| IRB TEMPLATE: Standard Protocol Form | |
|---|---|
| NUMBER | VERSION DATE |
| HRP-UT901 | 10/3/2025 |

# About this Form

This form is required for research studies that are greater than minimal risk, or minimal risk qualifying for expedited review. You can also use this form if you are unsure which review level and/or form is best.

Additional forms/tools are available for the following:

- Requesting a "Not Human Subjects Research" (NHSR) determination
- Exempt Research requiring only institutional review
- Secondary Use Research where there is no contact with participants
- Non-research treatment protocols (HUDs, EAPs/Compassionate Use, Emergency Use)

**Need help deciding which form to use? Refer to our IRB Template Decision Tree.** All protocol templates are available in the UTRMS-IRB Library.

For studies following a sponsor protocol, please use this guidance to assist in your completion of this form.

Be aware that other institutional requirements outside the scope of IRB review may apply to your research. Please see the UT Austin Human Research Navigation Tool for guidance on additional requirements that may apply.

# Instructions for Use

**Do not convert this Word document to PDF.** PDFs block certain review functionality in UTRMS-IRB (such as the ability for staff to see system-tracked changes when edits are made) which can hinder review.

**This form uses skip logic.** Complete the form in order and answer all questions unless instructed to skip via *special instructions* based on previous responses.

To fill in a text box, make sure your cursor is within the *grey text box* before typing or pasting text. Boxes will expand to accommodate the full length of text added.

Once complete, upload this form on the Basic Study Information section of the online application where prompted to upload the protocol (typically question 7 or 8 depending on previous responses).

**Please do not delete the Index.**

**Index**

# General Study Information

**Study Title:**

Neurocircuitry Mechanisms and Efficacy of Lumateperone as Adjunctive Therapy for Major Depressive Disorder and History of Early Life Abuse

## 1. Review Type (Choose one)

*Please choose which level of review best fits your research. This is an investigator's assessment of review and does not preclude the IRB from alternate determinations. In cases where the investigator and the IRB's determination of review conflict, the IRB's determination will be considered the official determination.*

*Note: "Expedited" review does not refer to the timeliness of the review of your protocol, but specific categories of research defined by OHRP. If you would like help determining which type of review best fits your research study, please contact the IRB staff in the Office of Research Support & Compliance: https://research.utexas.edu/ors/human-subjects/get-help/*

*Click on the appropriate check box (or double click and type an "X" if using Google Docs):*

☒ Full Committee – Greater than Minimal Risk Research

☐ Single Reviewer – Minimal Risk Research (expedited)

### 1a. Notification of UT IRB Fees

*Be aware that the UT IRB may charge fees for certain types of reviews. If your project qualifies for either of the project types listed below, check the appropriate box and review our website for more information about IRB fees that may apply. Please reach out to irb@austin.utexas.edu if you have questions.*

☒ Industry-sponsored Clinical Trial

☐ Federally-Funded multisite study for which UT IRB is serving as the single IRB of record *(for guidance, see our website for Single IRB Reliance)*

## 2. External Time Limitation

*Generally, the IRB will review applications in the order in which they are received. When possible, the IRB can assign higher priority to research with externally-imposed urgency that is beyond the control of the researcher (example: grant deadlines, research responding to a sudden or emerging event, etc.).*

*Completing this section provides the IRB with information but does not guarantee priority review is possible or that a requested deadline can be met. Researchers are encouraged to communicate with the IRB as soon as possible when there is an urgent situation (ideally before submitting the IRB application), and we will do our best to accommodate requests, as possible: https://research.utexas.edu/ors/human-subjects/get-help/*

**Are you requesting the IRB consider priority review due to an *externally-imposed* deadline or time limitation affecting this submission?**

☐ No

☒ Yes → *If yes, briefly describe the urgency or deadline below, including the reason for it:*

The sponsor has requested expedited review in order to ensure funds are available for this project.

## 3. Is the research taking place at or using data from any of the following:

*Knowing when UT's external clinical partners are involved helps inform IRB review and reporting.*

☒ None of these

☐ Heath Discovery Labs

☐ Central Health

☐ CommUnity Care

☐ Ascension locations → *Submit a request to the Seton Site Approval Tool (SAT) and upload the confirmation email that states the request has been submitted in UTRMS under "Other Documents." Please note, we do NOT need the final approval letter (you will not receive SAT approval until after IRB approval is granted). If you encounter issues or have questions about SAT, please reach out to siteapproval@seton.org.*

## 4. Research Hypotheses

*Please describe the research aims and hypotheses in the box below. Note: Procedures will be explained in a separate section below.*

**Aim 1:** To assess the efficacy of lumateperone 42 mg administered once daily compared with placebo in the treatment of patients with Major Depressive Disorder and early life abuse, as measured by change from baseline to end of Week 6 in MADRS total score.
**Aim 2:** To assess neurocircuitry encoding of threat and reward learning as predictors of lumateperone response and as mechanisms of treatment action, and assess the change from pre-dose to post-dose of task-evoked brain activation.
**Aim 3:** MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at Week 6 of Lumateperone as compared to Placebo.
**Aim 4:** MADRS remission rate (proportion of subjects with a MADRS total score ≤10) at Week 6 of Lumateperone as compared to Placebo.
**Aim 5:** To assess the efficacy of lumateperone 42 mg administered once daily compared with placebo in the treatment of patients with Major depressive Disorder and early life abuse, as measured by change from baseline to end of Week 6 in Clinical Global Impression-Severity (CGI-S) score.

## 5. Study Background

*Provide the rationale and the scientific or scholarly background for the proposed activity, based on existing literature (or clinical knowledge). Describe the gaps in current knowledge that the project is intended to address.*

Early life trauma is widely documented as a robust risk factor for development of major depressive disorder (MDD), in addition to many other mental health disorders[1,2]. Further, comorbid history of early life trauma among those with MDD predicts worse response to first-line pharmacotherapy for MDD[2]. Among the different types of early life traumas, physical and sexual assault tend to be associated with particularly worse outcomes in adulthood[3]. As such, there is a clear need to develop adjunctive therapies for those with MDD and histories of early life abuse in order to mitigate the typical poor clinical response seen in this population.

An emerging computational neuroscience literature has demonstrated altered neurocircuitry encoding of threat and reward learning as a key mechanism linking early life abuse to worse mental health outcomes in adulthood. This emerging computational literature complements and extends the well-established link between MDD and poor reward learning and decreased reward sensitivity[4–6]. Indeed, in a prior study we demonstrated that decreased prospective reward representations in the striatum mediated poorer reward learning and depression symptoms among individuals with histories of early life physical or sexual assault[7]. We've also demonstrated decreased encoding of reward prediction errors among women exposed to physical or sexual assault in the striatum and anterior insula[8,9], and decreased social reward prediction error encoding among adolescent girls who experienced physical or sexual assault. Similarly, recent work demonstrated altered integration of threat and reward learning (i.e., approach-avoidance conflict) in depression[10,11], potentially mediated by altered encoding of reward in the striatum. These findings are in line with our prior computational work investigating neurocircuitry mechanisms of approach-avoidance conflict demonstrating that biased prospective representations of reward vs threat in

the salience network mediates decisions to approach reward vs avoid threat[12] and that individuals with assault histories demonstrate altered approach-avoidance conflict learning[13,14]. Overall, the emerging literature clearly points to altered computational encoding of threat and reward learning as a mechanism underlying development of MDD among those with histories of early life assault.

The neurocircuitry implicated in altered threat and reward learning as mechanisms of risk for MDD includes the salience network (dorsal anterior cingulate cortex and anterior insula) and striatum. Notably, this neurocircuitry overlaps with dopaminergic and serotonergic pathways targeted by atypical antipsychotic medications[15,16]. As such, altered neurocircuitry encoding of threat and reward learning could potentially be predictive of clinical outcomes for adjunctive therapies that target these pathways, such as lumateperone. There are two main routes by which these pathways could have clinically predictive significance. First, individual differences in neurocircuitry encoding of threat and reward learning could operate as markers of who would vs would not benefit from lumateperone adjunctive therapy. Second, pre- to post-treatment changes in neurocircuitry encoding of reward and threat learning could operate as a mechanism of symptom reduction (e.g., lumateperone induced improvements in reward and threat neurocircuitry encoding mediate reductions in depression symptoms). These possibilities are not mutually exclusive, and both would have considerable clinical significance for enabling precision medicine approaches to the treatment of MDD among early life trauma populations.

## 6. Design and Methodology

*Provide a brief description of the overall study design or data collection methodologies. Details regarding protocol specific research procedures will be discussed in the next section below.*

This is a single site investigator initiated randomized, double-blind, placebo controlled, fixed-dose study in patients with a primary diagnosis of MDD, a history of early life abuse, and who have an inadequate response to on-going SSRI treatment. The study will enroll a total of 50 participants (n=50) with 25 randomized to treatment and 25 to a placebo, and will be conducted in 3 phases:

**Screening Period -** After signing the ICF, an identification number will be assigned to the subject. Prior to randomization, all subjects will enter a 2 week-day screening period (Screening) to determine eligibility. Eligible subjects must meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for MDD without psychotic features, based on the DIAMOND (Diagnostic Interview for Anxiety, Mood, and Other Neuropsychiatric Disorders), with a current major depressive episode of at least 8 weeks in duration. They must have had an inadequate response (<50% symptom reduction) to an adequate trial of at least 1 antidepressant therapy (ADT) (as determined by administering the Massachusetts General Hospital Antidepressant Treatment History Questionnaire [ATRQ]) in their current Major Depressive Episode (MDE). During Screening Period (2 weeks) patient eligibility will be assessed and a Pre-dose fMRI performed.

**Double-blind Treatment Period** - Double-blind Treatment Period (6 weeks) during which all eligible patients will be randomized to receive lumateperone 42 mg or placebo in 1:1 ratio. At Baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomized to either lumateperone or placebo.

**Safety Follow-up Period** in which all patients will return to the clinic for a safety follow-up visit approximately one week after the last dose of study treatment. All patients will complete a post dose MRI 1 week after the 6-week study period is completed.

- During the Pre-Dose and Post-dose MRI, Participants will undergo standard structural imaging as well as functional imaging during computational threat and reward learning tasks. Computational neuroimaging approaches will characterize neurocircuitry encoding of anticipating and delivery of threat and reward outcomes, enabling testing of predictors of lumateperone clinical response and mechanism of treatment action.

- Patients who discontinue study drug prior to Week 6 but agree to continue participation in the Double-blind Treatment Period (DBTP) should be seen at all subsequent protocol-defined visits up to week 6 and should also return for the SFU Visit for post dose MRI. Study drug will no longer be dispensed for these patients and the clinical management of these patients will be at the discretion of the Investigator.
- Patients who discontinue study drug prior to Week 6 and do not agree to continue participation in the DBTP should be seen for an early termination (ET) Visit as soon as possible and should also return for the SFU Visit 1 week after the ET Visit. Study drug will no longer be dispensed for these patients and the clinical management of these patients will be at the discretion of the Investigator;

Safety Follow-up Period (1 week) during which all patients will return to the clinic for a safety follow-up (SFU) Visit approximately one week after the end of DBTP, or ET Visit if the patient does not complete the DBTP.

## 7. Study Procedure Description

*Provide a step-by-step narrative of what enrolled participants will be asked to do or allow, and/or how data/specimens will be collected and used, such that someone else could replicate the procedures based on this description.*

*Recruitment and consent procedures will be covered in later sections. The description below should cover all procedures involving enrolled subjects or participants (or their data/specimens) from start to finish, in sequential order. Include details of all the following, as applicable:*

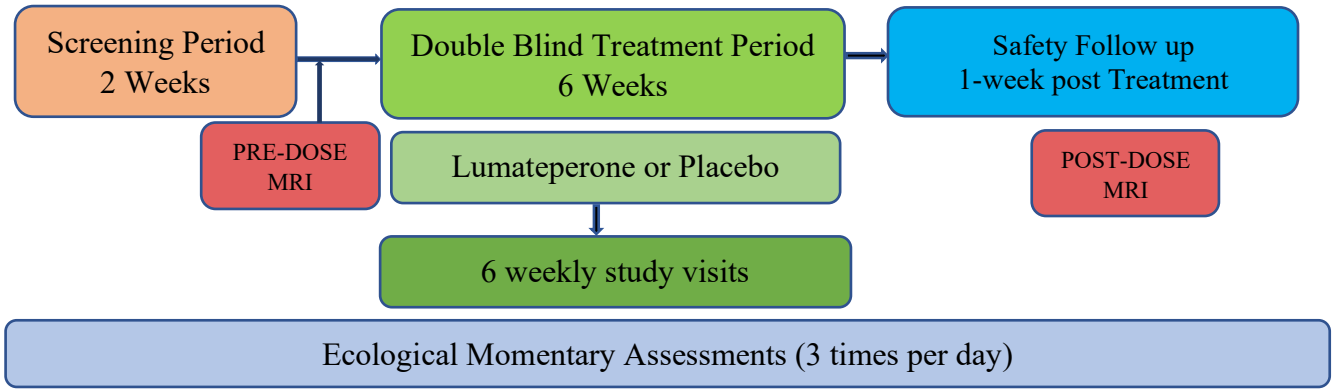
- *Research measures/tests/data collection tools that will be used.* ***Upload copies of all surveys, interview guides, assessments, questionnaires, and any other data collection tools to UTRMS-IRB in the "Other Attachments" section.***
- *Research interventions and activities, including all stimuli/tasks/instructions that participants will see, hear, or experience as part of their participation.* ***Upload copies of all intervention materials (including videos, audio files, handouts, photos, scripts, etc.) to UTRMS-IRB in the "Other Attachments" section.***
- *Biospecimens that will be collected as part of the research procedures, including the type of specimen, method of collection, schedule/frequency of collection.*
- *Secondary data or specimens that will be obtained, how they are collected and used, from what source(s).*
- *Total duration of all research activities (i.e. expected time commitment of participants).*

*Note: if this is a Multi-Site or Collaborative Study include the following:*

- *This is a "Multi-Site Study that involves more than one site performing ALL aspects of the research procedures as outlined above." OR "This is a Collaborative Study that involves UT Austin researchers working with external researchers who are engaged in performing the following study activities (list activities)."*
- *For assistance with Multi-Site/Collaborative research, review UT Guidance: Submitting Studies Relying on UT IRB, download HRP-UT932 Request to Rely Assessment Form from the UTRMS-IRB Library and email irbreliance@austin.utexas.edu.*

This is a single site, randomized, double-blind, placebo-controlled study to evaluate the efficacy of lumateperone as an adjunctive treatment of patients with MDD and a history of early childhood abuse. During the study subjects currently receiving approved dosing regimen of ADT, who experience an inadequate therapeutic response according to MADRS score at Baseline, will be randomized in a 1:1 ratio to Lumateperone 42mg or placebo, and receive treatment for 6 weeks. The primary efficacy analysis will be based on the week 6 assessment of the primary and secondary efficacy endpoints.
The overall duration of the study, including Screening and intervention period, will be approximately 9 weeks per subject: a 2-week screening period, 6 weeks of double-blind treatment, and a 1-week safety follow-up visit.
The study design is presented in Figure 1.

Figure 1.




The study will be conducted as follows:

- Screening Period (2 weeks):

o A 2-week Screening Period during which patient eligibility will be assessed. After obtaining written informed consent, diagnostic interviews and physical examinations will be conducted, vital signs and ECGs will be assessed, and blood and urine samples will be collected for laboratory assessments. With the exception of stable, allowed concomitant medications, patients must discontinue prohibited psychotropic drugs during the Screening Period. The following rating scales will be administered.

Clinician Rater: CAPS-5, MADRS, DIAMOND, SCID-5 Borderline Personality module, CGI-S, MGH-ATRQ, CSSRS

PROS, GAD-7, QIDS-SR-16, EQ 5D-5L, CTQ, GASS, PCL-5, NWS, MCI

Once deemed eligible, the subject will also be offered to enroll in the optional EMA wellness app to be completed 3X daily from screening visit to the end of study visit

- Double-blind Treatment Period (DBTP, 6 weeks):

  - At Baseline (Visit 2), patients who continue to meet all eligibility criteria will be randomized to 1 of 2 treatment arms, lumateperone 42 mg or matching placebo, and will enter the 6-week DBTP. Patients will be administered the first dose of study drug in the evening of the Baseline Visit (Visit 2/Day 1). A single dose will be taken each evening, with or without food, for the duration of the 6-week DBTP.

  - MRI assessments will be completed at baseline Pre- dose and post dose at 1-week safety follow up visit.

### 1.1.1 Dose Selection

Lumateperone capsules are approved in the US by the FDA for the treatment of schizophrenia in adults and for the treatment of depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate. The recommended dosage regimen is lumateperone 42 mg administered orally once daily. Several studies have shown that lumateperone has a

favorable safety profile, exhibiting a similar tolerance to placebo, with no significant adverse effects reported. The purpose of this study is to determine the efficacy and safety of once daily lumateperone 42 mg as an adjunctive therapy for the treatment of patients with a history of childhood abuse and MDD. Symptoms of depression may or may not improve during participation in this study; half of the patients in this study will receive placebo. However, the information obtained from this study may help to treat people suffering from MDD with history of childhood abuse.

## 2. Study Population

### 2.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following inclusion criteria:

1. Provide written informed consent before the initiation of any study-specific procedures. See informed consent requirements;

NOTE: Patients who are unable to independently provide informed consent will be ineligible to participate in this study.

2. Male or female, between the ages of 21 and 70 years, inclusive;
3. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR)criteria for MDD without psychotic symptoms, as confirmed by a trained rater using the modified Structured Clinical Interview (DIAMOND) for DSM-5,
4. MADRS total score ≥ 22 at Screening (Visit 1) and Baseline (Visit 2)
5. Endorse >=1 physical or sexual assault prior to age 16 on the interview-based trauma assessment.

   Many studies refer to early life trauma as prior to age 18. Here we define early life assault as less than 16, rather than 18, in order to ensure a clearer separation between early life and adulthood. While another option might be to restrict even further (e.g., age of trauma < 10), for feasibility (e.g., facilitating recruitment) and generalizability (e.g., results extend to MDD and early life trauma more broadly than just early childhood trauma), we decided on physical or sexual assault prior to age 16.

   Regarding the focus on physical or sexual assault, there are two main reasons. First, the definition of physical and sexual assault can more easily be operationalized through a behavioral description of an event (e.g., has anyone hit you with a fist, has anyone hit you with an object, etc), enabling more precise assessment and detection. Second, there is a robustly elevated risk for mood disorders following assaultive traumas relative to non-assaultive traumas. As such, there is greater clinical need to establish adjunctive treatments among those experiencing assaultive traumas.

6. Participants must have been treated with the same dose of antidepressant therapy for at least 6 weeks, with less than 50% improvement, and be committed to stay on the same stable dosing regimen for the Screening period and for the entire study, at or above the minimally adequate dose in the ATRQ. Documentation of stable and ongoing ADT must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician, or other qualified healthcare professional.
7. Females of childbearing potential agree to use at least an acceptable method of birth control (including but not limited to hormonal contraception, intrauterine device, vasectomized partner, bilateral tubal occlusion, condom with or without spermicide, cap with spermicide, diaphragm with spermicide, sponge with spermicide, or double barrier methods) from the time informed consent is provided through the end of the SFU period. *NOTE:* Females of non-childbearing potential (defined as either permanently sterilized, or post-menopausal females [defined as at least one year with no menses without an alternative medical explanation]) are exempt from the birth control requirement.
8. Ability to follow study instructions and likely to complete all required visits.

### 2.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

***Psychiatric Criteria***

1. Has a **current primary** DSM-5-TR psychiatric diagnosis other than Major depressive disorder. These include:
    i. PTSD, OCD, Bipolar Disorder, Schizophrenia, schizoaffective disorder, or other psychotic disorders;
    ii. Intellectual disability, Dementia or other cognitive disorders;
    iii. Moderate or severe substance use disorder (excluding for nicotine);
2. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during the course of his/her participation in the study or
    i. At Screening (Visit 1), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS within 6 months prior to Screening; or
    ii. At Screening (Visit 1), the patient has history of suicidal attempt(s) within 1 year prior to Screening (Visit 1); or
    iii. At Baseline/randomization (Visit 2), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS since the Screening Visit; or
    iv. At Screening (Visit 1) or Baseline (Visit 2), scores ≥ 4 on Item 10 (suicidal thoughts) on the rater administered MADRS; or
    v. Considered to be an imminent danger to himself/herself or others.

***Treatment-related Criteria:***

3. MRI contraindications: History of shrapnel or other metal or electronic implants in the body(such as pacemakers, aneurysm clips, ferrous surgical devices, metallic tattoos on the head, etc.). The patient has received electroconvulsive therapy (ECT), vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the past 1 year;
4. The patient has known hypersensitivity or intolerance to lumateperone, or to any of the excipients;
5. Treatment with a depot/long-acting injectable antipsychotic within 1 cycle before Screening (Visit 1);
6. The following agents are excluded and must be discontinued at Screening (Visit 1):
    i. Any moderate or strong cytochrome P450 3A4 inhibitor (CYP3A4), or any CYP3A4 inducer;
    ii. Central opioid agonists/antagonists, including tramadol;
    iii. Anticonvulsants, mood stabilizers, antidepressants, stimulants, antipsychotics, and non-benzodiazepine anxiolytics;
    iv. Dietary supplements and medical foods unless approved by the Sponsor or designee. Daily multivitamin use is permitted;
7. Monoamine oxidase inhibitors within 14 days prior to Baseline/Randomization (Visit 2);
8. Other drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system.
9. The patient plans to initiate psychotherapy or make changes to existing psychotherapy during the study (patients who are participating in stable psychotherapy or psychotherapy as a part of their treatment are allowed to enroll);
10. The patient has participated in a previous clinical trial with lumateperone, or has had exposure to any investigational product within 6 months of the baseline visit or participated in > 2 clinical studies

of an investigational product with a central nervous system indication.

***Other Medical Criteria:***

11. The patient is pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1). On Day 1 (Baseline/Visit 2), female patients of childbearing potential must have a negative urine pregnancy test prior to study drug administration;
12. The patient has a positive test for alcohol or drugs of abuse (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, or opioids/opiates) at Screening (Visit 1).
13. The patient has abnormal laboratory values or clinical findings at Screening (Visit 1) including, but not limited to:
    i. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN);
    ii. Total bilirubin > 1.0 × ULN;
    iii. Hemoglobin < 8 g/dL (80 g/L) for females and < 9 g/dL (90 g/L) for males;
    iv. Absolute neutrophil count (ANC) < 1200 cells/μL ($1.2 \times 10^9$ cells/L);
    v. Thyroid-stimulating hormone (TSH) outside of normal reference range AND free T3 or free T4 outside of the reference range. Free T3 and Free T4 will only be evaluated if TSH is outside of reference range;
    vi. Poorly controlled diabetes as defined by a glycosylated hemoglobin (HbA1c) >7.5%, despite standard care [> 58 mmol/mol];
    vii. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at screening; positive hepatitis C antibody at Screening (Visit 1), with the exception of a patient for whom the reflex HCV RNA test is negative;
    viii. Any other clinically significant abnormal laboratory result obtained at screening (Visit 1);
14. ECG abnormalities where the patient has corrected QT interval using the Fridericia formula (QTcF) > 450 msec for males or > 470 msec for females and/or heart rate < 50 bpm, or evidence of clinically significant bundle-branch blocks at Screening (Visit 1);
15. The patient has any of the following conditions:
    i. Cardiac: uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation, or any other cardiac disorder;
    ii. Malignancy: Any diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years;
    iii. Gastrointestinal: history of gastric bypass or any other condition that results in malabsorption;
    iv. Endocrine: hypo- or hyperthyroidism unless treated and stable with no medication changes for at least three months prior to screening, diabetes, unless considered stable with no changes in treatment for at least three months prior to screening;
    v. Hepatic: Hepatitis B or Hepatitis C; moderate or severe hepatic impairment (Child-Pugh B or C);
    vi. Pulmonary: history of diagnosed and untreated obstructive sleep apnea;
    vii. Neurological: history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or central sleep apnea, or significant brain trauma, or other cognitive disorder; History of movement disorders.
    viii. Infectious: History of human immunodeficiency virus (HIV) infection.

***Note:*** Any other medical condition, or medical conditions that are stable with treatment (eg, hypertension, hypercholesterolemia, or thyroid abnormalities) are allowed as long as the condition has been stable for at least 3 months prior to Screening (Visit 1); treatments for these conditions are documented, kept stable, and are expected to be unchanged during the study; and the condition is

not thought to affect safe participation in the study or relevant study outcomes in the opinion of the Investigator.

***Other Criteria:***

16. The patient is judged by the Investigator to be inappropriate for the study;
17. Patient is homeless;
18. Patient does not speak english;

### 2.3 Rescreening

Individuals who sign the ICF to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore are not randomized (screen failures), may be rescreened once, at the discretion of the Principal investigator with the exception of subjects presenting with alcohol or drug abuse or previously undisclosed psychoactive drugs; subjects excluded because of QTc prolongation or other serious medical conditions at initial screening.

### 2.4 Study Withdrawal or Removal from the Study

Patients can be prematurely discontinued from the study drug or the study for one of the following reasons:

- Death
- AE
- Lack of efficacy or insufficient therapeutic response
- Lost to follow-up
- Protocol violation
- Study terminated by Investigator
- Withdrawal of consent (by the patient)
- Pregnancy
- Other (such as site closure, administrative reasons, etc)

***NOTE****:* If a patient discontinues due to withdrawal of consent and either a concurrent AE was reported or concurrent lack of efficacy was documented, the study staff will confirm the primary reason for discontinuation and record the primary reason for discontinuation in the subject binder (CRF).

Patients who discontinue from the study and do not return to the study site for final assessments must be requested in writing to return to the site for a final assessment. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded in the subject study binder.

## 3. Treatment

### 3.1 Study Drug Administration

Lumateperone 42 mg or matching placebo Capsules will be dispensed at Baseline (Week 1), and weekly thereafter until week 5 for oral administration administered once daily. Study drug will be dispensed to eligible patients under the supervision of the Investigator or Sub-Investigator, or the designated personnel authorized to administer treatment. Study drug should be taken at approximately the same time in the evening, with or without food, once daily.

Table 2. provides formulation information for study drugs. Study drugs will be labeled according to local laws and regulations.

Table 2.

| **Investigational Product** | **Lumateperone 42 mg** | **Placebo** |
|---|---|---|
| **Dose frequency** | Once daily in the evening | Once daily in the evening |
| **Route** | oral | oral |
| **Formulation** | capsule | capsule |
| **Appearance** | White opaque hard gelatin capsule | White opaque hard gelatin capsule |

The study drug will bear the following information:

- Protocol Number or study ID
- Statement indicating that the drug is an investigational drug
- Recommended storage conditions of drug
- Bottle number
- Lot number and date of expiration of the drug
- Quantity of drug per package

### 3.1.1 Storage and Handling of Study Drug

All study drug received, will be stored, and handled strictly in accordance with the product label and the site standard operating procedures (SOPs). Upon receipt, the study drug will be promptly transferred to the environmentally controlled Drug storage area. The research staff will examine the shipment and temperature monitoring devices (if applicable) to verify that the study drug was received in acceptable condition. Once inspected, the study drug will be stored in a restricted access, secured area with access limited to authorized research study staff, under physical conditions consistent with the study drug's specific requirements. After study drug is dispensed to subjects, the remaining study drug will be returned to storage in a restricted access, secured area under physical conditions consistent with the study drug's specific requirements. Study participants will be instructed to store the investigational product at room temperature at home, out of the reach of children.

## 3.2 Study Drug Accountability

The Investigator and designated study staff will maintain accurate records of receipt of all study drugs, including dates of receipt. The study staff will enter the lot number and expiration date on the Master IP accountability log. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen will be recorded.

## 3.3 Method of Assigning Patients to Treatment Groups

After a patient signs the ICF at Screening (Visit 1), The investigator will randomly assign a study drug kit number for dispensing the study drug. The Kit number, expiration date will be noted on the individual IP dispensing log.

## 3.4 Blinding

The study will be performed in a double-blind manner. All study drugs will be supplied in identical treatment cards and packaging, and will be similar in color, smell, taste, and appearance, thereby enabling double-blind conditions.

## 3.5 Unblinding

Unblinding will be done only in an emergency that requires the study drug to be identified for the medical management of the patient. The Investigator will notify the Sponsor or designee immediately and a full written explanation must be provided if the blind is broken. Breaking the blinding code will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Drug Safety for regulatory reporting purposes. In such cases, the study center staff will be kept blinded and the patient will not need to be disqualified from the study.

## 3.6 Monitoring Treatment Compliance

Study drug adherence will be emphasized at every visit. Study drug compliance during the DBTP will be closely monitored. The study staff will count the number of capsules remaining and compliance will be assessed based on the number of capsules prescribed and the number of capsules taken. Every effort will be made to collect unused study drug that has been dispensed to the patient., Any irregularities in study drug adherence should be discussed with the patient at every visit. Non-compliance is defined as taking less than 80% or more than 120% of study drug during any visit to visit evaluation period. Discontinuation for non-compliance will be at the Investigator's discretion and will to be recorded on the subject CRF. All errors in study drug dispensing or administration will be carefully documented in the subject study binder.

## 3.7 Prior and Concomitant Medications and Therapies

All medications taken and therapies received within 6 months prior to Screening must be noted on the eCRF. Medications taken and therapies received related to the primary indication (MDD) within the 5 years prior to Screening will also be recorded on the Concomitant medication CRF. The reported concomitant medications and/or therapies will be reviewed and evaluated by the Investigator to determine if they affect a subject's eligibility or continued participation in the study.

Medications for the acute treatment of extrapyramidal symptoms and akathisia are allowed, but should not be administered within 8 hours prior to movement disorder assessments.
Zolpidem may be taken for insomnia, in the evening at bedtime and prior to midnight, but no more than 3 times per week during the Screening Period and the first 2 weeks of the DBTP only for the treatment of insomnia.
Lorazepam (or other benzodiazepines) may be taken for anxiety, agitation, irritability, hostility, and restlessness. Daily doses should not exceed 3.0 mg/day during the Screening Period and through the first week of the DBTP. From Week 2 to week 6 daily dose should not exceed 2 mg/day. Doses may not be given on a standing basis, and the lowest effective dose should be used.
Zolpidem or lorazepam, or their equivalents, should not administered within 8 hours prior to efficacy assessments.
Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the ConMed CRF. The entry must include the dose, regimen, route, indication, and dates of use.
All medications and other treatments taken by the subject during the study, including those treatments initiated before the start of the study, must be recorded on the ConMed CRF.

#### 3.7.1 Prohibited Medications

Use of the following products during the study is prohibited: any known 5-HT2A receptor antagonist or inverse agonist, any moderate or strong CYP3A4 inhibitor or any CYP3A4 inducer, or any drugs with known psychotropic properties other than those listed in Section 6.7 or any non-psychotropic drugs with potential central nervous system effects.

### 3.8 Treatment After Discontinuation of Study Drug or from the Study

Patients whose MDD symptoms worsen or are determined by the Investigator not to be adequately controlled prior to completing the DBTP may be discontinued from the DBTP in order to start appropriate treatment at the Investigator's discretion. The Investigator will refer the study subject to their provider for new treatment and will not be provide the treatment themselves. Patients who initiate a new treatment during the study must be discontinued from the study drug.

Patients who discontinue study drug prior to Week 6 but agree to continue participation in the Double-blind Treatment Period (DBTP) should be seen at all subsequent protocol-defined visits up to week 6 and should also return for the SFU Visit. Study drug will no longer be dispensed for these patients and the clinical management of these patients will be at the discretion of the Investigator;

Patients who discontinue study drug prior to Week 6 and do not agree to continue participation in the DBTP should be seen for an early termination (ET) Visit as soon as possible and should also return for the SFU Visit 1 week after the ET Visit. Study drug will no longer be dispensed for these patients.

### 3.9 Contraceptive Precautions

WOCBP (women of childbearing potential; not surgically sterilized and between menarche and 1-year post-menopause) must agree to use at least 1 highly effective method of contraception from Screening through at Safety follow up one week after the last study drug administration. Women who are not of childbearing potential must be congenitally or surgically sterile (hysterectomy and/or bilateral oophorectomy/salpingo-oophorectomy, as determined by the subject's medical history) or must be post-menopausal. For men with female sexual partners of childbearing potential, examples of medically acceptable forms of contraception include vasectomy or male condom for subjects, plus an additional method of contraception for their female partners

Effective methods of contraception are those that have a failure rate of <1% (when implemented consistently and correctly) and include:

- Intrauterine device (IUD)
- Bilateral tubal ligation, bilateral salpingectomy, or bilateral tubal occlusive procedure
- Hormonal contraceptives (e.g., oral, patch, or injectable)

• A double-barrier protection method (e.g., condom, sponge, or vaginal diaphragm with spermicide cream, foam, or gel)
• Abstinence from heterosexual intercourse is accepted if this is the subject's usual lifestyle and must be continued until at least 2 months after the last dose of study drug.
Women who are lactating are prohibited from participating in the study.

## 4. Study Procedures

Table 1. outlines the timing of procedures and assessments to be performed throughout the study.

Table 1.

| **Study Phase** | **Screening Period** | **Double-blind Treatment Period** | | | | | | **Safety Follow-up Period** |
|---|---|---|---|---|---|---|---|---|
| **Visit Number** | **1 (Screening)** | **2 (Baseline)** | **3** | **4** | **5** | **6** | **7** | **8/ET[2]** |
| **Study Week** | **Week -2** | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** |
| **Study Day** | **Up to 15 days prior to baseline** | | **(± 2 days)** | | | | | |
| Informed consent | X | | | | | | | |
| I/E criteria | X | X | | | | | | |
| Medical history and demographics | X | | | | | | | |
| Physical examination | X | | | | | | X | |
| Vital signs | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | X | | | X | |
| Clinical laboratory tests | | | | | | | | |
| Hematology | X | | | X | | | X | X |
| Biochemistry | X | | | | | | | X |
| Urinalysis (Dipstick) | X | X | | | | | | |
| TSH | X | | X | | | | | X |
| Hepatitis serology | X | | | | | | | |
| Urine Drug Screen and Breath Alcohol Test | X | X | | | | | | |
| Serum/Urine Pregnancy test | X | X | | | | | | |
| Study Assessments | | | | | | | | |
| SCID- | X | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Borderline personality disorder module | | | | | | | | |
| Diamond | X | | | | | | | |
| CAPS-5 | X | | | | | | | X |
| CGI-S | X | X | | X | | X | | X |
| MCI | X | | | | | | | |
| MADRS | X | X | X | X | X | X | X | X |
| C-SSRS | X | X | X | X | X | X | X | X |
| MGH-ATRQ | X | | | | | | | |
| GASS | | | X | | X | | X | X |
| GAD-7 QIDS-SR-16, EQ 5D-5L | X | X | X | X | X | X | X | X |
| PCL-5 | | X | | | X | | X | X |
| Trauma Questionnaire | X | | | | | | | |
| CTQ | X | | | | | | | |
| EMA | X | X | X | X | X | X | X | X |
| Study drug dispensing | | X | X | X | X | X | | |
| Study drug compliance | | | X | X | X | X | | |
| fMRI | | X | | | | | | X |
| Prior/concomitant medication | X | | | | | | | |
| Adverse events | | | | | | | | |

### 4.1 Informed Consent

Before performing any study-related procedures, the Investigator (or designee) will obtain signed informed consent from the subject.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number.

### 4.2 Order of Assessments

#### 4.2.1 Screening (Visit-1 Week-2)

All subjects agreeing to participate in the study must give informed consent by signing the ICF before any study-related procedures are performed. Screening begins after ICF has been signed and dated by the subject and the Investigator or other appropriate site staff. The duration of the Screening will be 2 weeks.

The following procedures should be performed in order after the ICF is reviewed and signed:

1. Collection of medical and psychiatric history, concomitant medications and demographic information. Physical examination, ECG and pulse oximetry need to be performed, and height, weight, BMI and vital signs recorded.
2. Standardized assessments to include:

Clinician Rater: CAPS-5, MADRS, DIAMOND, SCID borderline personality module, CGI-S, MGH-ATRQ, CSSRS

PROs:, GAD-7, , QIDS-SR-16, EQ 5D-5L, CTQ, PCL-5, NSW, MCI

3. Collection of urine sample for urinalysis and drug screen analysis.

4. Blood sample collection to obtain hematology, biochemistry, hepatitis B and C, HIV, TSH and FSH data. A serum pregnancy test (b-HCG) is performed at screening for females of childbearing potential.
5. Breath alcohol test.
6. EMA wellness app activation

Subjects that meet all eligibility and inclusion and no exclusion criteria, will undergo Visit 2 (Baseline).

#### 4.2.2 Baseline (Visit 2 Week-1)

Subjects continuing to meet all eligibility and inclusion criteria and no exclusion criteria, will be randomized within each group at Baseline to start the study treatment.

1. Assessment scales: MADRS, CGI-S C-SSRS, HAMD-17, GAD-7, PHQ-9, QIDS-SR-16, and EQ 5D-5L.
2. Vital signs, including body temperature, systolic and diastolic BP, HR, pulse oximetry, and RR measures after the subject has been resting for at least 3 minutes.
3. ECGs taken pre-dose.
4. fMRI will be obtained.
5. EMA wellness App
6. AE if applicable
7. Laboratory tests, consisting of: blood sample for Hematology
8. POC: Urine drug test, pregnancy test (if applicable) and Breath Alcohol test

#### 4.2.3 Double-blind Treatment Visits (Visits 3-7 ;Weeks 2-6)

**1.** Record AEs as reported by patient or observed by Investigator
**2.** Review concomitant medications
**3.** Study drug compliance check, return unused Meds at each visit
**4.** Vital signs (BP, pulse rate, body temperature, respiratory rate) and weight
**5.** Assessment Scales: MADRS, CGI-S C-SSRS, HAMD-17, GAD-7, PHQ-9, QIDS-SR-16, EQ 5D-5L and GASS
**6.** Lab tests for Hematology for CBC will be completed at wee4 and week6 visits and Complete BW similar to screening visit will be completed at Week-7
**7.** EMA Wellness App (Optional)

#### 7.2.4 Safety Follow up (Visit 8: Week 7)

1. Record AEs as reported by patient or observed by Investigator
2. Review concomitant medications
3. Study drug compliance check, return unused Meds
4. Vital signs (BP, pulse rate, body temperature, respiratory rate) and weight
5. fMRI Assessments.

### 7.3 Entry Criteria Measurements

#### 7.3.1 Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)

The CAPS-5 is a 30-item, clinician-administered assessment tool used to diagnose and measure the severity of post-traumatic stress disorder (PTSD) according to the DSM-5 criteria. Administered by a trained study staff.[17]

#### 7.3.2 Diagnostic Interview for Anxiety, Mood, and other Disorders (DIAMOND)

The Diamond is a semi-structured interview guide to ensure consistency with the DSM 5 diagnostic classification. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. It provides diagnostic information, including severity, or many DSM-5 disorders, including MDD. [18]

#### 7.3.3 Antidepressant Treatment Response Questionnaire (ATRQ)

The ATRQ examines the efficacy and adequacy of any antidepressant treatment in a step-by-step procedure. This widely accepted questionnaire evaluates improvement (0% to 100%) and adequacy (adequate duration and dose) [19]

#### 7.3.4. SCID-5 Borderline Personality Disorder Module.

The SCID-5 borderline personality disorder module is a semi-structured interview for BPD to ensure consistency with DSM-5 criteria. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria.[20]

### 7.4 Efficacy Assessments

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing. For assessment scales performed at each visit, MADRS must be the first assessment performed by the rater at the site. Subsequent assessments, following MADRS, can be conducted in any order as determined by the investigator's discretion. The following order of assessments is recommended, from the least to the most invasive procedure: all assessment scales, vital signs, ECGs and lastly blood draw as indicated in Table 1.

#### 7.4.1 Primary Efficacy Assessment -Montgomery-Åsberg Depression Rating Scale (MADRS)

The MADRS is a 10-item questionnaire with each item scored between 0 and 6, resulting in a total score between 0 and 60, with scores above 34 indicating severe depression. Higher MADRS scores indicate more severe depression. The questionnaire is most frequently used in clinical studies to measure outcomes in antidepressant efficacy studies. This scale exhibits construct validity (internal homogeneity) and the concepts of endogenous and non-endogenous depression. The questionnaire includes questions on the following symptoms: (1) apparent sadness; (2) reported sadness; (3) inner tension; (4) reduced sleep; (5) reduced appetite; (6) concentration difficulties; (7) lassitude; (8) inability to feel; (9) pessimistic thoughts; (10) suicidal thoughts. The MADRS must be administered using the Structured Interview Guide for the MADRS (SIGMA). The MADRS total score at screening is a major inclusion criterion of the study, as well as the primary outcome measure for the study. The MADRS will be administered at Screening and Baseline and subsequent weekly visits.[21]

#### 7.4.2 Secondary Efficacy Assessment-Clinical Global Impression of Severity (CGI-S)

The CGI-S measures the severity of the disease using a 7-point Likert scale ranging from 1=normal, not at all ill to 7=among the most extremely ill subjects[22]

**7.4.3 Ecological Momentary Assessment**. Using EMA Wellness software, participants will complete a daily assessment of mood and anxiety as well as positive and negative affectivity ratings twice daily.

Specific assessments of mood and anxiety include: PHQ-9; GAD-7. Specific assessment of positive and negative affect: happy, sad, anxious, relaxed. Participants start EMA assessment during two-week run-in period. QOL assessment once a week will also occur.

### 7.5 Columbia–Suicide Severity Rating Scale

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior [23]The C-SSRS will be completed by a trained and approved rater. The C-SSRS will be completed at all study visits. At Screening (Visit 1), the C-SSRS will be completed for the patient's lifetime history of suicidal ideation and behavior ("Baseline/Screening" version). At all other visits, the C-SSRS will be completed for suicidal ideation and behavior since the previous visit ("Since Last Visit" version).

### 7.6 Extrapyramidal Symptom Assessment

Glasgow Antipsychotic symptom scale: The Glasgow Antipsychotic Side-effect Scale is a patient self-report scale used to screen for antipsychotic side effects.[24]

### 7.7 Vital Signs

Vital signs (systolic and diastolic blood pressure [BP], pulse rate, respiratory rate, and body temperature) will be assessed at every visit during the study as specified in the Schedule of Assessments (Table 1.)

Blood pressure and pulse rate will be measured in both the supine and standing positions with measurements performed after at least 5 minutes lying down and then at least 3 minutes after rising from the supine position to the standing position. BP may be measured using the same method consistently for each patient throughout the study.

Body weight, and height will be assessed as specified in the Schedule of Assessments (Table 1.)

### 7.8 Electrocardiogram

A 12-lead ECG will be performed as specified in the Schedule of assessments (Table 1.) Each ECG assessment will be conducted after the patient has been resting quietly in the supine position and will comprise ten-second epochs from 12-lead ECGs. ECG parameters to be measured include HR, QRS, PR, QT, QTcB, QTcF and RR intervals.

## 8. Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory tests will be collected as specified in the Schedule of Evaluations Table 4. If possible, patients should fast for at least 8 hours before the collection of clinical laboratory blood tests. During Screening, the Investigator/sub-investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory. Patients with abnormal screening laboratory results judged to be clinically significant will be excluded from the study.

Laboratory results will be reviewed by the Investigator/Sub-Investigator throughout the study. The following clinical laboratory levels will be measured:

- Hematology: hematocrit; hemoglobin; HbA1c (at Screening [Visit 1] only); red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration); reticulocytes; white blood cell count and differential (neutrophils, absolute neutrophil count, lymphocytes, monocytes, eosinophils, and basophils) reported as percent (%) and absolute values; and platelet count.
- Chemistry: albumin; ALP; ALT; AST; bilirubin (total, direct); blood urea nitrogen; calcium; chloride; cholesterol (total; high-density lipoprotein [HDL] and low-density lipoprotein [LDL] will be calculated and reported); creatinine; creatine phosphokinase; gamma-glutamyl transferase; glucose; insulin; lactate dehydrogenase; phosphate; potassium; prolactin; sodium; triglycerides; total protein; uric acid. TSH (reflex free T3 and free T4) will be measured at Screening (Visit 1) and Visit 7 (Week-6)/ET only.
    - Urinalysis: macroscopic (pH, specific gravity, glucose, protein, ketones, bilirubin, nitrites, blood) and microscopic (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation). Urine Drug Screen (UDS): Urine drug tests for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, or opioids/opiates will be performed Screening (Visit 1) and Visit 6 (Day 22)/ET.
    - Alcohol Testing: An alcohol test (urine or breath) will be performed at Screening (Visit 1) and Visit 7 (Week-6)/ET.
    - Urine and serum pregnancy tests: Female patients who are of childbearing potential will undergo a serum pregnancy test at Screening (Visit 1), and a urine pregnancy test at Baseline (Visit 2/Week 1). Unscheduled serum/urine pregnancy tests may be administered at any time at the discretion of the Investigator. Serum pregnancy testing will be performed using blood collected as part of protocol-specified sample; urine pregnancy testing will use a urine dipstick.
    - Hepatitis screening: Blood samples will be collected at Screening (Visit 1) from all patients in order to perform serology testing for hepatitis B and hepatitis C.

Table 4.

| Hematology | Serum Chemistry | Urinalysis (Dipstick)* (onsite) |
|---|---|---|

| | | |
|---|---|---|
| hemoglobin<br>hematocrit<br>erythrocytes<br>platelets<br>leukocytes with differential (including eosinophils, neutrophils, basophils,<br>lymphocytes and monocytes) | eGFR (screening only)<br>HbA1c (Screening only)<br>creatinine<br>total bilirubin (and fractionation of bilirubin >ULN)<br>albumin<br>blood urea nitrogen<br>total protein<br>alkaline phosphatase<br>aspartate aminotransferase<br>alanine aminotransferase<br>glucose<br>sodium<br>potassium<br>magnesium<br>calcium<br>chloride<br>phosphate<br>bicarbonate<br>TSH (Screening only) | pH<br>specific gravity<br>protein<br>glucose<br>ketones<br>bilirubin<br>occult blood<br>nitrite<br>urobilinogen<br>leukocyte esterase<br><br>* Reflex microscopy when indicated |
| Pregnancy testing: A serum FSH test will be conducted for all females at Screening. A urine pregnancy test, and serum pregnancy test (b-HCG) will be conducted on all WOCBP at Screening. Negative pregnancy test results are required for enrollment in the study; a negative urine pregnancy test will be required at Baseline (Week 1) for confirmation. | | |
| Urine drug and alcohol screen at Screening and Baseline: Drug and alcohol abuse testing will be performed according to the assessment schedule. Screening for drugs will include: tetrahydrocannabinol, opiates (including oxycodone), amphetamines, cocaine, and benzodiazepines. | | |
| Serologic testing for hepatitis B surface antigens, hepatitis C antibodies, and HIV antibody testing will be performed at the Screening visit. | | |

## 9. Adverse Events

The Investigator and research study staff will responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE. Procedures for managing AEs and SAEs are detailed in the research site's SOPs.

### 9.1 Adverse Event Definition

An AE is any untoward medical occurrence in a study subject administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, regardless of its relationship to the medicinal (investigational) product. During the study, an AE can also occur outside the time that the study drug(s) was given (e.g., during the time from discontinuation of prohibited medications). Preexisting conditions, diseases, or disorders are not considered AEs unless there is a change in severity, frequency, or quality.

### 9.2 Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose

- Results in death,
- Is life-threatening (at the time of the event),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

## 9.3 Adverse Event Reporting Procedures

### 9.3.1 Reporting Adverse Events

All AEs, including overdose with sequelae or intentional overdose of study drug or other medication, must be recorded on the appropriate AE reporting page of the subject's AE log whether or not they are considered causally related to study drug.

For every AE, the Investigator must:

**9.3.1.1** Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship to the study drug.

**9.3.1.2** Document all actions taken with regard to study drug;

**9.3.1.3** Detail any other treatment measures taken for the AE.

Any AEs that are ongoing at the time of the End of study visit will be followed until the condition returns to pre-study status, has resolved, or stabilized, or can be explained as being unrelated to study drug. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the last known dose of study drug.

### 9.3.2 Reporting Serious Adverse Events

The Investigator will inform the Sponsor ( ITI) and regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study center personnel must report the event to the Sponsor on the SAE Report Form.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

Table 2. describes the Classification of Adverse Event Causality and Table 3. Outlines the Outcomes of AEs or SAEs

Table2.

| Classification | Definition |
|---|---|
| Unrelated | The AE or SAE is judged to be *clearly and incontrovertibly due only to extraneous causes* (e.g., disease, environment) and does not meet the criteria for study drug relationship listed under probable, possible, or unlikely. |
| Unlikely | The AE or SAE is *unlikely related* to the study drug, when the AE or SAE:<br>• Does not follow a reasonable temporal sequence from administration of the study drug.<br>• May readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.<br>• Does not follow a known pattern of response to the study drug.<br>• Does not reappear or worsen when the study drug is re-administered. |
| Possible | The AE or SAE is *possibly related* to the study drug when the connection to the study drug appears unlikely but cannot be ruled out with certainty. This causal relationship is assigned when the AE or SAE:<br>• Follows a reasonable temporal sequence from administration of the study drug.<br>• May have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. |

| | |
|---|---|
| Probable | The AE or SAE is *probably related* to the study drug when the connection to study drug can be made with a high degree of certainty. This causal relationship is assigned when the AE or SAE:<br>• Follows a reasonable temporal sequence from administration of the study drug.<br>• Cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.<br>• Disappears or decreases upon cessation or reduction in dose (note that there are important exceptions when an AE or SAE does not disappear upon discontinuation of the study drug, yet drug relatedness clearly exists e.g., bone marrow depression or tardive dyskinesia).<br>• Follows a known pattern of response to the suspected study drug. |
| Definite | The AE or SAE is *definitely related* to the study drug when the event:<br>• Follows a reasonable temporal sequence from administration of the study drug.<br>• Follows a known pattern of response to the suspected study drug.<br>• Is confirmed by improvement on stopping and reappearance of the event on repeated exposure to the study drug.<br>• Cannot be reasonably explained by the known characteristics of the subject's clinical state. |

Table 3.

| **Classification** | **Definition** |
|---|---|
| Fatal | The study subject died. |
| Resolved | The AE or SAE has ended. |
| Resolved with Sequelae | The AE or SAE has ended but changes are noted from Baseline. |
| Unresolved | The AE has not ended.<br>An AE outcome can only be categorized as unresolved if the AE is:<br>• *Ongoing* at the end of the reporting period (i.e., 30 days after the last dose of study drug), and the Investigator deems that further follow-up is not medically required.<br>• *Lost to follow-up* after repeated unsuccessful attempts to contact the subject.<br>• *Ongoing and referred* to the subject's physician or a specialist for follow-up. |

**Reporting Procedure:**

SAE Reporting E-mail: clinicalsafety@propharmagroup.com

SAE Reporting Fax Number: +1 (866) 681-1063

Medical Emergency Contact numbers:

Americas (North and South America)/APAC
+1 (973) 659-6677 (Primary)

+1 (512) 652-0191 (Alternate)

**10. Neuroimaging procedures.**

Whole brain fMRI will be acquired using a 3T Siemens Vida MRI scanner with a 64-channel head coil at the Biomedical Imaging Center at the University of Texas at Austin. A high-resolution T1-weighted structural volume (256x256x192, 1-mm$^3$ resolution) will be acquired for coregistration and normalization. Functional images will be collected using an adapted version of the ABCD project protocol used in our Biomedical Imaging Center, enabling both high temporal (TR=786ms) and spatial (2.4mm isotropic voxels) resolution, using a 32 channel head coil. We use fMRIPREP to preprocess the data. Standard preprocessing steps will occur prior to within-subject and between-subject analyses.

**Approach-Avoidance Learning Task.** Participants are instructed to learn, through trial-and-error, which of three responses, indicated with distinct stimuli, to select to achieve a particular outcome. Critically, each response option is associated with a probability of *both* a reward outcome (points) *and* an aversive outcome (i.e., a mild electric shock). Consistent with reinforcement tasks, the response-outcome contingencies (e.g., which option is most likely to lead to reward) switch throughout the task, such that half the time the option that is most likely to lead to reward is also most likely to lead to a shock, and half the time the highest reward option is least likely to lead to shock. Thus, the task systematically manipulates congruency and conflict between reward-threat outcomes and additionally introduces a reversal learning[61,147] probe for both reward and threat. To motivate adherence to instructions, participants are told they will receive monetary compensation in proportion to how well they perform. In contrast to fear conditioning tasks that instruct participants to select a shock intensity that nears painful (7/10 Likert scale), we would have participants select a level that is annoying and mildly uncomfortable (5/10) to enable tolerance of repeated stimulations, as the number of shocks delivered could be higher than during standard conditioning tasks. There would be 150 trials of the task. Each initial cue is presented until the participant makes a selection, followed by a jittered anticipation phase (2-4s), and then the threat outcome (mild electric shock) and reward outcome (points) would be presented sequentially and separated by a jittered ITI of 3-6s. Given that outcomes are driven probabilistically following participant choices, the total number of shocks delivered can vary.

## 8. Data Analysis

*Describe the data analysis plan, including any statistical procedures or power analysis.*

**11. Statistical Analysis**

**11.2 Statistical And Analytic Plan**

The primary efficacy endpoint is the change from baseline to end of Week 6(EOT) in MADRS total score. Based on the primary hypothetical estimand strategy which assumes patients are on study drug up to the primary time point (end of Week 6), MADRS assessments collected off-treatment (ie, efficacy assessment performed more than 3 days after last dose of study drug) and/or after starting new treatment for MDD will be set to missing (except those collected for patients discontinued due to and will not be included in the primary analysis). The missing data in patients who discontinued due to lack of efficacy (LOE) or due to taking non-study treatment for MDD will be assumed missing-not-at-random. The missing data in patients who discontinued due to other reasons will be assumed as missing- at-random. Missing data will be imputed accordingly to recent recommendations using the 'mice' package in R. [25,26]

The primary analysis will use a mixed-effects model for repeated measures (MMRM) to analyze the change from baseline to end of Week 6 in MADRS total score. Similar MMRM models will be used for secondary endpoints. An additional analysis will examine slopes of MADRS scores over the 6 week period, testing the hypothesis that the active drug group will have a steeper slope of MADRS over the 6 week period. Additional models will test for non-linear patterns of change as well. Similar analyses will be conducted on secondary outcomes (e.g. CGI, PTSD

symptom severity, etc.).

For imaging data, following standard preprocessing, beta coefficients of voxelwise brain activity will be defined using standard general linear models. These coefficients will be used in multivariate pattern analysis (MVPA) to build classifiers, using support vector machines (SVM), of reward and threat using leave-one-out cross-validation and quantify reward and threat anticipation during the task. MVPA classifier output will be analyzed using mixed effects models. Threat and reward anticipation as predictors of treatment outcome will be analyzed by including these variables as a predictor in the MMRM described above. Threat and reward anticipation as targets of treatment will be analyzed in mixed effects model with post-treatment classifier output as the dependent measure and including predictors of drug group and including pre-treatment classifier output as a covariate.

**11.3 Primary Endpoint Estimand**

The primary efficacy endpoint is the absolute change in MADRS total scores from Baseline to end of Treatment visit at Week 6 in subjects on ADT plus Lumateperone or matching placebo.

The main estimand for the primary efficacy endpoint is defined as follows:

- Target population(TP):Total Population: All randomized participants with MDD and history of early life abuse (Baseline MADRS score ≥22) as defined by the study inclusion/exclusion criteria who are randomized and dosed
- Variable: Change from Baseline to Week 6 in the MADRS total scores (Visit 7)

Intercurrent events (ICE)

1. Study or treatment discontinuation
a. Due to lack of efficacy
b. Due to adverse event related to study medication
c. Due to adverse event unrelated to study medication
d. Due to other reasons
2. Treatment with prohibited medication
3. Death
a. Related to MDD
b. Unrelated to MDD

- ICE strategy

o ICE 1a, 1b, 2: A hypothetical strategy will be applied assuming that patients after the ICE follow the course of patients receiving placebo.

o ICE 1c, 1d, 3b: A hypothetical strategy will be applied assuming that patients after the ICE follow the course of the arm they were randomized to.

o ICE 3a: A composite strategy will be applied by imputing values after the ICE with the worst possible MADRS score (=60).

10.2Secondary Endpoint Estimand: The key secondary efficacy endpoint is the change from baseline to end of Week 6 in the CGI-S score.

**11.4 Efficacy Estimand Analysis**

Main estimands are defined for the primary efficacy variable:

- Absolute change from Baseline to Week 6 of the MADRS total score

and for the following 3 key secondary efficacy variables in hierarchical rank order of the hypothesis testing procedure:

- MADRS response rate (proportion of subjects with an improvement ≥50% in the Baseline MADRS total score) at End of Treatment (EOT) Week 6, Lumateperone as compared to placebo
- MADRS remission rate (proportion of subjects with a MADRS total score ≤10) EOT Week 6, Lumateperone as compared to placebo
- Change from Baseline to EOT Week -6 in the Clinical Global Impression of Severity (CGI-S) score, Lumateperone as compared to placebo

Confirmatory testing will be performed only for these main estimands, whereby the testing of the key secondary estimands will follow the ordered hierarchical approach.

The primary statistical analysis of all confirmatory tested estimands will be performed on the Total Population, using the mixed-effect model repeated measure (MMRM) analysis. For the main primary estimand, the changes from baseline in MADRS total score will be analyzed using a Mixed Model with

Repeated Measures (MMRM). This model will include Treatment, Visit, Treatment-by-Visit interaction and the number of failed prior treatments (1 or more than 1) as fixed effects, Baseline value as a covariate, and Visit as the repeated effect. The estimated means for each arm as well as the estimated treatment effect (Lumateperone – Placebo) along with the 95% confidence intervals for the treatment effect will be presented for each visit. The primary estimand will be estimated as the difference between treatment means (MMRM least-squares) at the EOT Week 6 (Visit 7).
As a sensitivity analysis for all estimands, the MMRM analysis will be performed using a range of missing value imputations. For the main estimand of the primary efficacy, a tipping point analysis will be applied to investigate the robustness of the analysis results.

# Study Elements Requiring Additional Information or Approvals

## 9. Public Registration and Reporting Requirements

*Federal regulations, policy, and some journal guidelines require public registration and results reporting for studies that meet the definition of a clinical trial.*

*Note that the various definitions of "clinical trial" subject to these requirements can be quite broad and include things like behavioral interventions conducted outside of traditional healthcare settings.*

*Answer the following questions and review the linked guidance to see if any of these requirements apply to this study.*

**9a. Does this study involve prospectively assigning participants, or groups of participants, to one or more research intervention(s)?**

*Intervention includes both physical procedures by which data/specimens are gathered and manipulation of the participant or the participant's environment for research purposes. Can include control groups.*

☐ No → *Skip to item 10*
☒ Yes

**9b. Is the intention of the study to evaluate the effect of a research intervention on *health-related* biomedical or behavioral outcomes?**

☐ No → *Skip to item 10*
☒ Yes

**9c. If yes to the above, go to UT Guidance on Clinical Trials Registration and Results Reporting and review requirements that may be applicable and select which of the following apply to this study:**

☐ Intended to be submitted for publication in a journal subject to International Committee of Medical Journal Editors (ICMJE) requirements
☐ NIH-funded Clinical Trial *(be sure list funding on the Study Funding section of the UTRMS application)*
☒ FDA-defined Applicable Clinical Trial
☐ Intended to have routine clinical trial costs covered by the Center for Medicare and Medicaid Services (CMS)
☐ Registration is required per the terms of the award/funding agency
☐ Meets none of the above requirements but will register voluntarily
☐ None of the above

**9d. Will the UT Austin study team register this study on ClinicalTrials.gov?**

*Click here for information on how to identify the "Responsible Party" for registration.*

☒ Yes
☐ No – This is a multi-site study and the UT PI is not the Responsible Party for registration. The external Responsible Party is aware of their duty to register the study.

☐ No – This study involves an IND or IDE held by someone other than the UT PI, the IND/IDE holder is the Responsible Party and is aware of their duty to register the study.
☐ No – This study meets none of the requirements in item 9c above and the study team prefers not to register

**9e. Attest that all relevant reporting requirements for the study will be followed as applicable (regardless of ClinicalTrials.gov registration).**
*Use the linked guidance in item 9c and review the section titled "Reporting Results" for guidance. This box must be checked to confirm you have reviewed the requirements, even if you determine no reporting requirements apply to you.*
☒ Confirm

**10. Does the research involve biospecimens of any kind (e.g. blood, tissue, saliva, etc.), biohazards, recombinant DNA, or gene transfer?**

☐ No → *Skip to item 11*
☒ Yes

**10a. Does the research involve human embryonic, human induced pluripotent, or human totipotent stem cells; or human gametes or embryos?**

☒ No
☐ Yes → *Be aware that additional review criteria may apply, see UT IRB Policies & Procedures section 18 for guidance.*

**10b. Will biospecimens be used and stored at UT?**

☒ No, biospecimens collected will be stored at an external site that has responsibility for biosafety
☐ Yes → UT Institutional Biosafety Committee (IBC) approval *is needed. Provide the UT IBC number in the text box below:*

**10c. Does the research involve prospective collection of blood from participants?**

☐ No → *Skip to item 11*
☒ Yes

**10d. Select all methods that will be used to collect blood samples:**
*Note that procedures for all forms of specimen collection should be described in the Study Procedures section above. The IRB requires the following specific details for blood collection to determine the appropriate review level.*
☐ Research sample collected at the same time as non-research blood collection (i.e. extra blood collected)
☒ Individual needle stick(s)
☐ Indwelling catheter placed solely for this study
☐ Accessing indwelling catheter placed for non-research purposes
☐ Other, specify in text box below:

**10e. Specify the timing and frequency of blood collection and the volume of blood obtained at each collection:**

Blood will be collected four times during the study; the total amount of blood each draw is two tubes, 1 tube that is 9 mL of blood and another that is 8.5 mL. *Reference the study procedures chart as well as the clinical assessments section for frequency.*

**11. Does the research involve genetic testing/analysis?**

*This may include research involving identification and location of specific genes, study of gene products, inherited human traits, or identification and analysis of DNA mutations.*

☒ No → *Skip to item 12*

☐ Yes

**11a. Describe the genetic testing/analysis involved in this study:**

*If this is already described earlier in the form (such in the Study Procedures or Data Analysis items), please reference the appropriate sections where this can be found in the box below.*

**11b. Are participants able to opt-out of or withdraw from the genetic testing part of the research while continuing with other parts of the research?**

*Be sure this response aligns with language included in the consent form(s).*

☐ Yes

☐ No

**11c. Will or might genetic testing/analysis reveal clinically relevant findings for participants?**

*For example, medical conditions that could be treated or information about paternity/lineage.*

☐ No → *Skip to item 12*

☐ Yes → *Describe potential findings below:*

**11d. Describe the procedures for providing clinically relevant genetic results to participants:**

*Include whether or not genetic counseling will be offered to participants. Specify whether or not participants will be offered the option to decline learning the results, or if any results will not be provided (and if so, why). Be sure this response aligns with language provided in the consent form(s).*

**11e. Will genetic tests be run in a CLIA-certified laboratory?**

☐ Yes

☐ No → *If no, explain below why this is not necessary:*

**12. For this study, will the researchers obtain, use, or disclose Protected Health Information (PHI) regulated under the Health Insurance Portability and Accountability Act (HIPAA)?**

*This typically applies to research involving access to medical records. This does not include self-reported health information disclosed as part of research surveys/interviews. Guidance on HIPAA protected PHI is available here.*

☐ No → *Skip to item 13*

☒ Yes

**12a. Select all HIPAA-covered entities providing PHI:**

☒ UT Health Austin
☐ Ascension Seton/other Ascension locations*
☐ UT Austin University Health Services
☐ Dell Children's Medical Center*
☐ CommUnity Care
☐ Central Health
☒ Other, specify: Clinical Pathologies Laboratory, Biomedical Imaging Center

***For studies obtaining data from Ascension facilities,** please submit a request to the Seton Site Approval Tool (SAT) and upload the confirmation email that states the request has been submitted in UTRMS under "Other Documents." Please note, we do NOT need the final approval letter (you will not receive SAT approval until after IRB approval is granted). If you encounter issues or have questions about SAT, please reach out to siteapproval@seton.org.*

**12b. List the data points or attach a list of the data to be collected about each subject from their medical records or other HIPAA protected data source(s).** *Select one of the following:*

☐ This list is uploaded to UTRMS on the Local Site Documents page under "Other Attachments"
☒ All data points listed in the text box below:

Medical History will be self-reported by the participant, as listed in the protocol. The following will be collected as participation in this study:

- Lab & Pathology Results
- MRI Imaging

**12c. Select all pathways for obtaining HIPAA authorization for accessing PHI for this research:**

*NOTE: If obtaining authorization from Ascension patients, use of Ascension's stand-alone HIPAA authorization form is required and this form should be uploaded on the Local Site Documents page in UTRMS under "Other Attachments." Otherwise, non-Ascension HIPAA authorization may be combined with Informed Consent using the HIPAA template language embedded within the 920 Standard Consent Template. All UT Austin IRB templates are available in the Templates tab of the UTRMS-IRB Library.*

☒ Obtaining HIPAA authorization from participants to access PHI → *Skip to item 13 if only this box is checked*
☐ Requesting *full* waiver of participant authorization
☐ Requesting *partial* waiver of authorization to access PHI for screening or recruitment only

*All of the following must be checked to qualify for a partial waiver for screening or recruitment:*

- ☐ Attest that PHI will be accessed ONLY to identify eligible subjects for recruitment in this research. Continued access to PHI will be limited to those who later volunteer for the study and provide written authorization.
- ☐ Attest that PHI will be accessed only by individuals who have authorization to access the records outside of the research context.
- ☐ Attest that researchers will not move or transmit identifiable PHI from the covered entity (i.e. the institution holding the records, such as the clinic).

**12d. Complete the following if requesting a *full or partial* waiver of HIPAA authorization:**

**I. Specify the date range of records that will be accessed:**

Start date (month/year):
End date (month/year):

**II. Provide a justification for why the research could not practically be conducted without access to PHI and the waiver of patient authorization requested:**

☐ Identification/recruitment: *– access to records is needed to identify eligible subjects (e.g., chart reviews, partial waiver for recruitment, etc.)*

☐ Large number of subjects projected *– potential subject population includes a large number of records to review and it is not feasible to attempt contact with all subjects*

☐ Outdated records *– This is a retrospective study involving subjects who may have moved or expired and researchers cannot feasibly attempt to contact required sample*

☐ Total population required - *The nature of the research is such that findings will not be valid, or will be significantly skewed, if the total eligible population is not included.*

---

*Select all that apply above OR provide different justification below.*

☐ None of the above; specify other justification:

*Note that inconvenience or limited time/resources alone are not sufficient justifications for waiving a patient's right to authorize disclosure of their PHI.*

**III. Attest that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research where the use or disclosure of the PHI meets IRB and HIPAA requirements.**

*This box must be checked.*

☐ Confirm

**IV. The HIPAA regulation requires reasonable efforts to limit protected health information to the minimum necessary to accomplish the intended purpose of the use, disclosure or request. Review the linked guidance and attest below that you are obtaining only the minimum information necessary to complete the waived activities:**

*This box must be checked.*

☐ Confirm

**V. Provide any additional information you'd like the IRB to consider for why/how all the listed data points in item 12b are necessary to answer the research question and comply with the minimum necessary requirement described above** *(if none, this can be left blank):*

## 13. Does this study involve Deception and/or Incomplete Disclosure?

*See IRB Policies and Procedures Section 15 for a description of deception.*

*Deception (as applies to research) means intentionally giving research subjects false information in order to establish false beliefs during the course of a research study.*

*Incomplete disclosure means that the investigator withholds some information about the real purpose of the study or the nature of the research procedures.*

☒ No → *skip to item 14*

☐ Yes → *Note that an alteration of informed consent may need to be requested in the Consent Pathways section. Please address items below:*

**13a. Describe the nature of deception/incomplete disclosure and why it is necessary to conduct the research.**

**13b. Will participants be debriefed (i.e. provided additional pertinent information about the nature of the deception/incomplete disclosure) after research activities are completed?**

☐ Yes

☐ No → *provide a strong justification below for why this will not occur, then skip to item 14:*

**13c. Describe debriefing procedures.**

*NOTE: Upload the debriefing form to UTRMS-IRB in the "Local Site Documents" section.*

**13d. Will research participants have the opportunity to withdraw their data during/after debriefing?**

☐ Yes → *Be sure to include language about this option in the uploaded debriefing script.*

☐ No → *Provide a strong justification below for why this will not occur:*

## 14. Research Activities Requiring Supplemental Forms or Additional Oversight

| *Select each of the items below that are relevant to your research. If none apply, this section can be left blank.* | *For each item selected, complete and upload the associated Supplemental Form in UTRMS-IRB under "Other Attachments" or review the linked guidance and follow instructions as applicable.* |
|---|---|
| ☒ Investigational Drugs, Biologics, Supplements, or other regulated non-device products | UT Supplement 906 – Investigational Drugs, Biologics, and Non-Devices |
| ☐ Investigational Device | UT Supplement 905 - Investigational Device |
| ☐ International Research<br>*This includes research conducted outside the US, direct remote interactions with international participants (i.e. Zoom interviews), and research that will collect identifiable data from international participants (including online surveys).* | UT Supplement 908 - International Research |
| ☐ Department of Defense (DoD)<br>*This includes all research involving DoD funding, facilities, data, or personnel (i.e. active military personnel are targeted/discernible in the data collected). See Policies & Procedures section 25.1 for guidance on DoD applicability.* | UT Supplement 911 - Department of Defense |

| | |
|---|---|
| ☐ Energy introduced to the subject (electrical, magnetic, light)<br><br>☐ Radiation exposure without direct clinical benefit | *For research involving these activities, be aware that the IRB may solicit ancillary review from the UT Austin Environmental Health & Safety (EHS) office. Any additional requirements may be communicated during review. Guidance on EHS policies and reviews is available here:* ***IRB-ML101-Guidance for Institutional Reviews and Approvals of Human Research at UT Austin (PDF)***. |
| ☐ Use of Artificial Intelligence (AI) in research | *As part of UT ISO's mission and with the growing use of AI in research, all research that involves use of AI should be in alignment with ISO's Acceptable Use of AI Policy.*<br><br>*If your AI platform use is not listed or in alignment with the policy above, contact UT ISO at security@utexas.edu prior to conducting any research with that AI tool. It is strongly recommended to confirm acceptability prior to submitting to the IRB.* |

# Subject Population

**15. Sample Size**

*Enter the maximum total anticipated sample size, including a breakdown of target sample size per participant group (if more than one). Note that the IRB is looking for the number of individual human subjects you plan to enroll.*

50 Participants Total: 25 enrolled in a placebo group and 25 enrolled into the treatment group

Participants are those who have MDD and history of early life trauma.

*Refer to inclusion/exclusion criteria for detailed list of criteria necessary to meet enrollment.*

**16. Sample size rationale**

*Describe your sample size rational below.*

Sample size is chosen to have moderate statistical power and still ensure feasibility for study completion.

**17. Research Participant Information**

*Describe the general characteristics of the subject populations or groups including gender, health status, and any other relevant characteristics.* ***If you have multiple research populations (e.g. teachers and students), clearly outline characteristics for each group.***

Male and Female inpatient, who have Major Depressive Disorder MDD and history of early life trauma who have an inadequate response to on-going SSRI treatment

**18. Age range (minimum and maximum)**

*Include the age range for target population. If there is no maximum age, this can be noted, but a minimum age required for inclusion must be explicitly stated. If you have multiple research populations, clearly state the age range for each group.*

21-70 years old inclusive

## 20. Inclusion/Exclusion Criteria

*Describe the specific criteria that will be used to decide who will be included in and excluded from the research from the population of interested or potential subjects. Define technical terms in lay language, as applicable.*

To be eligible to participate in the study, patients must meet the following inclusion criteria:

9. Provide written informed consent before the initiation of any study-specific procedures. See for informed consent requirements;

NOTE: Patients who are unable to independently provide informed consent will be ineligible to participate in this study.

10. Male or female, between the ages of 21 and 70 years, inclusive;
11. Meets the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR)criteria for MDD without psychotic symptoms, as confirmed by a trained rater using the modified Structured Clinical Interview (DIAMOND) for DSM-5,
12. MADRS total score ≥ 22 at Screening (Visit 1) and Baseline (Visit 2)
13. Endorse >=1 physical or sexual assault prior to age 16 on the NSW.

    Many studies refer to early life trauma as prior to age 18. Here we define early life assault as less than 16, rather than 18, in order to ensure a clearer separation between early life and adulthood. While another option might be to restrict even further (e.g., age of trauma < 10), for feasibility (e.g., facilitating recruitment) and generalizability (e.g., results extend to MDD and early life trauma more broadly than just early childhood trauma), we decided on physical or sexual assault prior to age 16.

    Regarding the focus on physical or sexual assault, there are two main reasons. First, the definition of physical and sexual assault can more easily be operationalized through a behavioral description of an event (e.g., has anyone hit you with a fist, has anyone hit you with an object, etc), enabling more precise assessment and detection. Second, there is a robustly elevated risk for mood disorders following assaultive traumas relative to non-assaultive traumas. As such, there is greater clinical need to establish adjunctive treatments among those experiencing assaultive traumas.

14. Participants must have been treated with the same dose of antidepressant therapy for at least 6 weeks, with less than 50% improvement, and be committed to on the same stable dosing regimen for the Screening period and for the entire study, at or above the minimally adequate dose in the ATRQ. Documentation of stable and ongoing ADT must be verified by documentation from the subject's psychiatrist, pharmacist, primary care physician or other qualified healthcare professional.
15. Female of childbearing potential and agrees to use at least an acceptable method of birth control (including but not limited to hormonal contraception, intrauterine device, vasectomized partner, bilateral tubal occlusion, condom with or without spermicide, cap with spermicide, diaphragm with spermicide, sponge with spermicide, or double barrier methods) from the time informed consent is provided through the end of the SFU period. *NOTE:* Females of non-childbearing potential (defined as either permanently sterilized, or post-menopausal females [defined as at least one year with no menses without an alternative medical explanation]) are exempt from the birth control requirement.
16. Ability to follow study instructions and likely to complete all required visits.

**4.3 Exclusion Criteria**

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study.

***Psychiatric Criteria***

19. Has a **current primary** DSM-5-TR psychiatric diagnosis other than Major depressive disorder. These include:
    i. PTSD, OCD, Bipolar Disorder, Schizophrenia, schizoaffective disorder, or other psychotic disorders;
    ii. Intellectual disability, Dementia or other cognitive disorders;
    iii. Moderate or severe substance use disorder (excluding for nicotine);
20. In the opinion of the Investigator, the patient has a significant risk for suicidal behavior during the course of his/her participation in the study or
    i. At Screening (Visit 1), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS within 6 months prior to Screening; or
    ii. At Screening (Visit 1), the patient has history of suicidal attempt(s) within 1 year prior to Screening (Visit 1); or
    iii. At Baseline/randomization (Visit 2), the patient scores "yes" on Items 4 or 5 in the Suicidal Ideation section of the C-SSRS since the Screening Visit; or
    iv. At Screening (Visit 1) or Baseline (Visit 2), scores ≥ 4 on Item 10 (suicidal thoughts) on the rater administered MADRS; or
    v. Considered to be an imminent danger to himself/herself or others.

***Treatment-related Criteria:***

21. MRI contraindications :History of shrapnel or other metal or electronic implants in the body(such as pacemakers, aneurysm clips, ferrous surgical devices, metallic tattoos on the head, etc.)The patient has received electroconvulsive therapy (ECT), vagal nerve stimulation, or repetitive trans-cranial magnetic stimulation within the past 1 year;
22. The patient has known hypersensitivity or intolerance to lumateperone, or to any of the excipients;
23. Treatment with a depot/long-acting injectable antipsychotic within 1 cycle before Screening (Visit 1);
24. The following agents are excluded and must be discontinued at Screening (Visit 1):
    i. Any moderate or strong cytochrome P450 3A4 inhibitor (CYP3A4), or any CYP3A4 inducer;
    ii. Central opioid agonists/antagonists, including tramadol;
    iii. Anticonvulsants, mood stabilizers, antidepressants, stimulants, antipsychotics, and non-benzodiazepine anxiolytics;
    iv. Dietary supplements and medical foods unless approved by the Sponsor or designee. Daily multivitamin use is permitted;
25. Monoamine oxidase inhibitors within 14 days prior to Baseline/Randomization (Visit 2);
26. Other drugs with known psychotropic properties or any non-psychotropic drugs with known or potentially significant central nervous system.
27. The patient plans to initiate psychotherapy or make changes to existing psychotherapy during the study (patients who are participating in stable psychotherapy or psychotherapy as a part of their treatment are allowed to enroll);
28. The patient has participated in a previous clinical trial with lumateperone, or has had exposure to

any investigational product within 6 months of the baseline visit or participated in > 2 clinical studies of an investigational product with a central nervous system indication.

***Other Medical Criteria:***

29. The patient is pregnant or breast-feeding. Female patients of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1). On Day 1 (Baseline/Visit 2), female patients of childbearing potential must have a negative urine pregnancy test prior to study drug administration;
30. The patient has a positive test for alcohol or drugs of abuse (eg, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, or opioids/opiates) at Screening (Visit 1).
31. The patient has abnormal laboratory values or clinical findings at Screening (Visit 1) including, but not limited to:
    i. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 × the upper limit of normal (ULN);
    ii. Total bilirubin > 1.0 × ULN;
    iii. Hemoglobin < 8 g/dL (80 g/L) for females and < 9 g/dL (90 g/L) for males;
    iv. Absolute neutrophil count (ANC) < 1200 cells/μL ($1.2 \times 10^9$ cells/L);
    v. Thyroid-stimulating hormone (TSH) outside of normal reference range AND free T3 or free T4 outside of the reference range. Free T3 and Free T4 will only be evaluated if TSH is outside of reference range;
    vi. Poorly controlled diabetes as defined by a glycosylated hemoglobin (HbA1c) >7.5%, despite standard care [> 58 mmol/mol];
    vii. Positive test for hepatitis B surface antigen and/or hepatitis B core antibody immunoglobulin M at screening; positive hepatitis C antibody at Screening (Visit 1), with the exception of a patient for whom the reflex HCV RNA test is negative;
    viii. Any other clinically significant abnormal laboratory result obtained at screening (Visit 1);
32. ECG abnormalities where the patient has corrected QT interval using the Fridericia formula (QTcF) > 450 msec for males or > 470 msec for females and/or heart rate < 50 bpm, or evidence of clinically significant bundle-branch blocks at Screening (Visit 1);
33. The patient has any of the following conditions:
    i. Cardiac: uncontrolled angina, or history of a myocardial infarction within 3 months prior to screening, or history of a clinically significant cardiac arrhythmia including antipsychotic drug-induced corrected QT interval prolongation, or any other cardiac disorder;
    ii. Malignancy: Any diagnosis of cancer (except basal or squamous cell skin carcinoma), unless in remission for at least 5 years;
    iii. Gastrointestinal: history of gastric bypass or any other condition that results in malabsorption;
    iv. Endocrine: hypo- or hyperthyroidism unless treated and stable with no medication changes for at least three months prior to screening, diabetes, unless considered stable with no changes in treatment for at least three months prior to screening;
    v. Hepatic: Hepatitis B or Hepatitis C; moderate or severe hepatic impairment (Child-Pugh B or C);
    vi. Pulmonary: history of diagnosed and untreated obstructive sleep apnea;
    vii. Neurological: history of epilepsy, seizure or convulsion, or electroencephalogram with clinically significant abnormalities, delirium, dementia, amnestic, or central sleep apnea, or significant brain trauma, or other cognitive disorder; History of movement disorders.
    viii. Infectious: History of human immunodeficiency virus (HIV) infection.

***Note:*** Any other medical condition, or medical conditions that are stable with treatment (eg, hypertension, hypercholesterolemia, or thyroid abnormalities) are allowed as long as the condition has been stable for at least 3 months prior to Screening (Visit 1); treatments for these conditions

are documented, kept stable, and are expected to be unchanged during the study; and the condition is not thought to affect safe participation in the study or relevant study outcomes in the opinion of the Investigator.

***Other Criteria:***

34. The patient is judged by the Investigator to be inappropriate for the study;
35. Patient is homeless;
36. Patient does not speak English

## 22. Justification for Target Population(s)

*If the inclusion/exclusion criteria target or exclude a particular segment of the population(s) relevant to the research topic, provide a rationale for why this target population is appropriate to address the research questions. Specific groups should not be targeted for research based solely on convenience/availability.*
*For example, if **only** UT students are targeted for research affecting a broader population, explain why this is equitable and appropriate for this study.*

Early life trauma is widely documented as a robust risk factor for development of major depressive disorder (MDD), in addition to many other mental health disorders[1,2]. Further, comorbid history of early life trauma among those with MDD predicts worse response to first-line pharmacotherapy for MDD[2]. Among the different types of early life traumas, physical and sexual assault tend to be associated with particularly worse outcomes in adulthood[3]. As such, there is a clear need to develop adjunctive therapies for those with MDD and histories of early life abuse in order to mitigate the typical poor clinical response seen in this population.

An emerging computational neuroscience literature has demonstrated altered neurocircuitry encoding of threat and reward learning as a key mechanism linking early life abuse to worse mental health outcomes in adulthood. This emerging computational literature complements and extends the well-established link between MDD and poor reward learning and decreased reward sensitivity[4–6]. Indeed, in a prior study we demonstrated that decreased prospective reward representations in the striatum mediated poorer reward learning and depression symptoms among individuals with histories of early life physical or sexual assault[7]. We've also demonstrated decreased encoding of reward prediction errors among women exposed to physical or sexual assault in the striatum and anterior insula[8,9], and decreased social reward prediction error encoding among adolescent girls who experienced physical or sexual assault. Similarly, recent work demonstrated altered integration of threat and reward learning (i.e., approach-avoidance conflict) in depression[10,11], potentially mediated by altered encoding of reward in the striatum. These findings are in line with our prior computational work investigating neurocircuitry mechanisms of approach-avoidance conflict demonstrating that biased prospective representations of reward vs threat in the salience network mediates decisions to approach reward vs avoid threat[12] and that individuals with assault histories demonstrate altered approach-avoidance conflict learning[13,14]. Overall, the emerging literature clearly points to altered computational encoding of threat and reward learning as a mechanism underlying development of MDD among those with histories of early life assault.

The neurocircuitry implicated in altered threat and reward learning as mechanisms of risk for MDD includes the salience network (dorsal anterior cingulate cortex and anterior insula) and striatum. Notably, this neurocircuitry overlaps with dopaminergic and serotonergic pathways targeted by atypical antipsychotic medications[15,16]. As such, altered neurocircuitry encoding of threat and reward learning could potentially be predictive of clinical outcomes for adjunctive therapies that target these pathways, such as lumateperone. There are two main routes by which these pathways could have clinically predictive significance. First, individual differences in neurocircuitry encoding of threat and reward learning could operate as markers of who would vs would not benefit from lumateperone adjunctive

therapy. Second, pre- to post-treatment changes in neurocircuitry encoding of reward and threat learning could operate as a mechanism of symptom reduction (e.g., lumateperone induced improvements in reward and threat neurocircuitry encoding mediate reductions in depression symptoms). These possibilities are not mutually exclusive, and both would have considerable clinical significance for enabling precision medicine approaches to the treatment of MDD among early life trauma populations.

Non-English Speakers will be excluded due to inability to provide informed written consent.

**23. Will the study involve recruitment of the researchers' students or personal contacts/friends/family?**

☒ No → *Skip to item 24*

☐ Yes → *Explain below how the study procedures will be designed to mitigate potential for coercion or undue influence to participate or continue participation:*

**24. Will you recruit or obtain data from individuals you know to be prisoners?**

*"Prisoner" is defined in federal regulations under **45 CFR 46.303(c)** as "any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing."*

☒ No → *skip to item 25*

☐ Yes

**24a. Provide the rationale for including this population in your research** *(i.e. why is a prisoner population necessary to answer the research questions)***:**

**24b. Describe how study procedures will be designed to address each of the following:**

*(a) Recruitment and subject selection procedures will be fair to all eligible prisoners;*

*(b) Prison authorities or other prisoners will not be able to arbitrarily prevent or require participation of particular prisoners;*

*(c) When applicable, control subjects will be randomly selected from the group of available prisoners meeting inclusion criteria (or provide a justification if selection will not be random);*

*(d) When applicable, provisions will be in place to provide follow-up examinations or care of participants, taking into account the varying lengths of individual prisoners' sentences, and all participants will receive information about how this will occur.*

**24c. Describe how you will mitigate potential for undue coercion for prisoners to take part in the study:**

*Consider whether the effect of participation on prisoners' general living conditions, medical care, quality of food, amenities, and opportunity for earnings in prison might be so great as to make it difficult for prisoners to adequately consider the research risks.*

**24d. Check the appropriate box(es) to attest to the following:**

☐ Researchers for this study will not encourage or facilitate the use of a prisoner's participation in the research to influence parole decisions.

☐ When applicable, each prisoner will be clearly informed in advance that participation in the research will have no effect on his or her parole. *(Consider adding language about this in the relevant consent form(s))*

**25. Is your research likely to have subjects who become prisoners while participating in your study?**

*For example, a longitudinal study of youth with drug problems may be likely to have subjects who will be prisoners at some point during the study.*

☒ No → *Skip to item 26*

☐ Yes

**25a. If a subject becomes a prisoner while participating in your study, will you continue the study procedures and/or data collection while the subject is a prisoner?**

☒ No

☐ Yes → *Describe the procedures and/or data collection you plan to continue with prisoner subjects:*

**26. Other Protected Populations**

*In this section, check the box for **all other protected groups that will be intentionally targeted/discernible in your research** (you do **not** need to check all groups that might be* incidentally *included but will not be knowingly enrolled or discernible as a population of study from the data collected).*

| *Select all that apply to this research. If none apply, this section can be left blank.* | *Review the special considerations for selected group(s).* | *Provide the rationale for targeting this protected group in your research. If this has already been addressed in item 22 above or elsewhere, reference earlier responses here, as applicable.*<br><br>*Also, include any additional information you'd like the IRB to consider when reviewing additional requirements outlined in the linked policy(ies).* |
|---|---|---|
| ☐ **Minors (children)**<br><br>☐ **Children who are wards of the state**<br><br>*Note: children are considered subjects of the research if:*<br><br>*1) the study involves collecting data about a child through an intervention or interaction with the child (regardless of identifiability of the data),* ***OR***<br>*2) private, identifiable information about a child is collected from any source (e.g. interview with parent, medical records, educational records, etc.).* | *Review for additional IRB considerations:*<br>UT Austin IRB Policies & Procedures section 12.4: Research Involving Children<br><br>UT Austin IRB Policies & Procedures section 12.4.9: Wards<br><br>*NOTE: In the Consent/Assent Pathways section of this form, you will need to complete items **29 and 30** to address special consent/assent considerations and waiver options for minors.* | |
| ☐ **Impaired/Incapacitated Adults**<br>*Check this box if researchers will knowingly and prospectively enroll adults with conditions that impact their ability to make decisions for themselves* | *Review for additional IRB considerations:*<br>UT Austin IRB Policies & Procedures section 12.5.1: Research Involving Decisionally-Impaired Adults | |

| | | |
|---|---|---|
| *and/or adults who are unconscious or incapacitated due to illness or condition.* | *NOTE: In the Consent/Assent Pathways section of this form, you will need to complete items **29 and 31** to address special consent/assent considerations and waiver options for this group.* | |
| ☐ **Pregnant women and fetuses**<br><br>☐ **Neonates of unknown viability**<br><br>☐ **Non-viable neonates** | *Review for additional IRB considerations:*<br>UT Austin IRB Policies & Procedures section 12.2: Pregnant Women, Fetuses, and Neonates | |

# Recruitment & Screening

## 27. Recruitment Procedures and Materials

| *Select each type of recruitment method that will be used AND **upload copies of all materials to UTRMS-IRB in the "Recruitment Materials" section.*** | *Describe the use of the selected method to recruit participants, addressing the specific points listed for it, when applicable.* | *Provide the schedule and frequency of recruitment attempts using this method, when applicable.* |
|---|---|---|
| ☐ **E-mail/Letter**<br><br>*Explain how emails/mailing addresses for potential subjects will be identified and obtained by the study team. Describe the initial invitation and any follow-up reminders, and address if there will be a way for recipients to opt-out of future emails. Templates should include subject line(s).* | | |
| ☐ **Flyer(s)**<br>*Include the types of location(s) where these will be posted.* | | |
| ☐ **Social Media/Web Posts**<br><br>*Address which sites and accounts will be used to post ads. Templates should include all text/images that will be included in posts. Guidance for creating templates for social media recruitment can be found on our Education & Guidance webpage.* | | |
| ☐ **Text/Direct Messaging** | | |

*Describe sites/accounts that will be used. Explain how participants' contact information is obtained, when applicable. Templates should include the initial invitation and any follow-up reminders.*

☐ **Study-specific Website**

*This refers to websites created specifically for this research study. Templates should include screenshots/mock-ups of all aspects of the website that will be created; include all text/images.*

☐ **In-Person or Phone Scripts/Presentations**

*Explain how phone numbers for potential subjects will be obtained by the study team, when applicable. If researchers will be cold-calling subjects, provide a rationale for why this method is needed to accomplish the research.*

☐ **Research Recruitment pool**

*Specify which pool will be used (e.g. SONA, Prolific, Amazon MTurk, etc.) and describe how offered studies are advertised to users. Provide templates of all researcher-provided advertising language that will be posted and confirm it meets the pool's standards for formatting, content, word limits, etc.*

☐ **Newspaper ads/TV spots/Radio ads**

*When applicable, include scripts and descriptions for planned ads; final versions can be provided in a modification after IRB approval.*

☐ **Medical Record Review**

*If your study includes identifying potential participants using PHI (e.g., a partial HIPAA waiver for recruitment is needed), note this here and be sure you have completed item 12 in the Study Elements section of this form to request a waiver.*

| | | |
|---|---|---|
| ☒ **Other recruitment material/method** | Department referral registry 2020040046 (IRB number) | |

## 28. Screening Procedures

*Describe the procedures to screen individuals to determine whether inclusion/exclusion criteria are met. Be sure to specify the following specific details:*

- *Will screening procedures occur before or after consent?*
- *For any screening data collected prior to consent, how will this data be used? For example, will it be used only to confirm eligibility, screen failure analyses, or will it be used to answer the research questions as well?*

*Please upload all screening questionnaires/tools in the "Other Attachments" section in UTRMS.*

- A 2-week Screening Period during which patient eligibility will be assessed. After obtaining written informed consent, diagnostic interviews and physical examinations will be conducted, vital signs and ECGs will be assessed, and blood and urine samples will be collected for laboratory assessments. With the exception of stable, allowed concomitant medications, patients must discontinue prohibited psychotropic drugs during the Screening Period. The following rating scales will be administered.

  Clinician Rater: CAPS-5, MADRS, DIAMOND, SCID-5 Borderline Personality module, CGI-S, MGH-ATRQ, CSSRS

  PROs, GAD-7,QIDS-SR-16, EQ 5D-5L, CTQ, GASS, PCL-5, NWS

  Once deemed eligible, the subject will also be offered to enroll in the optional EMA wellness app to be completed 3x daily from screening visit to the end of study visit

# Consent /Assent Pathways

## 29. Consent Pathways

*Obtaining informed consent is the default expectation for enrolling subjects to your research. For all human subjects included in the research (either via direct participation or having their private, identifiable data included in the study), researchers must have a pathway either to obtain informed consent or request and meet criteria for waiving informed consent.*

***Select all consent pathways that will be used to enroll subjects into the study***.
*Examples:*
*1) If you will obtain consent from one group of adult participants but are requesting a waiver for another group (such as a retrospective chart review group), both "Obtaining Consent from Adult Participants" and "Requesting Waiver" should be checked.*
*2) If adults will provide consent for their own participation and provide consent for their child's participation, both "Obtaining Consent from Adult Participants" and "Obtaining Parent/Guardian Consent for Minor Participants" should be checked, etc.*

☒ Obtaining Informed Consent *(verbal or written)* from:
- ☒ Adult Participants for their own participation
- ☐ Parent(s)/Guardian(s) for Minor (child) Participants
- ☐ Legally Authorized Representative (LAR) for impaired/incapacitated adult participants

☐ Requesting Waiver or Alteration of Required Elements of Informed Consent
☐ Obtaining Short Form Consent with a witness *(rare, limited applicability, see Policies & Procedures section 6.4.2)*

**29a. Obtaining Consent Description** → *if not obtaining consent for any group, skip to 29b*

*In the box below, specify how each "obtaining consent" method checked in the table above will be used and with which participant group(s).*
*For each method checked, include who will obtain consent, where consent will be obtained, and when the consent process will occur in such a manner that participants will have sufficient time for adequate consideration.*

*NOTE: Upload copies of all consent/permission forms/scripts to UTRMS-IRB in the "Consent Forms" section. This is required for UTRMS-IRB to appropriately stamp consent forms for approval.*

During the screening period, the participant will be given a written and verbal description of the study and informed consent. The PI or designated staff will discuss the informed consent form with the subject volunteer. The consent process will take place in a quiet and private room. Subjects may take as much time as needed to decide about their participation and may take the document home if desired. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and follow-up requirements of the study. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. No research-related procedures will be performed prior to obtaining informed consent. All signatures and dates will be obtained. A copy of the signed consent will be given to the participant. The informed consent process will be documented in each subject's research record.

**29b. Waiver or Alteration of Informed Consent Requested**

*Select the type(s) of consent waivers being requested or select "None requested".*
*Note this section is for requesting a full consent waiver or waiving part(s) of the required information typically provided in consent forms. Signature-only waivers are addressed in item 29d below.*

*Select all that apply.*

☐ Waiver of Informed Consent for Adult Participants
☐ Waiver of Parental/LAR Consent for Child or Impaired/Incapacitated Adult
☐ Alteration of Required Elements of Informed Consent and/or Parental or LAR consent *(e.g. Deception research where the nature of the research cannot be fully disclosed)*
☐ None requested → *Skip to item 29d*

**29c. Qualification for Waiver or Alteration**

*To approve a waiver or alteration of informed consent **all of the following criteria below must be met.***

Criterion 1: The research involves no more than minimal risk to the subjects.
*Provide protocol specific information as to how this criterion is met. Consider how the risk(s) of the research activity(ies) for which consent is being waived compare to the risks the average person might reasonably anticipate experiencing in everyday life:*

Criterion 2: The waiver or alteration will not adversely affect the rights and welfare of the subjects.
*Provide protocol specific information as to how this criterion is met. Consider whether this waiver may violate the rights of subjects or adversely affect their welfare in any way. For example, if the research proposes to use data that was originally collected under an explicit agreement that it would not be used for research purposes, this waiver might violate participants' rights.*

Criterion 3: The research could not practicably be carried out without the waiver or alteration (i.e. the research would not be achievable or viable if obtaining consent is required).

*Provide protocol specific information as to how this criterion is met. Acceptable justifications should be based on the study's scientific design rather than issues of time or inconvenience. For example, is there evidence to suggest significant portions of the sample would be unreachable and present significant sampling bias? Is the nature of the research such that a total population sample is necessary to answer the research questions?*

Criterion 4: The research either does not involve using identifiable private information or identifiable biospecimens, **or** if identifiable data/specimens *are* used, the research could not feasibly be carried out without using such information or biospecimens in an identifiable format.

*i.e. Why would it be impossible to conduct the study using only anonymous information/specimens? Provide protocol specific information as to how this criterion is met:*

**29d. Consent Signature Type**

*Select the method(s) for obtaining participant signatures for informed consent. Select all that apply to your research.*

☒ Written Signature *(on paper or with finger/mouse/stylus on touchpad or computer)*
☐ Electronically-generated Signature using standard validation service *(such as DocuSign or REDCap)*
☐ Electronically-generated Signature using externally-hosted validation service that is Part 11 compliant → *see note:*

*Part 11 compliance is required for studies falling within FDA regulations (i.e. investigational drugs/devices). At this time, the UT system accounts for REDCap and DocuSign are not compliant with the requirements of Part 11. FDA-regulated studies conducted at UT that collect electronically-generated consent signatures may utilize an FDA-compliant account managed by an external sponsor or a collaborating institution (as applicable); otherwise, researchers must utilize written consent. For additional guidance on Part 11 compliance, contact regsupport@austin.utexas.edu.*

☐ Obtaining consent without valid signature – waiver of signature requirement requested → *Complete Section 29e*
☐ N/A - Not Obtaining Consent

**29e. Waiver of Documentation (signature) of Informed Consent** → *if not requesting, skip to item 30*

*Only complete this section if you are requesting to waive the requirement to collect a written or validated electronic signature of informed consent from participants (an informed consent form/script is still required). To approve a waiver of documentation of consent, all criteria for one of the following options must be adequately justified by the researcher.*

*Please choose **one** waiver option and address the listed criteria as prompted. **Waiver Option 1 is most common.***

**i. Waiver Option 1 – Minimal Risk Research**

*Each criterion listed below must be met to qualify for Waiver 1.*

Criterion 1: The study is minimal risk.

*Provide protocol specific information as to how this criterion is met. Consider how the risk(s) of the research activity(ies) for which consent is being waived compare to the risks the average person might reasonably anticipate experiencing in everyday life:*

Criterion 2: Written consent would not be required outside the research context.
*Provide protocol specific information as to how this criterion is met. For example, if laws or other regulations requiring signed consent would normally be applicable to the type of research activity for which signed consent is being waived outside of a research context, this criterion is not met (e.g. consent for clinical care, consent for release of educational records, signing a housing application or similar contract, etc.).*

Criterion 3: There will be an appropriate alternative mechanism for documenting that informed consent was obtained.
*Briefly explain how the researcher will document that consent was obtained from participants:*

**ii. Waiver Option 2 – High Risk for Confidentiality Breach** *(rare)*
*Each criterion listed below must be met to qualify for Waiver 2.*
*NOTE: This is the only applicable waiver of documentation option for greater than minimal risk research. If your study is greater than minimal risk and does not meet Option 2 criteria, you will need to obtain signed consent.*

Criterion 1: The only record linking the subject and the research would be the consent document.
*Provide protocol specific information as to how this criterion is met.*

Criterion 2: The principal risk would be potential harm resulting from a breach of confidentiality.
*Provide protocol specific information as to how this criterion is met.*

Criterion 3: Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.
*Provide protocol specific information as to how this criterion is met. Note that under this waiver, participants must be given the option to sign or not, so the consent form(s) will still need signature lines.*

Criterion 4: There will be an appropriate alternative mechanism for documenting that informed consent was obtained.
*Briefly explain how the researcher will document that consent was obtained from participants who do not sign.*

**iii. Waiver Option 3 – Cultural Norms** *(rare)*
*Each criterion listed below must be met to qualify for Waiver 3.*

Criterion 1: The subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm.
*Describe the cultural group or community and explain how this criterion applies:*

Criterion 2: The research presents no more than minimal risk of harm to subjects.
*Provide protocol specific information as to how this criterion is met. Consider how the risk(s) of the research activity(ies) for which consent is being waived compare to the risks the average person might reasonably anticipate experiencing in everyday life:*

Criterion 3: There is an appropriate alternative mechanism for documenting that informed consent was obtained.
*Provide protocol specific information as to how this criterion is met and describe the mechanism for documenting that informed consent was obtained:*

## 30. Assent Pathways for Research Involving Minors (children)

*This section is required for all studies involving minors as subjects (see the Other Protected Populations section for guidance). If this study does not involve minors, skip to item 31.*

*Select all that apply:*
☐ Obtaining Assent from Minor (child) Participants
☒ Not Obtaining Assent → *If only this box is checked, skip to item 30b*

### 30a. Assent Process Description

*Provide a detailed description of assent procedures in the box below. Include: who will obtain assent, where assent will be obtained, how assent is obtained, how assent is documented, and when the assent process will occur.*

*NOTE: Upload copies of all consent/assent/permission forms/scripts to UTRMS-IRB in the "Consent Forms" section. This is required for UTRMS-IRB to appropriately stamp consent forms for approval.*

**30b. Waiver of Assent for Minors Requested**

*Note: Assent is generally not required for children age 0-6, so a waiver does not need to be requested for this age group.*

☐ Waiver of Assent for Children age 7+
☒ None requested → *skip to item 30f*

**30c. Qualification for Waiver of Assent from Minors (children) age 7+** *(select all that apply)*

☐ **Some or all children age 7+ included in this research will not be capable of providing assent based on their developmental status or impact of illness/condition**. → *If checked, explain below:*

☐ **Requesting a waiver of assent from some or all children age 7+ who are otherwise capable of providing assent** → *If checked, address all of the following. All of the following criteria must be met to request a waiver:*

Criterion 1: The research involves no more than minimal risk to the subjects.
*Provide protocol specific information as to how this criterion is met. Consider how the risk(s) of the research activity for which consent is being waived compare to the risks the average child might reasonably anticipate experiencing in everyday life:*

Criterion 2: The waiver or alteration will not adversely affect the rights and welfare of the subjects.
*Provide protocol specific information as to how this criterion is met. Consider whether this waiver may violate the rights of subjects or adversely affect their welfare in any way.*

Criterion 3: The research could not practicably be carried out without the waiver or alteration (i.e. the research would not be achievable or viable if obtaining assent is required).
*Provide protocol specific information as to how this criterion is met. Acceptable justifications should be based on the study's scientific design rather than issues of time or inconvenience.*

Criterion 4: The research either does not involve using identifiable private information or identifiable biospecimens, **or** if identifiable data/specimens *are* used, the research could not feasibly be carried out without using such information or biospecimens in an identifiable format.
*i.e. Why would it be impossible to conduct the study using only anonymous information/specimens from minors?*
*Provide protocol specific information as to how this criterion is met:*

**30d. Minor Assent Signature Type**

*Select the method(s) for obtaining participant signatures for assent. Select all that apply to your research. Note that validation services such as DocuSign cannot be used to validate signatures from minors.*

☐ Written Signature *(on paper or with finger/mouse/stylus on touchpad or computer)*
☐ Obtaining assent without signature for children age 12 and younger
☐ Obtaining assent without signature for children age 13-17 → *Complete 30e below*
☐ N/A - Not Obtaining Assent

**30e. Request to waive Assent Signature Requirement for Minors (children) age 13-17** → *if not requesting, skip to item 30f.*

*Only complete this section if you are requesting to waive the policy requirement to collect a written signature of assent from participants age 13-17. The IRB will assess the rationale provided by the researcher for appropriateness based on the specific study procedures and population.*

**i. Provide a protocol specific justification for why written assent signature will not be obtained:**

**ii. Describe the mechanism for documenting that assent was obtained.**

*Briefly explain how the researcher will document that assent was obtained from participants*

**30f. Age of Majority Re-Consent Process**

*The age of majority is the age at which a person is legally considered an adult and can provide informed consent for their own participation in research. In most states, including Texas, the age of majority is 18, but this can vary depending on where the research is conducted.*

*If the research involves minors as subjects, either Option 1 or Option 2 below must be checked:*

☐ Option 1: All study activities with minors will be complete AND all data collected from minors will be anonymized before any participants will reach age of majority.

☐ Option 2: The study enrolls minors who may reach age of majority while study activities and/or research use of their identifiable data is ongoing.

*If true, specify the method of obtaining adult informed consent from these participants upon reaching age of majority.* ***At least one of the following must be checked:***

☐ Participants will be re-consented using an adult consent form/script

*Describe the re-consent procedures below. Be sure to upload an adult consent document that will be used for this group. If signature will not be collected (e.g. if re-consent is conducted via phone or other remote method), please complete item 29e to request a waiver of documentation (signature).*

*NOTE: Upload copies of all consent/assent/permission forms/scripts to UTRMS-IRB in the "Consent Forms" section.*

☐ A waiver of adult re-consent is requested in the Waiver or Alteration of Informed Consent section of this form.

**31. Assent Pathways for Research Involving Impaired/Incapacitated Adults**

*This section is required for all studies where impaired/incapacitated adults are knowingly and prospectively enrolled (see the Other Protected Populations section for guidance). If this study does not involve this population, skip to item 32.*

**31a. Capacity for Consent/Decision-Making Capacity**

*Describe the process you will use (if any) to determine whether a cognitively impaired individual is capable of consent decision making with respect to this research protocol and setting.*
*Consent pathways for adults who are capable of providing full informed consent (instead of assent) should be covered in item 29 above.*

**31b. Impaired/Incapacitated Adult Assent Pathway** *Select all that apply*

☐ Obtaining Assent from Adult Participant
☒ Not Obtaining Assent → *if only this box is checked, skip to item 32*

**31c. Assent Process Description**

*Describe whether assent will be required for all or some of the subjects. If some, indicate which subjects will be required to assent and which will not (and why not).*
*Provide a detailed description of assent procedures in the box below. Include: who will obtain assent, where will assent be obtained, how is assent obtained and documented, and when the assent process will occur in such a manner that participants will have sufficient time for adequate consideration.*

*NOTE: Upload copies of all consent/assent/permission forms/scripts to UTRMS-IRB in the "Consent Forms" section. This is required for UTRMS-IRB to appropriately stamp forms for approval.*

**31d. Impaired/Incapacitated Adult Assent Signature Type** *Select all that apply*

☐ Written Signature obtained when possible *(on paper or with finger/mouse/stylus on touchpad or computer)*
☐ Electronically-generated Signature obtained when possible, using validation service *(such as DocuSign)*
☐ Obtaining assent without signature

## Additional Consent Considerations and Disclosures

**32. Will the study population likely include participants whose limited English-speaking status requires translation of the consent/assent documents and other relevant study materials?**

☒ No → *skip to item 33*
☐ Yes

**32a. Translation Process**

*Complete the below information describing the translation process. One of the following must be checked.*

☐ The consent documents and other relevant study materials will be translated by a certified translator.
☐ A non-certified translator will translate the consent documents and other relevant study materials and another individual will confirm the translation is accurate and appropriate. → *If selected, describe the translator's qualifications in the text below:*

**33. Required Consent Disclosures**
*Identify each element below that may require additional information to be disclosed in the consent form.*

☒ It is reasonable that researchers could discover or suspect child or elder abuse.
*Add appropriate disclosure in consent form(s).*

☒ It is reasonable that researchers could learn of an incident that could require reporting under Title IX.
*Add appropriate disclosure in consent form(s). See Title IX and Research Guidance for more information on this requirement.*

☒ It is reasonable that researchers could discover incidental findings or other information of medical interest about a participant's previously unknown condition. → *answer the following:*

**33a. Articulate methods for addressing and reporting incidental findings, if applicable.**
*If results will not be shared, provide a justification for why this will not occur. Ensure appropriate information is in consent form(s), as applicable. If the study involves genetic testing that could result in relevant findings, this should be addressed in item 11d and that response can be referenced below.*

During the MRI there is a small chance that incidental findings may occur. If this happens, researchers will send the images to the Biomedical Imaging Center's Safety Panel where they will be reviewed by the Medical Director or designated qualified radiologist.

**33b. If research will be conducted at the UT Biomedical Imaging Center (BIC), check the box below to attest that researchers will comply with BIC requirements for reporting incidental findings, as outlined in the BIC Wiki.** *Ensure appropriate language is included in all relevant consent forms. As a reminder, research conducted at the BIC is required to comply with all BIC policies/requirements. This can be left blank if not applicable (i.e. no research activities at the BIC).*
☒ Confirm

# Compensation & Costs

**34. Will subjects receive any compensation for their participation in the research?**
*See P&P section 4.8 for guidance on compensation.*
☐ No → *skip to item 35*
☒ Yes

**34a. Specify the type/total amount of compensation that will be provided to each participant:**

You will receive a stipend of $50 for each study visit you complete. In addition, you will receive an extra $50 for Visit 2 and Visit 8 if you complete the imaging procedures scheduled during those visits. This means you may receive additional compensation for participating in specific procedures that require more time or effort.

All stipends will be provided through Tango Cards, which can be redeemed for a variety of gift cards or charitable donations.

**34b. Indicate the type(s) of compensation offered:** *Select all that apply*

☐ Cash ☐ ClinCard
☐ Check ☒ Tango Card
☐ Gift Card ☐ Course Credit
☐ Other, describe in the text box below:

**34c. Will monetary payments be pro-rated so that participants who are unable to complete the research may still receive some part of payment?** *(e.g. hourly rate, split across multiple study sessions, payment per activity completed, etc.)*
*It is recommended that payment be prorated for the time of participation in the study rather than delayed until study completion, as making payment contingent on completing multiple sessions could unduly influence a subject's decision to exercise their right to withdraw at any time. It is acceptable, with an appropriate justification, to offer an additional incentive or completion bonus to subjects that complete all study activities, provided the incentive is not so large as to unduly influence subjects to stay in a study when they otherwise would have withdrawn.*

☐ No → *skip to item 35*
☒ Yes → *describe the proration schedule in the text box below*:

For each task/visit a participant completes, they will receive $50. In addition, you will receive an extra $50 for Visit 2 and Visit 8 if you complete the imaging procedures scheduled during those visits. .

## 35. Costs

*One of the following must be checked:*

☒ Participants will have no costs associated with this study → *skip to item 36*
☐ Participants will have the following costs associated with this study:
- ☐ Standard of care procedures contributing to study data
- ☐ Research procedures/services not associated with standard of care
- ☐ Administration of drugs/devices
- ☐ Study drugs or devices
- ☐ Transportation and parking
- ☐ Other, describe below:

# Benefits

## 36. Benefits to Society

*Describe the scientific and societal benefit(s) below.*

There is a great unmet need for novel treatments for MDD. There are few approved medications, for Major Depressive Disorder, and although effective, similar to evidence-based therapies, they produce a significant improvement in symptom severity scores, but bring few patients into remission. The purpose of the study is to determine if Lumateperone (oral) reduces MDD symptom severity in adult subjects diagnosed with MDD and have a history early life trauma.

**37. Potential Direct Benefits to Participants**

*Click on the applicable check box. One of the following must be checked.*

☐ There is no anticipated direct benefit to participants.

☒ There are anticipated benefits to participants. → *Describe potential direct benefits to participants below. Note that compensation (addressed in previous section) is not considered a "benefit" of research participation:*

Patients might notice a reduction in MDD symptoms.

**38. Alternatives to Participation in this Study**

*Provide a description of any alternative procedures or treatments that might be advantageous to the subjects. For example, earning extra class credit in some time-equivalent way other than research participation; obtaining supportive care or standard clinical treatment from a health care provider instead of participating in research with an experimental drug or intervention, etc.*

## Risks & Discomforts

**39. Describe <u>all</u> reasonably foreseeable risks and discomforts associated with each activity in this research:**

*Transparency about all risks/discomforts, even those that are minimal, increases participant trust in the research enterprise and helps to prevent unanticipated problems or complaints. It is rarely acceptable to state there are "no risks." However, you are encouraged to provide your evaluation of the probability and magnitude of potential risks listed.*

*Categories of possible risks to consider may include (but are not limited to) the following:*

- ***Physical** (e.g. bodily harms or discomforts, side effects, etc.);*
- ***Psychological/emotional** (e.g. boredom or mental fatigue, discomfort answering questions or providing personal information, learning unpleasant information about oneself or others, etc.);*
- ***Social or legal** (e.g. impacts on relationships or reputation, legal or criminal justice actions for self or others, etc.);*
- ***Financial or economic** (e.g. impacts on income, employability, or insurability, loss of services, etc.);*
- ***Research Design-specific risks** (e.g. unforeseeable risks of experimental procedures, disappointment with randomization outcomes, washout risks, placebo effects, withholding or delaying care/services, deception, etc.).*

***General loss of privacy/confidentiality** is an assumed, foreseeable risk that applies to all studies as data breaches or other errors of this nature are not uncommon. This general risk does not need to be reiterated below, but if there are more specific privacy/confidentiality risks associated with the research, these can be described. All foreseeable risks/discomforts must also be outlined in the consent form(s).*

**Privacy:** There is a low risk of loss of confidentiality of your personal information. While every effort will be made to protect the confidentiality of your information, absolute confidentiality cannot be guaranteed. However, steps have been taken to help make sure this will not happen. You will read more about the protection of your personal information in Part 3 of this information sheet.

**ECG:** Some areas where the electrodes (sticky patches) will be placed may need to be shaved. The test is painless, but the electrodes may irritate your skin.

**Blood tests:** Drawing blood may cause discomfort, bruising, and very rarely, infection at the puncture site, or damage to a vessel or a nerve. You may also experience dizziness, nausea, or fainting during the blood-taking procedure. Please tell the study doctor or study team if you do not feel well after having your blood drawn.

**Questionnaires and interviews:** Some of the questions that you may be asked during the study may be sensitive, which can be distressing for some people. If you feel uncomfortable as a result of the study questionnaires or an interview, please tell the study doctor or a member of the study team.

**Fasting:** Fasting could cause dizziness, headache, stomach discomfort, or fainting.

**MRI Scan:** No serious ill effects have been reported to date from facilities in the United States operating with a magnetic field strength of 3 Tesla (the magnetic field strength used in this study); these types of magnets are widely used for clinical practice. Since the study involves entering a confined space, you may not be able to participate if you have a history of claustrophobia or if you experience anxiousness when entering the magnet tube.

The risks due to exposure to the magnet itself are primarily related to the slight possibility of a sensation of dizziness or nausea as you move in and out of the magnet or move your head in the magnet. The magnet is thought to be able to exert a force on the fluid within the semicircular canals near the ears thus possibly giving a sensation of dizziness. The sensations go away if your head is not in motion or if you are not moving in/out of the magnetic field. Less than 10% of subjects experience this dizziness, which generally lasts 1-2 minutes or less. You will be exposed to noise from the machine for which earplugs and/or earphones are provided. There are no other known risks to being in the magnetic field.

Magnetic items move in a high magnetic field and by doing so, can be dangerous. The Biomedical Imaging Centers (BIC) at the University of Texas at Austin is careful to maintain an environment safe from these objects. We require you to do the same, being careful to ensure that you carry no metallic items into the MRI room. You will be asked to change into MRI-approved clothing for the MRI scans.

We want you to read and answer very carefully the questions on the MR Safety Questionnaire related to your personal safety. Take a moment now to be sure that you have read the MR Safety Questionnaire and be sure to tell us any information about you that you think might be important.

**Electrical shocks:** During the MRI scan you will complete a task during which you will receive mild electrical shocks. Prior to entering the scanner, you will select a level of shock that is annoying and mildly uncomfortable but not painful. If the shocks become too uncomfortable or distressing for you, you can stop the MRI scan at any time by alerting the research staff.

**Harm to the unborn child:** Currently, we are not fully aware of the effects of the study drug on unborn babies, or people who are pregnant or breastfeeding. If you can become pregnant, use of the study drug may lead to new, previously unknown, side effects that we currently do not know about, and this may involve risks to your unborn baby. Because of this, subjects who can have children will have pregnancy tests (blood and/or urine) during the study. Sexually active subjects who can become pregnant must be using an effective form of birth control from the screening visit until the end of the follow-up. The study doctor will discuss effective birth control methods with you.

If you become (or your partner becomes) pregnant during the study, you should immediately tell the study doctor. If you become pregnant, you will have to stop taking the study drug. Your pregnancy and health will be followed carefully by the study team. Female partners of male subjects who become pregnant will be asked to provide consent for the study team to follow their pregnancy and health until the end of the pregnancy.

**40. Describe how each risk listed above is mitigated/minimized.**

*General privacy and confidentiality protections do not need to be outlined here as these are covered in their own section below. Mitigation strategies for all other risks/discomforts described above should be outlined. Risk mitigation should also be outlined in the consent form(s), when applicable.*

All study procedures occur after the Informed consent is obtained from participants which specifically outlines the risks associated with participation in the study and from blood draws and imaging procedures. Study participants will be educated about the procedures involved, including potential risks and what to expect before, during, and after these procedures are completed. Participants will be encouraged to report any unusual symptoms or reactions promptly. Only those personnel trained and experienced in performing these tasks safely and accurately will conduct all study related procedures such as blood draws and imaging. Study personnel will ensure all equipment for study procedures is properly calibrated, maintained, and validated for accuracy. Prompt reporting and documenting of any adverse events or reactions that occur during study procedures will be implemented to prevent recurrence.

**41. Early Withdrawal**

*Are there any planned or anticipated conditions under which a participant will be withdrawn from the study without their consent, **and/or** any safety issues for participants who choose to withdraw early? Be sure your response aligns with any information about withdrawal included in the consent form(s):*

☐ No → *skip to item 42*
☒ Yes → *answer the following:*

**41a. List the criteria for withdrawing individual participants from the study:**

*Examples may include, but are not limited to, safety or toxicity concerns, emotional distress, inability to comply with the protocol, or requirements from study sponsor, etc.*

Safety or toxicity concerns, emotional distress, inability to comply with the protocol, or requirements from study sponsor.

**41b. If applicable, describe any necessary procedures for ensuring the safety of a participant who withdraws/has been withdrawn early.**

**42. Data Safety Monitoring**

*Studies involving investigational drugs or devices are generally required to at least have a data safety management plan (DSMP), regardless of risk level. Studies that involve greater than minimal risk are strongly recommended to have a DSMP, and the IRB may require this in certain circumstances (e.g. if there is a known risk with expected frequency, etc.). Some studies, particularly those that are greater than minimal risk and involve sponsors or federal funding, may have a data safety monitoring board or committee that oversees ongoing safety reviews.*

*Otherwise, most minimal risk studies do not require a data safety plan or board, though sponsors or the IRB may require this under certain circumstances.*

*For additional information and reporting requirements regarding data safety monitoring boards and data safety monitoring plans, please see Section 21 of our Policies and Procedures.*

***After reviewing the information above, one of the following must be checked:***

☐ This study does not involve a Data Safety Monitoring Plan (DSMP) or a Data Safety Monitoring Board (DMSB). → *skip to item 44*
☐ This study has an internal plan to monitor data for safety (Data Safety Monitoring Plan (DSMP)).
☒ This study has a Data Safety Monitoring Board or Committee (DSMB/C).

**43. Data Safety Monitoring (Details)** *select all that apply*

☐ This study has a DSMP document or DSMB charter describing safety monitoring details (including the list of board members for DSMBs) uploaded to UTRMS → *if all details below are covered in the uploaded document, skip to item 44*
☒ Details of the DSMP/DSMB processes are provided below:

**43a. Describe the safety information that will be collected and reviewed for safety monitoring.**
*This description should include the following details:*

- *the type(s) of information that will be collected to monitor individual participant safety*
- *any additional cumulative data that will be collected to monitor overall study safety (if different from what is obtained for participant monitoring)*
- *the schedule and frequency of safety data collection*

1. **Adverse Events**
   Adverse events will be collected after the ICF has been signed through the end of the study. Medical conditions or AEs that occur after the ICF has been signed and prior to completion of screening will be captured on the Medical History CRF.
2. **Medical History**
   At screening the subject's clinically significant pre-existing medical conditions will be documented. The history should include demographic information and relevant medical history with an emphasis on the subject's history of present illness and treatment history. Surgical history will be recorded.
3. **Physical Exam**
   Body weight and height will be measured at screening. Any condition present at the post-treatment physical examination that was not present at or worsened since the baseline examination is to be documented as an AE. Whenever possible, the same individual is to perform all physical examinations. Physical examinations will include assessment of body systems (e.g., HEENT, heart, lungs, abdomen, and extremities) as well as cognitive and neurological examination and mental status examination.
4. **Vital Signs**
   Vital signs include oral temperature (°F), respiratory rate, heart rate, and blood pressure. A full set of vital signs will be obtained at all specified time points (±30 minutes), unless the subject is asleep between the hours of 23.00h and 06.00h each day.
5. **ECG**
   A baseline 12-lead ECG will be performed during screening. The following ECG parameters will be recorded: heart rate, PR, QRS, QT, and QTc. All ECG results will be interpreted by the Investigator as Normal, Abnormal; not clinically

significant (NCS), or Abnormal; clinically significant (CS). If Abnormal, details will be provided.

6. **Clinical Laboratory Tests**

   Blood samples will be collected for hematology, serum chemistry, coagulation, specific hormone parameters, and exploratory biochemistry; and pregnancy testing. Urine samples for urinalysis and selected drugs of abuse will also be collected. All samples will be analyzed at the local laboratory.

   All clinical laboratory test results outside the reference range will be interpreted by the Investigator as Abnormal; not clinically significant (NCS) or Abnormal; clinically significant (CS). Screening results considered Abnormal; CS will be recorded as medical history.

   Clinical laboratory results that are Abnormal; CS during the study and indicate a worsening from baseline will be considered AEs.

7. **Columbia Suicide Severity Rating Scale (C-SSRS)**

Suicidality will be monitored during the study using the C-SSRS (Posner et al., 2011). This scale consists of a screening/pre-dose evaluation that assesses the lifetime and recent experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes "yes" or "no" responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from1 to 5, with 5 being the most severe). The "Baseline/Screening" C-SSRS form will be completed at screening prior to dosing.

**43b. Describe the data safety monitoring review process.**

*This description should include the following details:*

- *Who will be responsible for reviewing safety data and identifying safety concerns?*
- *How frequently will safety data be reviewed by the responsible person(s)/board?*

The PI and DSMB will be ultimately responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with reporting requirements. Any adverse events (AE) that occur will be monitored in an ongoing way, as well as being formally reviewed by the investigators and at each annual review meeting. Any data accrued will be summarized and reviewed by the study investigators at each annual review meeting and after 50% of participants have been enrolled. Interim analyses will not be performed unless clinically indicated. All SAEs, such as death, hospitalization, will be reported to the IRB, FDA, and the sponsor under expedited reporting in accordance with policy. The procedures for this reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel. We will report major protocol amendments or changes in the informed consent to the sponsor, as well as any temporary or permanent suspension of patient accrual.

The board will include Zach Stowe, University of Wisconsin Madison, Thomas Adams, Yale University, and Ben Kelmendi, Yale University

**43c. Describe any pre-specified safety threshold or criteria that would trigger immediate suspension of the study, if applicable.**

It would depend on the evaluation of serious adverse events.

# Privacy & Confidentiality

## 44. Participant Privacy

*Privacy refers to an individual's right to control how others view, record, or obtain information about them. Privacy protections apply to people, while confidentiality protections (addressed in the next item), apply to data.*

*In this section, describe how the study team will protect participants' privacy throughout all phases of the research, including during identification, recruitment, screening, the consent process, the conduct of the study, and dissemination of data. For example, consider the locations where you will approach and question participants, the locations where data will be viewed/analyzed, how data collection procedures will limit the amount of sensitive or invasive data collected to only what is necessary to answer the research questions, how participants will be described in publications/presentations, etc.*

The study team is committed to safeguarding participant privacy throughout all phases of the research, including identification, recruitment, screening, consent, study conduct, and dissemination of findings. The following measures will be implemented:

- Potential participants will be identified through secure, IRB-approved databases or referrals from clinical providers, ensuring no unauthorized access to personal health information (PHI).
- Recruitment will occur in private settings (e.g., clinic rooms, secure telehealth platforms) to prevent inadvertent disclosure of participation.
- Screening will be conducted in private locations or via secure, encrypted platforms.
- Only data necessary to determine eligibility will be collected, minimizing exposure to sensitive information.
- The consent process will occur in a confidential setting, with ample time for participants to ask questions. Consent forms will clearly outline data privacy protections and participants' rights.
- Participants will be described in aggregate and no identifying information will be shared in any dissemination materials.
- Data analysis will be conducted on de-identified datasets whenever possible.

## 45. Data Confidentiality and Security Plan

*Confidentiality refers to the way private information about a participant or defined community is maintained and shared. It describes how the study's research materials (data, specimens, records, etc.) are protected from unauthorized access.*

*In this section, describe whether any participant identifiers (e.g. names, contact info, etc.) will be collected during the conduct of the research and if identifiers will be linked to research data for <u>any</u> period of time. Include the following, as applicable:*

- *If identifiers will be used for contact or compensation purposes only, and will <u>never</u> be linked to specific responses, describe the methods used to accomplish this.*

- *If identifiers will be coded/pseudonymized to protect confidentiality, describe whether or not a code key will be created linking study IDs/pseudonyms to identifiers, who will have access to the key, and how it will be stored separately from the research data.*

- Study procedures will be designed to collect only the minimum necessary data to answer the research questions, avoiding unnecessary invasiveness.
- All data will be collected using secure, encrypted systems
- Physical documents will be stored in locked cabinets in restricted-access areas; electronic data will be stored on password-protected, access-controlled servers.
- Only authorized study personnel will have access to identifiable data, and all team members will complete required subjects protection training.
- Data analysis will be conducted on de-identified datasets whenever possible.

Identifiers will be indirectly linked to the study data via a secure linking log that associates participant names with subject ID numbers. It will be stored exclusively on UT Austin's encrypted and access-controlled servers, and access will be restricted to IRB-approved study personnel.

Identifiable information will not be included in the primary study dataset used for analysis, and all identifiers will be destroyed following study closeout in accordance with UT data retention policies and IRB protocol. All study data used for analysis will be de-identified, and the linking log will be stored separately from the dataset to maintain confidentiality.

**46. Does the study have (or do you plan to apply for) a Certificate of Confidentiality from the National Institute of Health (NIH)?**

☐ No

☐ Yes - NIH has issued a Certificate of Confidentiality for this study.
*Ensure CoC language is included in the consent form(s).*

☒ Yes - a Certificate of Confidentiality has not been obtained, but there are plans to apply for one.
*Apply for a CoC for non-NIH funded research here: NIH Certificate of Confidentiality System. Once CoC is granted by NIH, you must submit a modification to add CoC language to the consent form and ensure a copy of the CoC approval (only for non-NIH funded research) is uploaded to UTRMS-IRB.*

**47. Electronic Materials - Storage and Access**

*In this section, select all methods that will be used to protect the confidentiality of research data.*
*At least one of the following must be checked, select all that apply.*

☒ Electronic data and records will be stored on a password-protected cloud service that is currently listed as approved on the UT Information Security Office (ISO) platform matrix. Access to data will be limited only to individuals who need access for purposes related directly to this research study. *(Strongly recommended)*
*The matrix of current UT Austin ISO approved platforms is available here: https://security.utexas.edu/iso-policies/cloud-services/decision-matrix*

☐ Electronic data and records will be stored on a third-party cloud service/platform that is not currently approved for research data storage by UT Austin's Information Security Office (ISO) and requires local ISO approval. → *If this box is checked, the study team must obtain security clearance from UT Austin ISO (or Dell Med IT, if*

*applicable) approving use of this platform to store research data for this study. UT IRB approval cannot be granted until documentation of ISO/IT approval has been uploaded to the study in UTRMS under "Other Attachments." To avoid delaying approval, consider selecting a different option for storing data, if possible.*

☐ Other method(s) of storing and limiting access to electronic data and records, describe in the text box below:
*Examples might include use of a platform hosted and approved by a collaborating institution or sponsor for this research, use of non-cloud-based electronic storage methods (e.g. hard drive), etc.:*

## 48. Physical Materials – Storage and Access

*One of the following must be checked.*

☒ Physical data/records/specimens *(e.g. signed research consent forms, paper surveys/notes, physical recordings, samples etc.)* will be stored in a secure location with access limited only to individuals who need access for purposes related directly to this research study.

☐ N/A – no physical materials

## 49. Research Records Retention Attestation

*Confirm that research records will be maintained in compliance with all relevant records retention policies.*

*UT Austin's research record retention policy requires that data and copies of relevant study documents (e.g. consent forms, protocol, recruitment materials, etc.) be maintained for at least 3 years from completion of the research project. Note that researchers are NOT required to maintain identifiers linked to data for 3 years. To protect confidentiality, identifiers can be unlinked from study data and destroyed as soon as feasible (described in the next item). UT Austin's records retention policies are available here: https://records.utexas.edu/utrrs*

*Some research may be subject to other retention policies that require longer retention periods and retention of other specific data or materials (e.g. collaborating institutions, funding agencies or sponsors, FDA, HIPAA, etc.). For example, studies that involve use of protected health information (PHI) covered by HIPAA must retain all relevant records for at least 6 years.*

*Check the box below to acknowledge the above information and confirm the study team will comply with UT Austin's policy as well as any other records retention policies that apply to this research.*

***This box must be checked.***

☒ Confirm

## 50. Destruction of Identifiable Information

*One of the following must be checked.*

☐ No identifiable information is recorded at any point in this research.

☐ Identifiable information will be destroyed. → *Specify at what point in the research process identifiable information about participants will be destroyed. One of the following must be checked:*

- ☐ Upon completion of procedures requiring use of identifiers *(i.e. compensation, data linkage, etc.)*
- ☐ After all data collection/cleaning/transcription is complete
- ☐ At the time of study closure/once study is complete
- ☐ Other, describe below:

☒ Identifiable information will not be destroyed.
*If checked, explain the rationale for retaining identifiers indefinitely and specify if identifiers will remain linked to research data (either directly or indirectly via a code key).*

For patients enrolled, we will keep their identifiable information in case of audit readiness and reporting by review boards. Identifiers will be indirectly linked to the study data via a secure linking log that associates participant names with subject ID numbers. This log is necessary for data entry validation, audit trails, and regulatory compliance. It will be stored exclusively on UT Austin's encrypted and access-controlled servers, and access will be restricted to IRB-approved study personnel. Identifiable information will not be included in the primary study dataset used for analysis, and all identifiers will be destroyed following study closeout in accordance with UT data retention policies and IRB protocol. All study data used for analysis will be de-identified, and the linking log will be stored separately from the dataset to maintain confidentiality.

## Data Sharing & Future Use

**51. Data Sharing and Future Use**

*Check the box below that best describes your plans for use and sharing of data beyond the scope of the current research. You are strongly encouraged to consider the broadest possible future plans you might have.* ***One of the following must be checked.***

☐ There are no plans to use or share data/specimens for other research purposes not related to this study. → *skip to item 53*

☒ Data/specimens may be shared with other researchers or banked (by this study team or other researchers) for future research purposes not related to the current research. → *address the following:*

**51a. Select which data sharing plans/future uses apply:**

*"Coded" refers to data that is indirectly identifiable via a code key that links study ID#s back to participant identifiers. Ensure this aligns with the description of future use in the consent form(s), when applicable.*

☒ Anonymized data/specimens may be shared or banked for future research → *skip to item 53*
☐ Coded data/specimens may be shared or banked for future research → *complete section 52*
☐ Identifiable data/specimens may be shared or banked for future research → *complete section 52*

**52. Data Registry/Specimen Repository (Details)**

*Select all that apply.*

☐ Contributing data/specimens to an existing registry/repository → *describe this registry below; if this registry is maintained by UT researchers, provide the IRB Study ID# and/or the registry name and Principal Investigator responsible for the registry:*

☐ Creating a new registry/repository → *complete the following:*

**52a. Describe the intended purpose and target area(s) for this registry:**

**52b. Describe any options that will be provided to participants to stipulate future use of their data/specimens. If participants will be given the option to be contacted regarding future uses, describe the procedure(s) for this contact.**

*Be sure to include all options and stipulations in the consent form(s). If no stipulations or future contact will be offered, explain this below.*

**52c. Who will be allowed access to registry data/specimens?**

☐ Only the PI of this study and/or other members of the current study team → *skip to item 53*

☐ Other researchers will be able to request data/specimens from the registry → *below, describe how other researchers will be able to request data/specimens from the registry, what criteria will be used to approve such requests (e.g., IRB approval, application process), and what methods will be used to release data/specimens to other researchers securely:*

# Conflicts of Interest

*Please confirm that all research personnel who meet the definition of "covered individuals" are designated as such in the Local Study Team Members section of the SmartForm application in UTRMS-IRB.*

## 53. Financial Conflicts of Interest

*Financial interest includes utilizing your licensed intellectual property in the study; serving as a paid consultant, or advisory board member, or officer/director with a related entity; and equity or business ownership in a company that is related to this project. Additional guidance on financial conflicts of interest is available on the COI website.*

*One of the following must be checked.*

☒ To the best of your knowledge, no one on the study team has a financial interest related to this study.

☐ The PI and/or other covered individual(s) has/have a financial interest related to this study.

*If so, please provide the name(s) of the covered individuals involved, and briefly describe the interest:*

## 54. Non-financial Conflicts of Interest

*Non-financial Interests could include such things as:*
*- utilizing your unlicensed intellectual property in the study,*
*- serving as an unpaid advisory board member or officer/director with a related entity,*
*- equity or business ownership in a company that has yet to make a profit and is related to this project,*
*- conflict of time/effort,*
*- personal and professional relationships/affiliations,*
*- personal beliefs/feelings impacting ability to conduct the study without bias,*
*- any other factors that could create bias in the study*

*One of the following must be checked.*

☒ To the best of your knowledge, no one on the study team has non-financial interest related to this study.

☐ The PI and/or other covered individual(s) has/have a non-financial interest related to this study.

*If so, please provide the name(s) of the covered individuals involved, and briefly describe the interest:*