A Pilot Dose-Response Biomarker Study of Brexpiprazole Treatment in PTSD (Terminated)

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1. Title: A Pilot Dose-Response Biomarker Study of Brexpiprazole Treatment in PTSD

2. Purpose of the Study: To determine if brexpiprazole treatment will be associated with a dose-dependent reduction in resting pupil diameter as a reflection of locus coeruleus (LC) norepinephrine (NE) neuron target engagement in a group of subjects with PTSD. To determine if brexpiprazole therapy will also be associated with a dose-dependent decrease in the clinician administered PTSD scale (CAPS-5) scores. To determine if the pre-post treatment change in resting pupil diameter will be statistically significantly correlated with the pre-post change in CAPS-5 score.

3. Primary Objectives:

Specific Aim 1: Evaluate the effects of two doses of brexpiprazole on locus coeruleus (LC) norepinephrine (NE) neuron activity.

Specific Aim 2: Determine the effect of brexpiprazole therapy on PTSD symptom severity.

Specific Aim 3: 1) Evaluate whether depression severity improves with treatment and assess how this relates to PTSD response; 2) Specifically evaluate the degree to which treatment improves nightmares; 3) Evaluate the effects of treatment on sleep disturbance.

4. Background & Significance: Post-traumatic stress disorder (PTSD) adversely affects an individual's emotional and physical well-being, quality of life, and functional abilities, and increases suicide risk (Finley et al., 2015). The lifetime prevalence of PTSD varies substantially depending on the population (military, police, general adult population), but lifetime estimates are reported to be at around 10% (7.8% in the United States, 9.2% in Canada and 12.2% in Australia). Hyper-arousal is extremely common in individuals with PTSD and is considered a hallmark of the disorder. Locus coeruleus (LC) norepinephrine (NE) neuron dysregulation is believed to contribute to dysfunctional arousal in patients with PTSD and is a neurobiological target of interest. For instance, LC NE reuptake transporter labeling using PET scans correspond with anxious-arousal symptoms such as hypervigilance in subjects with PTSD. Brexpiprazole is of interest as a treatment for reducing dysfunctional arousal in PTSD patients based on its receptor binding profile which includes 5-HT_{1A} receptor activation and 5-HT_2 receptor antagonism. The brainstem circuit which involves 5-HT neuron regulation of LC NE neuron activity is complex and includes 1) activation of 5-HT_{1A} receptors that decrease 5-HT neuron activity mediated 5-HT release and 2) 5-HT_2 receptor antagonism on GABAergic projection neurons to the LC, which 3) renders an increase in α_2-autoreceptor mediated regulation of NE neurons (Blier and Szabo, 2005). However, the effects of this agent on patients with PTSD have not been evaluated. A factor confounding pursuing a study of the effects of brexpiprazole in patients with PTSD is preclinical data which suggest that there might be an increase in LC function with brexpiprazole at least with some doses suggesting that this agent may have important dose-dependent effects on LC function which, in turn, suggests that the therapeutic effects in patients with PTSD might be highly dose-dependent. However, whether there is a dose-dependence to the effects on LC function in humans has yet to be determined. It is critical that the uncertainty as to the appropriate dosage be addressed before carrying out sizable studies of the effects of brexpiprazole on patients with PTSD to prevent such studies from being futile. In order to address this uncertainty we propose to carry out a biomarker study to establish the effects of brexpiprazole on LC NE activity as a function of dose where pupillometry will be employed as an indicator of LC NE activity.

Pupillometry is a well-established, non-invasive, inexpensive indicator of LC NE activity. LC NE neuron activity increases pupil size through activation of Edinger-Westphal neurons which project to sympathetic ganglia controlling pupil diameter. Recent work has validated pupillometry as a measure of LC NE activity by simultaneously obtaining EEG, fMRI, and pupillometric data. Furthermore, the utility of pupillometry as a

biomarker of PTSD is suggested by a recent study which found increased pupil responses to threatening pictures in subjects with PTSD compared to those without PTSD. Thus, we propose to carry out a study employing pupillometry as a means of establishing the dose-response function of brexpiprazole on a key target of PTSD therapy as a means of addressing the uncertainty in dose generated by preclinical work indicating that, at least at some dosages, brexpiprazole may increase LC NE activity. We will also collect preliminary data on the dose-response effects of brexpiprazole on the clinical symptomatology of PTSD. Overall, this study is intended to provide a basis for determining the potential of brexpiprazole to be an effective therapy for PTSD. If brexpiprazole appears to be a promising therapy for this condition, our study will also serve as a basis for indicating how best to carry out clinical trials.

The broad impetus for this effort is the urgent need to develop improved therapeutics for PTSD. Treatments for this condition are extremely limited and none have demonstrated robust efficacy. It is hoped that the proposed study will serve as a key step towards evaluating whether brexpiprazole could be a much needed efficacious treatment for the many patients suffering from PTSD.

5. Design & Procedures

5.1 Subject recruitment: Participants will be recruited by running approved study specific advertisements in local newspapers and posting study flyers.in the local area. We plan to consent up to 100 subjects to recruit 36 study qualifiers. Single site, double-blind, within-subjects, cross-over, dose-response study of brexpiprazole in subjects with PTSD to evaluate the effects of brexpiprazole dose on LC NE neuron activity using pupillometry and CAPS-5 ratings.

Inclusion/Exclusion Participants will be 18-65 years of age. All subjects will be evaluated by physical examination, ECG, standard blood chemistry, hematologic labs, toxicology testing, Compliance Panel and urinalysis at baseline and end of study. Results of these studies must demonstrate a lack of clinically significant abnormalities prior to enrollment. If results are outside of the normal reference range the study physician will be consulted to assess if clinically significant. Subjects will need to satisfy DSM-5 criteria for PTSD and receive a CAPS-5 score of 33 or greater on testing for study enrollment. Subjects will need to be free of psychotropic medications or treatments that could impact results of this study as deemed by the PI for at least 1 week. If the subject's primary psychiatrist or treating primary care physician are providing the subject with psychotropic medications they will be notified and a discussion about tapering current psychotropic medications prior to study enrollment will occur.

Exclusion Criteria.

The exclusion criteria is in accordance with the package insert for brexpiprazole and can be located at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205422s000lbl.pdf

1) Subjects will be excluded if they have significant medical or neurologic conditions (other than mild to moderate TBI), specifically seizures, or movement disorders,

2) have substance abuse within 12 months of study enrollment, substance dependence within past three months, per DSM-5 criteria (excluding caffeine and nicotine). The absence of substance use will be determined by self-report and confirmed by the results of urine toxicology at screening.

3) Women who are pregnant, breast-feeding, or planning to become pregnant while enrolled in this study will also be excluded.

4) Subjects with a history of severe drug allergy or hypersensitivity, or known hypersensitivity to the Brexpiprazole or its ingredients.

5) The subject has a history of tardive dyskinesia.

6) The subject has clinically significant extrapyramidal symptoms (EPS) including akathisia.

7) The subject has epilepsy or a history of seizures, except for a single seizure episode (e.g., childhood febrile seizure, post traumatic, or alcohol withdrawal).

8) The subject has chronic, uncontrolled, or unstable clinically relevant medical conditions Including:

-Uncontrolled hypertension defined as blood pressure greater than 180/90

-Hypotension defined as a blood pressure less than 90/60

-Moderate to severe hepatic impairment (Child-Pugh score ≥7)

-Moderate, Severe or End-Stage Renal Impairment (CrCL <60ml/min)

-Known CYP2DG Poor Metabolizers

-Heart failure NYHA Class III or IV

-Diabetes mellitus or HbA1c greater than 5.7% (which defines pre-diabetes)

-Hypertriglyceridemia defined as triglycerides greater than 200mg/dL

-Low white blood cell count (below lower range of normal)

-History of leukopenia or neutropenia

-Arrhythmia with heart rate greater than 100bpm

-Myocardial infarction in the past 6 months

-Cerebrovascular accident in the past 6 months

-Recurrent syncope

-Seizure disorder

-Currently receiving treatment for malignancy

-QTc interval of greater than 450ms on electrocardiogram

9) The subject has a neurodegenerative disorder (Alzheimer disease, Parkinson's disease, multiple sclerosis, Huntington disease, etc.).

5.2 Study Components: There are 3 treatments (placebo, 2mg, 4mg), each for six weeks (±3 days), separated by a 1 week (±3 days) wash-out period. Each subject will be randomly assigned to three of the treatments. Subjects will undergo three treatments and receive 42 doses of study drug during each of the three treatment phases. Each treatment phase lasts for 6 weeks (±3 days). For each subject, they will receive a total of 126 doses of study drug. For the brexpiprazole treatment arms, we will begin with 1mg PO q Day on Days 1 through 4 and titrate to 2mg q Day on Days 5 -7 (i.e., the 2mg brexpiprazole group will continue on 2mg daily for the remainder of the 6 weeks), and then to 4mg/day on Day 8 (i.e., this will be for the 4mg brexpiprazole group who will continue on this dose for the remainder of the 6 weeks). Irrespective of the treatment group, including placebo, subjects will be assigned three medication bottles indicated to be taken during days 1-4, days 5-7, and days 8 and up to ensure blinding during the three treatment arms. Otsuka will be providing the study medication as a bulk supply and each medication dose and placebo will look identical to each other. The study drug will be stored in a double locked medicine cabinet in the Duke Sleep Lab (Duke Clinic, 5th floor Red Zone). Dr. Szabo will be creating a randomization algorithm that will be given to an unblinded study staff member to use during randomizations. The unblinded study member will prepare the study drug to be dispensed to the subjects.

Subjects will be screened and will undergo pupil measures with rating scales on Day 1. Subject must be free of all psychotropic medications for one week before Day 1 assessment, except that prior fluoxetine treatment will require 4 weeks of abstinence, and MAOIs will require 2 weeks of abstinence. They will be randomized to study drug and issued six weeks of study medication on Day 1 to take home. A phone call will then occur for safety assessment and medication adherence at every week. They will present back to the study site on Day 42 and undergo pupil measures with rating scales. They will then undergo a one week washout period. On Day 49 they will then be given another study drug to take home with rating scales and pupil measures obtained that day. A phone call will then occur for safety assessment and medication adherence at every week. They will present back to the study site on Day 91 and undergo pupil measures with rating scales. They will then undergo a one week washout period. On Day 98 they will then be given another study drug to take home with rating scales and pupil measures obtained that day. A phone call will then occur for safety assessment and medication adherence at every week. They will present back to the study site on Day 140 and undergo pupil measures with rating scales. No more study medication will be provide on Day 140 and a final visit will be scheduled for on Day 147, one week later, for and end of study interview with labs and physical exam. At each visit, other than the final visit, subjects will complete the CAPS-5, LEC-5, MADRS, Insomnia Severity Index, Columbia Suicide Severity Rating Scale, and Clinician Assessment for Adverse Effects.

5.3 Pupillometry Procedure. We will employ Tobii Tracker Eyeglasses 2 (Stockholm, Sweden) fully mobile Eye-tracking Glasses, a non-invasive system designed to be used like a common pair of glasses (weight 75 g) in a wide range of environments, both indoors and outdoors. Pupil diameter will be recorded continuously from the each eye at a sampling rate of 50 - 100 Hz via glasses on the subject's face in a darkened room.

Primary Hypothesis: Brexpiprazole treatment will be associated with dose-dependent reduction in resting pupil diameter as a reflection of LC NE neuron target engagement in a group of subjects with PTSD.

Secondary Hypothesis: Brexpiprazole therapy will be associated with a dose-dependent decrease in CAPS-5 scores

Tertiary Hypothesis: The pre-post treatment change in resting pupil diameter will be statistically significantly correlated with the pre-post change in CAPS-5 score.

5.4 Sample Size Justification and Power Analysis: We chose an effect size of 0.3 as 6/8 prior trials of the effects of atypical antipsychotic medications on PTSD using the CAPS-5 had effect sizes larger than this and we felt that an effect of this size or larger would be clinically relevant (Liu et al., 2014). The effect-size calculation was based on the Cohen's D measure of effect size (mean difference divided by overall standard deviation). We are enrolling a sufficient number of subjects in a 3-way cross-over design study so that we could both detect this effect AND be able to detect the pupil size effect with at least 80% power. In order to address the issue of powering for 2 outcome measures we will employ Bonferoni correction to be conservative and to achieve 80% power to detect BOTH the CAPS-5 and pupil size effects at the alpha=0.025 level of significance (Bonferoni correction for 2 tests dictates that we divide the alpha=0.05 level by 2). We calculated that with 36 subjects we could achieve greater than 80% power to detect effects with BOTH the CAPS-5 and pupil measure at the alpha=0.025 level in a one-tailed test of significance (we are only interested in whether brexpiprazole is associated with lower CAPS-5 scores and pupil diameters than placebo and will only test this hypothesis and will not test whether placebo has a greater therapeutic effect than brexpiprazole). This calculation assumed an effect size of 0.3 for both the CAPS-5 score and for the pupil measure. It should be noted that the assumption of an effect size of 0.3 for the pupil measure is highly conservative. We can estimate the effect size for the between group differences in pupil size based on our pilot work where we compared pupil size in a group of patients with depression and anxiety (n=5) and healthy controls (n=5) using the pupillometric measure to be used in the proposed study. We hypothesize that the difference in locus coeruleus norepinephrine activity (which determines pupil size in this test) in PTSD subjects will be comparable to or larger than the differences in locus coeruleus activity in patients with depression associated anxiety. The basis for this hypothesis is that the patients we studied likely have less severe arousal-system dysfunction than PTSD patients who manifest symptoms of hypervigilance which is likely to activate locus coeruleus to a comparable or greater degree and be reflected in pupillometry. The effect size for the difference in resting pupil diameter in our anxious/depressed patients and healthy controls is 2.98 based on Cohen's D. However, it is appreciated that this is derived from a very small sample of subjects who are not the identical patient population that we will be studying so we assumed that it was most conservative to assume a lower effect size than 2.98. As a result, we assume an effect size of 0.3 which is likely quite conservative for power with respect to the pupil size measure. Thus, we propose to enroll 36 subjects in our study and believe that this is conservative for having more than 80% to detect effect sizes of 0.3 for both the CAPS-5 and pupil measures with an alpha=0.025, which is adjusted from 0.05 for detecting effects on 2 primary outcomes at the 0.05 level, in one-tailed tests of significance.

6. Subject Consent and Compensation: Those who appear to meet basic study criteria will be asked to the Duke Sleep Lab where they will be provided a full description of the study, asked to read and sign the consent form, and undergo a qualifying interview. The reviewed information will be obtained from the subject via face-to-face interview or over the phone and will be restricted to answers to questions intended to determine whether subjects meet entry criteria. All information obtained during this review will be handled confidentially. Subjects will be compensated $115 for each of the 8 visits for a total of $920 for partaking in the study.

6.1 Consent Process: Written Informed Consent will be obtained from each subject prior to enrollment into the study. 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. Once a subject has been consented, the screening process will begin. Verification consists of a detailed interview with the patient to obtain history of illness and treatments. When possible, and with the subjects permission, verification may be supplemented by a phone interview with the subject's attending physician/psychiatrist and a full review of the subject's medical records of present history, including pharmacy records. The Investigator will retain the original copy of the Informed Consent Form signed by the patient, a duplicate will be provided to the patient and a document signed by the Investigator confirming receipt of patient consent will be returned to the Sponsor. Only the consent form approved by the IRB will be used.

6.2 Subject's Capacity to Give Legally Effective Consent: Potential subjects who do not have the capacity to give legally effective consent will not be included in this study.

6.3 Risk/Benefit Assessment: Risks: Brexpiprazole may cause some, all, or none of the side-effects listed below. In the previous studies in patients with depression or other medical conditions, the reported side effects expected to occur during treatment with brexpiprazole are listed below:

- Low blood pressure, or dizziness, or loss of consciousness when standing up
- Fast heartbeat.
- Constipation, diarrhea, indigestion, dry mouth, nausea, vomiting
- Dehydration
- Exhaustion, irritability, difficulty sleeping, abnormal dreams
- Allergic reaction
- Stuffy or runny nose, upper respiratory tract infection like common cold or bronchitis
- Abnormal liver function test (a blood measurement for the state of the liver), blood creatine phosphokinase increase (a blood test to diagnose for example muscular damage).
- Increased appetite, weight gain
- Elevated blood sugar or development of diabetes mellitus
- Increase in blood cholesterol levels
- Back pain
- Restlessness, seizure, dizziness, movement disturbances, headache, sedation, drowsiness or fatigue trembling.
- Seizures
- Agitation, anxiety

For some patients, who have not responded to treatment with brexpiprazole, have experienced a re-occurrence of disease symptoms have been reported such as symptoms associated with schizophrenia, psychotic disorder, depression or suicidal thoughts.

Although a placebo has no known risk, it may be associated with higher rates of suicidal thoughts. Risks associated with drawing blood from the arm may include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely. There is also a risk that psychiatric symptoms may worsen during the study, particularly during the period where individuals may be tapering off of medications.

6.4 SOP for Increased Suicidality

Any patient meeting clinical worsening criteria per interviews will be seen for a safety assessment by a study team psychiatrist experienced in working with patients with PTSD. If the patient is determined to be a significant suicide risk, one of the following three courses of action will be pursued:

A. Patients who contract for safety with the study physician and will be observed 24 hours/day by a responsible family member will be sent home and monitored by phone or added office visits as determined by the study physician.

B. Patients who are unwilling or unable to contract for safety will be accompanied by a staff member to the Duke Emergency Department.

C. Patients who are unwilling or unable to contract for safety and are unwilling to go to the Duke Emergency Department will be involuntarily committed via the Duke Medical Center protocol for Involuntary Commitment:

1. MD or appointed staff member remains with patient at all times
2. Staff member contacts Katherine Fisher 970-0010 or Tawanda Eley 684-0100 , Notary to begin process of IC forms
3. Staff member notifies Duke Public Safety., 681-2444
4. Staff member notifies Duke Emergency Department, 684-2413
5. Staff member collects patient demographics for police report custody order papers
6. MD does custody order papers
7. Petition notarized by Katherine Fisher or Tawanda Eley
8. Police officer escorts patient to Duke Emergency Department
9. MD to put report in CRMI database
   The complete SOP for Increased Suicidality can be found in the Duke Sleep Center SOP book.

6.5 Safety Evaluations: Adverse effects will be assessed at every visit by study physician interview. Between visits, subjects will be called and a safety assessment will be carried out by the study coordinator during the call. The regular safety assessment calls will include assessment of suicidality, using the Columbia Suicide Severity Rating Scale items 4/5. If any adverse effects are identified, this will be discussed with a study physician and appropriate steps will be taken.

Benefits: Brexpiprazole has shown benefit in patients with schizophrenia and depression and it may also help PTSD symptoms. An improvement in PTSD symptoms, depression symptoms or in both may occur. The information learned from this study may benefit other patients with PTSD in the future.

6.6 Reproductive Risks: Although there is no human data available, caution should be advised in 3rd trimester pregnancies. Risk of neonatal extrapyramidal and withdrawal symptoms based on human data with other antipsychotics are known, there is currently no known risk of fetal harm based on animal data at up to 73x and 143x the maximum recommended human dose.

6.7 Costs to the Subject: There will be no charge to subjects for any of the tests, procedures, or professional services related to this study.

6.8 Subject Recruitment: Study participants will be recruited via bulletin/poster advertisements.

7. Privacy, Data Storage & Confidentiality:
1. Serious adverse events (SAEs) and other safety information will be collected and reported to the relevant government authority in accordance with the current Code of Federal Regulations
2. Safety Information is defined as, any information from any source containing information such as:
   - Adverse event or suspicion thereof
   - Lack of efficacy
   - Overdose/incorrect dosage (accidental or intentional)
   - Abuse/misuse (e.g., patients sharing medication) even without resulting adverse reaction

- Accidental exposure (e.g., child takes parent's medication)
- Medication error
- Withdrawal reactions
- Disease progression/exacerbation of existing disease
- Drug-drug/Drug-food interaction
- Reports of unexpected benefit
- Exposure to drug during pregnancy, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure).
- Exposure to drug during lactation (including uneventful)
- Suspected counterfeit product
- Suspected transfer of infectious disease/agent by the medicinal product concerned.
- Product complaint report (any deficiencies related to the identity, quality, labeling, durability, reliability, efficacy, performance of a medicinal product, suspected counterfeit product)
- Pediatric use (if not an approved use)
- Occupational exposure
- Off-label use (if not part of the study design)

3. SAEs and safety information will be collected from first use of an Otsuka product until 28 days after discontinuation.

8. Privacy, Data Storage & Confidentiality: Study records identifying subjects will be kept confidential by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS), except when required by law. For records disclosed outside of DUHS, subjects will be assigned a unique code number and key code kept in a locked file in Dr. Szabo's office. Study records may be reviewed to meet federal or state regulations. Reviewers may include representatives of the FDA and representatives of DUHS IRB. If subject records are reviewed by any of these groups, they may also need to review the entire medical record. Study results will be retained in research records and kept indefinitely.