if they are uncertain of what to expect.

3d. Skin Conductance Level. The skin conductance level will be acquired at a sampling rate of 1 kHz using the GSR module of the Biopac system. Two 5 mm Ag/AgCl disposable electrodes filled with isotonic paste will be attached to middle phalanges of the second and fourth finger of the non-dominant hand.

4. Neuropsychological Battery

4a. Rationale and Test Descriptions. Cognitive function will be assessed by Brief Assessment of Cognition in Schizophrenia (BAC-S) test battery with measures in: (1) list learning, (2) digit sequencing task, (3) token motor task, (4) verbal fluency, (5) tower of London test, and (6) symbol coding subtest. All BAC-S measures will be administered at specified time points, and the total composite z-scores will be compared to baseline total composite z-scores.

4b. Performance Based-Measures of Functional Capacity

For the assessment of functional capacity, we will use instrumentation previously developed for use in schizophrenia: the UCSD performance-based skills assessment (UPSA; Patterson et al 2001). The UPSA is the most widely used functional capacity measure in serious mental illness, but suffers from a lengthy assessment format (30 minutes), high-level reliance on props, and geographic specificity. The UPSA-B involves role-play tasks similar in complexity to those that a community-dwelling person is likely to encounter. Administration requires an average of 10 minutes. The UPSA-B's two domains result in a summary score ranging from 0 to 100 and we will use the summary score as the dependent variable.

K. Clinical Care

1. Discontinuation from study

At the end of the treatment trial or when a patient discontinues the study prematurely, the efficacy evaluations will be repeated. In addition, a physical exam, 12-lead EKG, vital signs, weight, and laboratory measurements will be obtained. Patients will also be assessed for adverse experiences. All subjects who complete the trial or discontinue because of lack of response or side effects will receive treatment as clinically appropriate and will then be referred for appropriate follow-up care.

Patients may withdraw at any time, or may be withdrawn by the investigator should medical contraindications to the assigned medication develop, intolerable adverse reactions occur, or mood or anxiety worsens to an extent that, in the clinicians' judgment, further participation would put the patient at risk.

Pregnancy

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Any female subject who becomes pregnant while participating will be withdrawn from the study. The investigator will record pregnancy information on the appropriate form and submit it to Dr. Philip Harvey at the University of Miami (Email: pharvey@med.miami.edu Fax: 305-243-1619) and to Takeda (Email: (takedasafetytgrd.com iFax: 1-224-554-1052) within 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as such.

SAE Reporting

All SAEs will be reported to Dr. Philip Harvey and to Takeda within 4 calendar days of the site investigator becoming aware of the event. All fatal or life-threatening SAEs will be reported by facsimile within 24 hours. The appropriate SAE form will be completed and emailed or faxed to Dr. Harvey and Takeda using the contact information listed in the Pregnancy section.

2. Suicide risk among patients treated with antidepressants

Subjects with major depressive disorder or with depression as part of bipolar disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. This guidance is consistent with global class

labelling for antidepressants. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain subjects, a causal role for antidepressants in inducing such behaviours has not been established. Nevertheless, subjects being treated with study medication will be observed closely for clinical worsening and suicidality, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration will be given to possibly discontinuing the investigational product in subjects whose depression is persistently worse or whose emergent suicidality is severe or abrupt in onset or was not part of the subject's presenting symptoms. To assess suicidal ideation and behaviors, the CSSRS will be used in this trial.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in patients being treated with antidepressants for major depressive disorder. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to possibly discontinuing the investigational product in subjects for whom such symptoms are severe, abrupt in onset, or were not part of the subject's presenting symptoms.

2. Provision of Clinical Care
All subjects who complete the trial or discontinue the study because of lack of response or side effects will receive assistance in transitioning their care to another provider.

VII. DATA ANALYSIS AND STATISTICAL PLAN

A. Approach to Data Management
Case report forms are developed from adaptations of NIH and industry-funded clinical trial protocols in PTSD. Study data will be recorded on paper forms and translated to a digital format without specific patient identifying information. Patient identifiers will be maintained in a separate code book that will be kept in a locked cabinet in the Principal Investigator's office at each site. These data will preserved on site with periodic monitoring by the primary site. At the end of the study, the databases for the different sites will be merged. Data will be entered sequentially and within a timely manner so that any queries for missing information can be resolved.

B. General Statistical Considerations
Possible risk factors/confounders: We expect the randomization procedure to equalize risk factors across treatment groups; however, we will produce summary statistics to explore any unexpected differences in the values of covariates in the treatment groups. While we do not expect differences in covariates in the treatment groups, it is very likely that the response groups will be different on some relevant clinical variables (e.g., comorbid conditions). However, these should affect only the analyses that include treatment response, and not analyses such as group-related change in CAPS. Thus, we will formally assess response group differences in possible covariates of interest and incorporate any covariates identified that are considered both statistically and clinically relevant as additional main effects for the response-based analyses. Specific types of interaction effects, such as effect modifiers specified a priori, will be the subject of exploratory analysis.

Site effects: Our assumption for the analysis plan and power calculations is that the protocols will be implemented sufficiently comparatively to avoid significant site effects in the results. Given that the randomization will be blocked by site, there is no reason to believe that the

subjects will have a different a priori probability of response or will be significantly different from a clinical perspective. However, we will test for site differences in all outcome measures with appropriate univariate comparisons to ensure that this is not a significant confounder. If there is evidence of significant site differences in response, we will proceed with stratified analyses in place of the proposed analyses.

Missing data: For those subjects randomized who do not complete treatment, an intent-to-treat approach will be implemented using linear and categorical mixed model methods. More specifically, all participants who are randomized to treatment group and have baseline measures will be included in the analysis. If the probability of a missing observation depends on either observed covariates in the model or the previous observations of the outcome variable (e.g. CAPS), these models will provide the correct conclusions (Little & Rubin, 2002). Any other missing data would be the result of incomplete recording of information or refusal of a subject to give information. Thus, the assumption that missing data are in fact missing at random (MAR), or that other variables under consideration will contain enough information to effectively model the outcome of interest, will be reasonable for these analyses.
Therefore, in the case of missing predictor variables, simple or multiple imputation methods (Little and Rubin, 2002) will be sufficient to provide “fill-in” methods so we can perform analyses of the full data set. All analyses described below will be performed on the complete data sets that result from this process. We will compare dropout patterns between groups and if there are concerns of informative dropout and/or informative intermittent missing data, we will perform sensitivity analyses to determine the effects of these assumptions on our main analyses (Molenberghs et al., 2004).

Analytic details: Continuous variables will be fit using SAS PROC MIXED, and categorical data will be fit using the gllamm add-on to Stata (Rabe-Hesketh et al; 2002). The gllamm method is preferred to SAS PROC GLIMMIX in that is a full likelihood method which uses numerical integration for the random effects rather than a partial likelihood approximation. In addition, it provides empirical Bayes estimates of the random effects for model checking. Prior to model fitting, we will examine the distributions of the continuous outcome variables using visual inspection of histograms and boxplots to identify potential outliers. If variables are not normally distributed or contain outliers, then log transformations will be considered or appropriate nonparametric procedures will be substituted for the analyses stated.

Multiple outcome measures: To address the possible increase in Type I errors due to multiple outcome variables, we have a priori selected a single outcome measure (CAPS total) which will maintain the significance level (α) 0.05 for the primary analysis. For secondary outcome measures, we will adjust p-values by controlling for the false discovery rate (Benjamini & Hochberg, 1995) and report both unadjusted and adjusted p-values.

Random effects: Given that the majority of outcomes are behavioral in nature, we expect that there will be significant individual level variance that will need to be incorporated into the model. Thus our overall analysis approach will be to use linear 2-level mixed models or generalized linear mixed models, as appropriate, to analyze the repeated measures data with at least a random intercept to incorporate individual level variation. We will also incorporate a random slope if necessary however, it is not always necessary in our experience, particularly with scales with a limited range such as MADRS.

VIII. HUMAN SUBJECTS

A. Subject Recruitment

Men and women between the ages of 18-65 with a primary diagnosis of PTSD using the DSM-V criteria will be eligible for the study. A total of 60 subjects will be randomized (30 to Vortioxetine and 30 to placebo). These subjects will be enrolled at 2 sites, Emory University School of Medicine and Miami Miller School of Medicine. Subjects will enter this study having been recruited through referrals from outpatient clinics, or referrals from other community clinics and community clinicians (psychiatrists, psychologists, and social workers) in the greater Atlanta and Miami regions. In addition, we will advertise locally in newspapers and radio and will post recruitment messages on internet sites.

Subjects will meet all inclusion/exclusion criteria outlined below. We will exclude subjects with history of bipolar disorder, psychosis, substance abuse or dependence that is current or existed 3 months prior to screening, history of borderline intellectual functioning or mental retardation, and clinically significant suicidal risk. We will exclude individuals with the following medical conditions, as evidenced by use of daily medications or prior treatment: cancer in past year, stroke, heart attack, angina, neurological disease (MS, epilepsy, Parkinson's), CNS lesions (head trauma), dementing illness, liver/kidney disease. The completion of self-report scales and cognitive tests requires a level of understanding that may not be present in those with low IQ. Medical illnesses and use of medication that may interfere with biological, and possibly psychological assessments, and current suicidality that requires immediate clinical intervention will be exclusionary for participation.

B. Inclusion/ Exclusion Criteria

Inclusion

CRITERION	METHOD OF ASCERTAINMENT
1. Males and Females between the ages of 18 and 65	History
2. Fulfills DSM-5 criteria for primary diagnosis of PTSD.	MINI
3. Willing and able to give consent	Clinical interview
4. A negative urine toxicology	Urine toxicology
5. For females of reproductive age, use of an effective birth control method* for the duration of the study or abstinence.	History
6. Duration of illness of PTSD for at least 3 months	History
7. An initial score at Screening, and Visit 2 (randomization) of ≥ 28 on the CAPS-5 for PTSD Studies	CAPS-5

***See specific criterion for effective birth control methods.**

Exclusion:

CRITERION	METHOD OF ASCERTAINMENT
1. Lifetime or current diagnosis of schizophrenia or other psychotic disorder, dementia, bipolar disorder.	MINI and Clinical Evaluation
2. Subject is currently participating in another clinical trial in which s/he is or will be exposed to an investigational or non-investigational drug or	Clinical Interview

device, or has done so within the preceding month.	
3. Subject has a prior unsuccessful trial of Vortioxetine at 20 mg/day or higher for 8 weeks or more	History
4. Current evidence or history of significant unstable medical illness or organic brain impairment, including stroke, CNS tumor, demyelinating disease, cardiac, pulmonary, gastrointestinal, renal or hepatic impairment that would likely interfere with the action, absorption, distribution, metabolism, or excretion of Vortioxetine. History of moderate or more severe TBI will also be exclusionary.	Medical chart review, clinical interview, physical exam, and laboratory testing
5. Patients who in the investigator's judgment pose a current suicidal or homicidal risk	Clinical Interview
6. DSM-5 substance abuse or dependence within the past 90 days. Subject has a positive urine toxicology test for illegal substances.	History, Urine Toxicology
7. Diagnosis of anorexia nervosa or bulimia in the past year.	MINI, History
8. Subject has a documented history of hepato-biliary disease including a history of, or positive laboratory results for hepatitis (hepatitis B surface antigen and/or hepatitis C antibody), AND clinically significant hepatic enzyme elevation, including any one of the following enzymes greater than 3 times the upper limit of normal (ULN) value (ALT, AST, ALP), or total bilirubin > 1.5 x ULN, unless consistent with presumed or diagnosed Gilbert's disease	History, Laboratory testing
9. Subject has taken systemic corticosteroids within 2 weeks of the Randomization Visit	History
10. Treatment with any other psychoactive medication within 2 weeks of Visit 1, including all antidepressants, psychoactive herbal or nutritional treatment (St Johns Wort, SAM-e), lithium, other mood stabilizers, oral antipsychotics, depot antipsychotics within 12 weeks, beta blockers, thioridazine, pimozide, opiates, anxiolytics, and sedatives (with the exception of zolpidem, eszopiclone, zaleplon, and diphenhydramine). Also any treatment with any medication that the PI judges not acceptable for this study.	History
11. Pregnancy or lactation*	Pregnancy test, assessment
12. Subjects who, in the opinion of the investigator, would be noncompliant with the visit schedule or study procedures (e.g. illiteracy, planned vacations, or planned hospitalizations during the study).	Interview/History

13. Any laboratory abnormality that in the investigator's judgment is considered to be clinically significant (blood pressure, ECG, TSH, LFT, etc.)	Laboratory testing
14. Patients who are receiving exposure-based psychotherapy that targets PTSD symptoms	Treatment History
15. Current or planned litigation or other actions related to secondary gain regarding the traumatic event	Interview
16. Subject has clinical evidence of, or EKG results indicating any of the following at either screen or Randomization Visit unless repeat EKG shows that the parameter had returned to within normal range by the Randomization Visit: ☐ QTc > 450 msec for men, or > 475 msec for women; ☐ Any cardiac condition or EKG evidence that the investigator feels may pose a potential safety concern.	EKG

* A serum pregnancy test is performed during the screening. Since this test might not detect the very early stage of pregnancy (i.e. maximum of 10 day period between fertilization and implantation), women of child-bearing age are excluded from the study if they do not use an effective birth control method for 15 days prior to receiving the study drug. Acceptable methods of birth control include: surgical sterility; post menopausal status (defined as no menses for at least 12 months); a double-barrier method (condoms plus diaphragm); hormonal contraceptives plus single barrier (birth control pills, implants [Norplant] or injections [Depo-Provera]), Intrauterine Device (IUD), or abstinence (no sexual activity).

E. Risks

1. General

By agreeing to participate in this study, subjects will be temporarily forgoing the opportunity to receive routine clinical care in the community. This will be clearly explained to all patients, along with the treatment strategies that are generally used in patients with PTSD. Patients will be told that standard alternative treatments exist for PTSD.

2. Screening and Evaluation

The risks and discomforts of the screening and baseline evaluations are minimal. No discomfort is expected to be associated with the physical examination or the clinical interview. Venipuncture may be associated with the momentary discomfort of the needle stick, as well as a small risk of hematoma (bruise). Subjects will be exposed to the discomfort of answering personal questions that they may find distressing.

3. Drug-free period and treatment trial

Since it is unknown whether the candidate is effective in the treatment of PTSD, participation in this trial could delay potentially effective therapy by 12 weeks. There may be a significant worsening of symptoms as the patient's medications are being discontinued, during the drug-free period or during the study itself. If the patient is discontinued from the study due to a worsening of their illness, they will be referred for standard care.

F. Procedure Specific Risks
Research interviews or study procedures will be interrupted if subjects become distressed or object to answering questions. We will not taper off medications that are clearly effective for the patient's current depression or PTSD.

Patients may withdraw at any time or be dropped from the study at the discretion of the investigator should medical contraindications to the assigned medication develop, if intolerable adverse reactions occur, if mood or anxiety worsens, or if in the clinician's judgment the patient has worsened to such a degree that further participation would put the patient at risk. If stopping criteria established by University of Miami guidelines are met, participants will be exited from the study and appropriately monitored.

In the startle testing, participants will be exposed to a Lemon Prep mild abrasive skin prepping lotion and gel for the electrodes. It is possible that subjects may experience allergic responses to the ingredients of the lotion or gels.

Risks Associated with Donation of Genetic Material
There are no physical risks associated with participation in genetic studies, apart from those routinely associated with phlebotomy, which are minimal. Psychological and social/economic risks associated with genetics studies of the kind described here are difficult to define, and remain the subject of heated controversy in the ethics community. The major risk, to the degree that any exists, is that a breech of confidentiality regarding genetic studies that resulted in third parties finding out genetic information about a person could theoretically place a person at risk for loss of insurance, loss of employment, etc. because of genotype-based discrimination. To our knowledge, no person has ever suffered harm for the reasons just described as a result of participating in a genetics research study. Regardless, our written informed consent process goes over these risks carefully. In addition, subjects have the right to "withdraw" from the research by having their DNA sample destroyed. Finally, all research records containing any subject-identifying information are stored under lock and key, or in secured computing environments. Personal identifiers are never associated directly with genotypes in the same data file—all genotype information is indexed only to de-identified subject codes. With these safeguards in place, we are confident the research is virtually without psycho-social-economic risk to subjects.

G. Protection against Risk
There are four areas in which safeguards to protect subjects from undue risk require discussion for study-related activities. These include the procedures used to obtain informed consent, procedures used to ensure confidentiality of the subjects' data, procedures used to minimize risks associated with study procedures, and risks associated with participating in the treatment study.

Informed Consent
In the consent form and discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator.

Confidentiality of Subjects' Responses

In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff at the research sites and the possible exception of state or federal regulatory personnel. All data will be carefully stored in a limited access, locked room. No names will be associated with computer files or data, and no names will be associated with any published reports. Access to participant data will be limited to study staff, on an as-needed basis. Results are published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity. Confidentiality may need to be broken in certain cases, such as when the subjects' safety is endangered.

Research Procedures
We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. Additionally, interviewers will receive training in the importance of study information confidentiality, and in how to manage any participant distress that may be associated with responding to research questions and interviews. Subjects will be observed closely during startle testing and the procedure will be stopped immediately if a subject indicates it is too aversive. Only one subject out of approximately 600 test sessions in the Duncan lab has requested that startle testing be stopped. We will terminate subjects from research participation if it is believed that such participation endangers their welfare. Any adverse events will be reported in compliance with IRB policies at Emory and Miami. If a clinically significant physical condition is identified during the course of participation, an appropriate referral to a medical treatment facility will be offered.

Study Medication
Subjects are monitored for potential reactions during the clinical trial. A physician is on call at all times between clinic visits so that adverse reactions can be evaluated and treated promptly.

H. Risk-Benefit Ratio
The potential risks detailed above are non-significant, and the investigators will make every effort to minimize their occurrence. The direct benefits from participating in this study may be decreased PTSD and depressive symptoms, but there may be no direct benefits to individual patients. Information obtained from the study will benefit society by increasing knowledge about PTSD.

I. Confidentiality of Data
All electronic records will be kept confidential to the extent permitted by law. Participants' names and other personal identifying information will be stored in electronically secured databases at the study sites. These databases are password protected and only study personnel will be given the password. Results will be published as group data without the use of characteristics that would identify individual subjects. The results of the genetic assessments will also be addressed in the same way.

J. Data and Safety Monitoring Plan
In compliance with local IRB guidelines, PIs will prepare a report annually that summarizes adverse event and protocol deviation data for the Data Safety Monitoring Board for the study. Each site will develop its own DSMB for the study.

K. Adverse Event Monitoring
Adverse events will be monitored throughout the study using the FIBSER and PRISE self-report forms, and through open-ended clinician inquiries. Monitoring will include assessment of

intensity (mild, moderate, severe) and assessment of causality (drug related, not drug related). All events will be followed to resolution or stabilization. All serious adverse events (SAE) will be collected and reported as appropriate per each site's IRB-requried reporting guidelines.

A serious adverse event is one that meets any of the following criteria:
--Fatal or life threatening
--Requires or prolongs inpatient hospitalization
--Results in persistent or significant disability/incapacity
--Congenital anomaly
--Important medical event that may jeopardize the patient or require intervention to prevent a serious outcome
--Cancer

An Adverse Event is:
--any abnormal laboratory test and felt to be clinical significant
--exacerbation of chronic/intermittent pre-existing condition
--New conditions detected or diagnosed
--Signs, symptoms or clinical sequelae of a suspected interaction

The University of Miami as the lead site will establish a Data Safety Monitoring Committee (DSMC) for the duration of this study in order to oversee the safety of study participants in the study. As part of the Clinical Operations Committee, the principal investigators and sub-investigators will be having conference calls monthly and will review all data and procedures on a monthly basis. Each site PI will be ultimately responsible for monitoring the data and safety at that site and will provide continuous, close monitoring of adverse events. In addition, the investigators and study coordinators will evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the various sites, and other factors that can affect study outcome. They will also consider factors external to the study, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

L. Financial Responsibilities of Subjects

Takeda intends to supply Vortioxetine and matching placebo tablets and will finance all aspects of the study. The subjects will not bear responsibility for any costs associated with study participation.

M. Subject Compensation

Participants will receive $40 for each post screening, in-office visit they attend, to compensate for their time and inconvenience in participating in the trial.

N. Site Monitoring

The Miami lead coordinator will be responsible for ensuring uniformity of study procedures across the two sites. The University of Miami as the lead site will establish a Data Safety Monitoring Committee (DSMC) for the duration of this study in order to oversee the safety of study participants in the study. The Committee will consist of members of the University of Miami's Department of Psychiatry and Behavioral Sciences. The committee will convene annually and will review the study activities by both study sites in a combined report. The Emory site will report their adverse events and all necessary events to the Miami site in a timely manner prior to the Miami site submitting to the Miami DSMC. Any communication, including

approval letters, from the DSMC will be distributed to the study sites and the study sponsor, as needed. The committee will also convene ad hoc as deemed necessary.

Responsibilities of a DSMC:
1. The primary responsibility of the DSMC is to review interim analyses of outcome data and to recommend whether the study needs to be changed or terminated based on these analyses.

2. The DSMC reviews interim toxicity data.

3. The DSMC reviews major modifications to the study prior to their implementation (e.g. termination, dropping an arm based on toxicity results, increasing target sample size).

IX. SOURCE OF RESEARCH MATERIALS

Blood will be collected and analyzed for the screening tests and genetic analyses. Urine samples will be collected and analyzed with a toxicology screen. We will also collect physical records in the form of questionnaires, phone screenings, and psychiatric interviews. We will request access to patient's medical records only for reasons related to patient safety. Patient charts will be kept in locked file cabinets in the offices of each study site.

Biological specimens are linked to the individual patient only through a unique research code. All documents that directly reveal the patient's identity, such as signed consent forms, are stored in charts that are marked on the outside only with the patient's code number.

Appendix A. Drugs Allowed (Y) and Drugs not Allowed (N) for Study Periods I and II

Drug Class	***Episodic Use***	**Chronic Use**
Alpidem	N	N
Amantadine	N	N
Analgesics (except narcotics)	Y	N
Anorexics	N	N
Antianginal agents (except calcium channel blockers)	Y	Y
Antiarrhythmics	N	N
Anticholinergics	Y	Y
Anticholinesterase inhibitors	N	N
Anticonvulsants	N	N
Antidepressants	N	N
Antidiarrheal preparations	Y	N
Antiemetics	Y	N
Antihypertensives	N	Y
Antipsychotics	N	N
Benzodiazepines	N	N
Buspirone	N	N
Carbamazepine	N	N
Chloral hydrate	N	N
Clonidine	N	N
Codeine	Y	N
Cough/Cold preparations	Y	N
Cyclosporine	N	N
DHEA	N	N
Ginko	N	N
Ginseng	N	N
Guanfacine	N	N
Loperimide	Y	N
Methyldopa	N	N
Metyrosine	N	N
Narcotics	N	N
Phenytoin	N	N
Pimozide	N	N
Prazosin	N	N
Psychostimulants	N	N
Quinidine	N	N
Reserpine	N	N
Rifampin	N	N
St. John's Wort	N	N
Steroids (oral)	Y	N
Thyroid hormone supplement[a]	N	Y
Tryptophan	N	N

[a]Subjects needing supplements must be on a stable thyroid supplement dose for at least 2 weeks prior to Visit 1.

Subjects may use zolpidem, eszopiclone, zaleplon, or diphenhydramine up to 3 nights per week during the trial.

Appendix B. Description of Scales

Brief Assessment of Cognition in Schizophrenia (BACS)

The Brief Assessment of Cognition in Schizophrenia (BACS) is a clinician-rated instrument that measures cognitive function. The domains of cognitive function that are assessed by the BACS include verbal memory, working memory, motor speed, attention, executive functions and verbal fluency. It is designed to require about 30 min of testing time. BACS A will be performed at V1 and Version B will be peformed at V9.

UCSD Performance-Based Skills Assessment- Brief Version (UPSA-B)

The UCSD Performance-Based Skills Assessment (UPSA-Brief) is a role-play test designed to evaluate a person's functional capacity in two selected areas of basic living skills. The UPSA-Brief (UPSA-B) was developed as an abbreviated alternative to the full version of the UPSA (Mausbach et al., 2007) and contains 2 of the original 5 subscales of the full UPSA (i.e., finance and communications subscales), which allows for shorter administration time (10–15 minutes) and reduced reliance on testing props. An UPSA-Brief Total Score (range = 0–100) is then obtained by summing the subscale scores.

Clinical Global Impressions Improvement Scale (CGI-I) and Severity Scale (CGI-S)

The CGI-I (Guy 1976) is a clinician-rated instrument that measures the degree of the patient's improvement. It is a 7-point scale where 1 = very much improved; 4 = no change; and 7 = very much worse. Baseline for assessing improvement for the CGI-I ratings will be the patient's clinical status at Visit 3. The CGI-S is a similar clinician-rated instrument that measures the overall severity of the patient's illness as compared to the overall study population. It is also a 7-point scale where 1= normal, not at all ill; 4 = moderately ill; and 7 = among the most extremely ill patients.

Clinician-Administered PTSD Scale (CAPS-5)

The CAPS is a structured clinical interview designed to assess the essential features of PTSD as defined by the DSM-5. The CAPS can be used to provide categorical ratings of diagnostic status as well as a quantitative index of symptom severity. The CAPS-5 Past-month version to be used in this study will include 22 items that assess the DSM-5 symptoms of PTSD during the screening visit and 20 items for all post screening visits, with each item scored from 0-4. Scores reflect an integration of each symptom's severity and frequency. The total score range is 0-80. Higher scores reflect a greater degree of symptoms severity.

Childhood Trauma Questionnaire (CTQ)

The CTQ (Bernstein, 2003) is a 28-item self-report instrument that assesses childhood trauma in the following areas: physical, sexual and emotional abuse and physical and emotional neglect. Each item is rated on a scale of 1 (never true) to 5 (very often true). The 5 subscales are then totaled, with scores ranging from 5-25 for each traumatic category.

Columbia Suicide Severity Rating Scale (CSSRS)

The CSSRS (Posner et al., 2007) is a brief, standardized, clinician-administered measure that uniquely assesses the essential information (behavior, ideation, lethality and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury. The CSSRS is composed of 3 questions addressing suicidal behavior and 5 questions assessing the severity.

Emory Treatment Resistance Interview for PTSD (E-TRIP)

The E-TRIP (Dunlop et al. 2014) is a clinician administered measure that assesses the level of treatment resistance in an individual with PTSD by evaluating past treatments and their

effectiveness, symptom onset, and primary symptoms. All past treatments are recorded and evaluated through 8 questions to determine whether the past treatment received an adequate trial and to determine the efficacy of any past adequate trials.

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)

The FIBSER (Wisniewski et al., 2006) is a self-report measure used to quantify the overall side effect burden a patient is experiencing over the previous 7 days, used in combination with the PRISE. It uses 3 global ratings on a 7-point Likert-type scale to estimate: 1) the frequency of side effects; 2) the intensity of side effects the patient believes stem from the study treatment; and 3) the overall burden or degree of interference in day-to-day activities and functioning due to side effects. The form takes less than 5 minutes to complete.

Hollingshead Four Factor Index of Social Status

The Hollingshead is a self-report measure assessing the socio-economic status (SES) of the participant as well as the participant's parents. The participant indicates the level of education obtained by their father, mother, and self using a scale ranging from 1 (less than 7th grade completed) to 7 (Graduate degree); in addition, the occupation of each of the three people is also indicated along the scale, where 1 is equivalent to a farm or day laborer, and 9 is a senior manager or professional. The raw scores obtained for each individual are weighted (and in the case of the parents, averaged), yielding total Hollingshead scores for the participant and the parents.

Life Experiences Survey

The LES (Sarason et al, 1978) is a 43 item scale that lists numerous events which individuals may experience and call for social readjustment. Subjects are asked to indicate events which they have experienced during the previous reporting period and whether these events were perceived as positive or negative. Additionally, subjects are asked to rate on a 7-point scale the degree of impact these events have on their lives. From these responses it is possible to derive three life change scores: positive, negative, and total.

Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS (Montgomery and Asberg 1979) is a 10-item instrument used for the evaluation of depressive symptoms in adults and for the assessment of any changes to those symptoms. The estimated time to administer this scale is 20 minutes. Each of the 10 items is rated on a scale of 0 to 6, with differing descriptors for each item. These individual item scores are added together to form a total score, which can range between 0 and 60 points.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI (Buysse et al., 1989) is composed of 19 self-rated questions and 5 questions rated by a bed partner (if available). The self-administered scale contains 15 multiple-choice items that inquire about frequency of sleep disturbances and subjective sleep quality and 4 write-in items that inquire about typical bedtime, wake-up, sleep latency and sleep duration. The PSQI generates seven scores corresponding to sleep domains. Each component score ranges from 0 (no difficulty) to 3 (severe difficulty). The component scores are summed to produce a global score (Range 0-21). A PSQI score >5 is considered to be suggestive of significant sleep disturbance. Most patients can complete the PSQI in 5-10 minutes.

The PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 (Blevins et al. 2015) is a 20-item self-report measure that assesses the 20 DSM-5 symptoms of PTSD. All items are answered on a 5 point scale from 0 (not at all) to 4 (extremely). Scoring can be done to measure overall symptom severity or cluster symptom

severity by dividing the questions into the following groups: Cluster B (items 1-5), Cluster C (items 6-7), Cluster D (items 8-14), and Cluster E (items 15-20).

The Patient Rated Inventory of Side Effects (PRISE)

The PRISE (Rush et al., 2004) is a 7-item self-report assessment of side effects in the following symptom domains: gastrointestinal, heart, skin, nervous system, eyes/ears, genital/urinary, sleep, sexual functioning, and other. Each domain has multiple symptoms which may be endorsed, and for each domain the patient rates whether or not the symptoms are tolerable or distressing. The time frame evaluated is the past 7 days. The form takes less than 5 minutes for the patient to complete.

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

The QIDS (Rush et. al., 2003) is a 16-item self rated instrument designed to assess the severity of depressive symptoms present in the past seven days. The 16 items cover the nine symptom domains of major depression, and are rated on a scale of 0-3. Total score range from 0 to 27, with ranges of 0-5 (normal), 6-10 (mild), 11-15(moderate), 16-20 (moderate to severe), and 21+ (severe).

Sheehan Disability Scale (SDS)

The SDS (Leon et al 1997) is a patient-rated instrument designed to assess the impact of perceived problems on work productivity, social/leisure activities, and family life/home responsibilities. The Sheehan Disability Scale consists of 3 questions rated on a visual analog scale (0 to 10). Higher scores represent greater impairment of activity.

Mini International Neuropsychiatric Interview (MINI)

The MINI is an abbreviated neuropsychiatric diagnostic interview. It examines all of the conditions that are included as both inclusion and exclusion criteria in this trial. The MINI generates diagnoses with high reliability and is easy to train raters to administer with high fidelity. We will use modules A, and C through P in this study to evaluate the inclusion and exclusion criteria. Module B for Suicidality will be excluded, as the CSSRS will be performed at screening and every study visit from randomization onward.

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