A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder

PI: James Murrough
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CLINICAL RESEARCH PROTOCOL

TITLE: **A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder**

SPONSOR: **James W. Murrough, MD, PhD**
Icahn School of Medicine at Mount Sinai
New York, New York

National Institute of Mental Health
National Institutes of Health

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Approval:

Effective Date: 9/30/2025
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PI or Sponsor Signature (Name and Title) Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Sponsor (Dr. James Murrough) with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 20-01383
Protocol Title: A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder

Protocol Date: 3/30/2022

_____ _____
Investigator Signature Date

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List of Abbreviations

ACC	Anterior cingulate cortex
AE	Adverse Event
ATRQ	Antidepressant Treatment History Questionnaire
AUA	American Urological Association
BPRS	Brief Psychiatric Rating Scale- 4 item
CFR	Code of Federal Regulations
CGI	Clinical Global Impression Scale
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-reactive protein
C-SSRS	The Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DS	Dorsal Striatum
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-fifth
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture System
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act of 1996
fMRI	functional Magnetic Resonance Imaging
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ITT	Intent-to-Treat
IFT	Incentive Flanker Task
IRB	Institutional Review Board
MADRS	Montgomery-Asberg Depression Rating Scale
MAR	Missing at Random
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MNAR	Data Missing is Not at Random
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NAc	Nucleus Accumbens
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
PI	Principal Investigator
PK	Pharmacokinetic
PRT	Probabilistic Reward Task



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QIDS-SR	The Quick Inventory of Depressive Symptomatology, Self-Report
SAE	Serious Adverse Event
SCID-5-RV	Structured Clinical Interview for DSM-5 Research Version
SHAPS	Snaith-Hamilton Pleasure Scale
TEPS	Temporal Experience of Pleasure Scale
UP	Unanticipated Problem
VS	Ventral Striatum
WHO	World Health Organization

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Protocol Synopsis

TITLE	A Proof of Concept Randomized Controlled Trial of XEN1101 for the Treatment of Major Depressive Disorder
SPONSOR	James W. Murrough, MD, PhD
FUNDING ORGANIZATION	National Institutes of Health (NIH) National Institute of Mental Health (NIMH)
NUMBER OF SITES	2
RATIONALE	Major Depressive Disorder (MDD) is one of the most disabling medical conditions worldwide and currently available treatments fall short of addressing this large public health burden. Dysfunction within the brain reward system is a core feature of depressive disorders, leading to symptoms including anhedonia. Evidence from preclinical studies has highlighted a KCNQ type of neuronal potassium (K+) channel (KCNQ2/3) as a novel target for the treatment of depressive disorders. Data from our NIMH R61 randomized clinical trial testing the KCNQ2/3 channel opener ezogabine (i.e. retigabine) suggests that targeting the KCNQ2/3 channel may be beneficial for the treatment of depression and anhedonia. Building on these data, the current project will assess change in depressive symptoms, anhedonia, and brain reward function following treatment with XEN1101 or placebo in participants with depression and anhedonia, and will examine the relationship between change in clinical symptoms and reward circuit activity. XEN1101 is a novel positive allosteric modulator ("opener") of the KCNQ2/3 channel developed by Xenon Pharmaceuticals for the treatment of epilepsy, with a MOA similar to ezogabine.
STUDY DESIGN	This is a phase II, randomized, parallel-arm, placebo-controlled clinical trial.
PRIMARY OBJECTIVE	To investigate the effect of XEN1101 on brain measures of reward (e.g. fMRI with reward task).
SECONDARY OBJECTIVES	To test the effect of XEN1101 compared to placebo on clinical measures of depression and anhedonia..
SAFETY OBJECTIVES	To assess the safety and tolerability of XEN1101 (up to 20 mg daily) for 8 weeks in individuals with MDD.
NUMBER OF PARTICIPANTS	N=60 participants with MDD will be randomized in a 1:1 fashion to XEN1101 (N=30) or matching placebo (N=30).
PARTICIPANT SELECTION CRITERIA	Inclusion Criteria: Participants will be aged 18-65 years, with clinically significant anhedonia (Snaith-Hamilton Pleasure Scale [SHAPS] ≥ 20), a current diagnosis of Major depressive disorder (MDD) according to DSM-5 and at least moderate current illness severity (Clinical Global Impression–Severity [CGI-S] Scale ≥ 4).

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	Exclusion Criteria: A primary psychiatric diagnosis other than MDD as defined by DSM-5, neurocognitive disorder, substance use disorder within the past 6 months, contraindication to MRI, and any unstable medication condition or any other condition that in the opinion of the investigator would compromise the safety of the participant or the quality of the data.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	XEN1101 capsules of 10 mg strength will be used in this study. Participants randomized to XEN1101 will ingest two capsules once daily for a total daily dose of 20 mg. In the event that an individual does not tolerate the 20 mg dose, the dose may be decreased to 10 mg once daily. Individuals who do not tolerate 10 mg daily will be discontinued from the study drug.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	The placebo product used in this study will be manufactured according to GMP and will contain inert substances (microcrystalline cellulose). Product will be administered orally.
DURATION OF PARTICIPATION AND DURATION OF STUDY	Participants will be in the study for up to 18 weeks. **Screening Period:** up to 6 weeks. **Treatment Period:** 8 weeks of treatment with XEN1101 20 mg daily or matching placebo. Assessment visits will occur weekly for the first two weeks following randomization and then biweekly until the primary outcome End of Treatment (EOT) visit at week 8. **Study Exit:** A study exit visit that includes medical and psychiatric assessments will be conducted 4 weeks following the EOT visit. The total duration of study enrollment is expected to be 24 months.
CONCOMMITANT MEDICATIONS	Participants will need to be free of prohibited medications as per the study protocol. In particular, participants will be required to be free of concomitant antidepressant agents and other psychotropic medications, including mood stabilizers and antipsychotic medication.
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	Change in bilateral ventral striatum activity as assessed by fMRI during the Incentive Flanker Task (IFT) from baseline (week 0) to end of treatment (week 8)
SECONDARY ENDPOINTS	• Change in depression severity as measured by the Montgomery-Asberg Depression Rating Scale or MADRS at baseline and 2-week intervals over 8 weeks from randomization.

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	• Change in clinical symptoms of anhedonia as measured by Snaith-Hamilton Pleasure Scale or SHAPS at baseline and 2-week intervals over 8 weeks from randomization.
OTHER EVALUATIONS	Symptoms of depression will be measured with the Quick Inventory of Depressive Symptomatology, Self-Report or QIDS-SR. Symptoms of anhedonia will also be measured with the Temporal Experience of Pleasure Scale or TEPS, a self-report instrument assessing pleasure experience. The TEPS is scored with two sub-scores (consummatory and anticipatory). We will also explore changes in global illness improvement and severity through The Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression - Severity (CGI-S). In the same manner as the primary endpoint, fMRI activation in other regions of the reward cortico-striatal circuit will be measured during the gain cue of the IFT and contrasted with neutral cue at baseline and week 8 post-randomization. Behavioral task outcomes will be measured with the Probabilistic Reward Task or PRT to assess reward bias and the Stock market task to assess value signal and reward prediction errors. Plasma concentration of XEN1101 and its metabolites will be determined at week 1 and week 8.
SAFETY EVALUATIONS	The incidence and frequency of all anticipated and unanticipated serious and non-serious adverse events (AEs) that occur between randomization and 12 weeks after randomization will be determined. The Columbia-Suicide Severity Rating Scale or C-SSRS will be collected as a safety endpoint for changes in suicidal ideation at baseline, weeks 1, 2, 4, 6, 8, and 12 post-randomization. The Brief Psychiatric Rating Scale- 4 item (BPRS-4) is used to assess acute behavioral changes during the administrations of the scale. This will be measured at baseline, weeks 1, 2, 4, 6, 8, and 12 post-randomization. The American Urological Association Symptom Score Questionnaire (AUA) is an index used to determine the presence and severity of urinary retention symptoms. It will be measured at baseline, weeks 4, 8 and 12 post-randomization. Emergent assessments from clinical laboratory tests (comprehensive metabolic panel, complete blood count, and thyroid stimulating hormone), vital signs (temperature, heart rate, and blood pressure), electrocardiograms, and physical examinations of the major body systems will be collected and reported.

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PLANNED INTERIM ANALYSES	None / Not applicable
STATISTICS **Analysis Plan**	The primary endpoint is the change in activation of the bilateral VS, a region of the rewards circuit in the brain. A mixed model with random intercept will be used to compare change in bilateral VS from baseline to week 8 between XEN1101 and placebo. The covariates in the model will include treatment, time and an interaction between treatment and time. Due to the small sample size, no additional covariates will be included. The analyses will be conducted at a two-sided 0.10 significance level in the ITT population. For the secondary measures, changes in MADRS and SHAPS over time across baseline, weeks 2, 4, 6, and 8 will be compared between randomization groups using a mixed model with random intercept and possibly random slope. The analyses will be conducted at a two-sided 0.10 significance level in the ITT population. All other evaluations will be considered exploratory and no formal hypothesis testing will be done.
Rationale for Number of Participants	In order to compare the effect of XEN1101 compared to placebo, we will use prior estimates of ventral striatum, the primary outcome, from the R61 trial with ezogabine and placebo of the mean difference between baseline and week 5 for ezogabine of 0.323 and for placebo of -0.1395. We assumed the variance of the random intercept of 0.1352 and residual variance of 0.3646. Using a random intercept model and assuming power of ≥80% and two-sided significance level of 0.10, for n=25 per group, we would be able to detect a difference between placebo and XEN1101 of 0.4 to 0.6, which is close to prior study estimates of 0.5. In addition, in order to handle uncertainties in recruitment at each site or at least a 20% dropout rate with 25 subjects/group, we will plan to enroll a total of 60 subjects or 30 subjects/group and be well powered to detect this difference.

1. Background

XEN1101 is a novel positive allosteric modulator ("opener") of the potassium channel KCNQ2/3 (Kv7.2/7.3) currently being developed by Xenon Pharmaceuticals Inc. for the treatment of partial onset (focal) epilepsy. XEN1101 shares a similar mechanism of action (MOA) to ezogabine (a.k.a. retigabine), an earlier generation Kv7 modulator that was approved by the Food and Drug

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Administration (FDA) as an adjunctive treatment for adults with focal seizures with or without secondary generalization. By activating KCNQ channels, it is thought to stabilize the resting membrane potential and reduce brain excitability. XEN1101 was designed to improve upon potency, selectivity and pharmacokinetics of ezogabine, and is not expected to have ezogabine's composition-specific tissue pigmentation effects.

1.1. Overview of Non-Clinical Studies Implicating KCNQ Channels in Depressive Phenotypes

Pre-clinical work demonstrates a causal role for the KCNQ-type K+ channel in reversing depressive phenotypes following social defeat stress (Chaudhury et al. 2013; Friedman et al. 2014). Mice manifesting the depressive/anhedonic phenotype (compared to resilient mice) show a failure to increase KCNQ channel activity within the ventral tegmental area (VTA) – Ventral Striatum (VS) reward circuit. This susceptible phenotype can be reversed through (a) overexpression of KCNQ channels, (b) direct VTA injection of KCNQ channel openers, or (c) peripheral injection of KCNQ channel openers. Remarkably, repeated peripheral daily administration of the KCNQ channel opener ezogabine completely reversed the depressive/anhedonic phenotype in susceptible mice. These results provide a direct validation of KCNQ channel openers as a completely novel class of antidepressants that have been investigated by our group in two humans trials described below.

1.2. Non-Clinical Studies of XEN1101

XEN1101 has been shown effective in several in vivo rodent models of electrically and chemically induced seizures and exhibits a selectivity for Kv7 channels over other ion channels and receptors. Moreover, XEN1101 was found to be relatively more selective for Kv7.2/7.3 over Kv7.3/7.5 and Kv7.4 channels, relevant for the efficacy and safety profile of the drug. In vitro studies suggested a low potential for drug-drug interactions through the inhibition of the cytochrome isoenzymes and data from studies in nonhuman primates showed a favorable pharmacokinetic profile. Phase I studies in humans have also been completed and are described below in paragraph 1.4 Overview of Clinical Studies of XEN1101.

1.3. Overview of Clinical Studies of Ezogabine in Depressive Phenotypes

In order to test the hypothesis that increasing KCNQ channel signaling can be beneficial for participants with depression and anhedonia, we conducted a series of two studies of the first-in-class KCNQ2/3 channel opener ezogabine. Ezogabine was marketed in the U.S. as adjunctive therapy in partial-onset seizures and its safety was established in 3 multicenter, randomized, double-blind, placebo-controlled studies in 1,239 adult participants (Ezogabine product information). The drug has since been voluntarily withdrawn from the market by the manufacturer due to low clinical utilization.

We conducted a first open-label proof-of-concept study on eighteen medication-free individuals with Major Depressive Disorder (MDD) in a major depressive episode (MDE) who received

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ezogabine up to 900 mg/day orally (within the approved range for seizure disorder) over the course of ten weeks. Resting state functional magnetic resonance imaging (fMRI) data were collected at baseline and post-treatment to examine brain reward circuitry. Reward learning was also measured using a computerized probabilistic reward task (PRT). After treatment with ezogabine, participants exhibited a significant reduction of depressive symptoms Montgomery–Åsberg Depression Rating Scale (MADRS) score change: −13.7±9.7, p<0.001, d=2.08] and anhedonic symptoms (Snaith-Hamilton Pleasure Scale (SHAPS) score change: −6.1±5.3, p<0.001, d=1.00), which remained significant even after controlling for overall depression severity. Improvement in depression was associated with decreased functional connectivity between the ventral caudate and clusters within the mid-cingulate cortex and posterior cingulate cortex (n=14, voxel-wise p<0.005), regions associated with reward and emotional processing. In addition, a subgroup of participants tested with a PRT showed increased reward learning following treatment.

Building on these results we then conducted a two-site randomized, placebo-controlled, clinical trial testing the effect of ezogabine on reward circuit activity and clinical outcomes in participants with depression funded by the National Institutes of Health (NIH). Forty-five depressed individuals were randomly assigned in a 1:1 ratio to a 5-week treatment period with ezogabine (target dose of 900 mg daily; N=21) as monotherapy or placebo (N=24). All randomized participants underwent fMRI during a reward incentive flanker task [IFT, a variant of the monetary incentive delay task (MID)] at baseline and following the treatment period and completed clinical assessments of depression and anhedonia symptoms at weekly visits. Relative to placebo, ezogabine was associated with a significantly larger improvement in MADRS (score change: -7.9±3, p<.001), SHAPS (score change: -6.9±3.2, p<.001), and other clinical endpoints. The ezogabine group also showed a trend towards the hypothesized increase in ventral striatum (VS) response to reward anticipation, compared to placebo from baseline to week 5 (t=1.85, DF=38, p=.07). The effect size for the mean difference between treatment groups on change in VS response was 0.58. In both trials, ezogabine was well tolerated and no serious adverse events occurred. Overall, our preliminary data are consistent with the ability of ezogabine to modulate reward circuit activity in humans and the plausibility of KCNQ potentiation as a novel treatment approach for depression and reward alterations.

1.4. Overview of Clinical Studies of XEN1101

Phase 1 (XPF 008 101a) and Phase 1b studies (XPF-008-101b) of XEN1101 in humans have already been completed and a Phase 2b clinical trial (XPF-008-201) in adult participants with focal epilepsy are currently ongoing. Participants in the XPF-008-101a study were exposed to single XEN1101 doses of 5, 10, 15, 20, 25, and 30 mg and repeat doses of 15 and 25 mg once daily (QD) for up to 10 days. Food has been found to enhance absorption, preferentially in participants with poor absorption in the fasted state. XEN1101 was absorbed relatively slowly (median T_{max} of 2-8 hours), displayed a long terminal elimination half-life (approximately 4-10 days), but reached near steady-state trough plasma levels approximately 1 week after dosing. XEN1101 was well tolerated with single and multiple doses up to 30 and 25 mg QD, respectively, with the majority

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of reported adverse events (AEs) being mild and reversible in healthy volunteers. The most common related AEs affected the central nervous system (CNS) and were consistent with anti-seizure medications (e.g. sedation, dizziness, and headache). The phase 1b study was conducted on N=20 healthy male volunteers and investigated the safety, tolerability, and pharmacodynamic profile of single doses of XEN1101 (20 mg) using a randomized, double-blind, placebo-controlled, two-period crossover design. Significant concentration related effects on cortical excitability were seen as quantitatively assessed through the use of transcranial magnetic stimulation with electroencephalography (TMS-EEG) techniques. Data available from this study show that the drug was overall safe and well tolerated. Compared to placebo, dizziness and somnolence were the most common related AEs. No SAEs or withdrawals due to AEs were reported. Moreover, no clinically significant changes in clinical laboratory evaluations, vital signs, or electrocardiogram (ECG) were detected.

The proposed project takes advantage of the availability of XEN1101 for human use to test the hypothesis that enhanced function of the KCNQ2/3 channel may represent a novel approach for the treatment of depression. This approach is hoped to speed novel drug discovery since crucial knowledge concerning pharmacokinetics (PK), toxicology, brain exposure and safety has already been established for XEN1101, thereby considerably de-risking its development.

2. STUDY RATIONALE

Major Depressive Disorder (MDD) is one of the most disabling medical conditions worldwide and currently available treatments fall short of addressing this large public health burden. Dysfunction within the brain reward system is a core feature of depressive disorders, in particular deficits in motivation, interest, and response to pleasure (e.g., anhedonia: markedly diminished response to pleasure). Evidence from a series of preclinical studies has highlighted a KCNQ subtype of neuronal potassium (K+) channel (KCNQ2/3) as a novel target for the treatment of depressive disorders. Data from our NIMH R61 randomized clinical trial (n=45) testing the KCNQ2/3 channel opener ezogabine shows an increased brain response to reward (as measured by fMRI) and a significant reduction in depressive and anhedonic symptoms following treatment with ezogabine compared to placebo. Building on these data, the current project will assess the effect of XEN1101 on activation within the bilateral ventral striatum (VS) as measured by fMRI during the Incentive Flanker Task (IFT). We will also assess change in depressive and other clinical symptoms following treatment with XEN1101 in depressed participants with anhedonia. XEN1101 is a novel positive allosteric modulator (“opener”) of the KCNQ2/3 channel developed by Xenon Pharmaceuticals for the treatment of focal epilepsy, with a mechanism of action (MOA) similar to ezogabine but with an advantageous PK and safety profile. Please see section 1 for additional background and rationale.

2.1. Risk / Benefit Assessment

Potential for Harms Related to Study Drug:

In the Phase I clinical studies, the majority of related adverse events were mild and CNS related and were consistent with this class of drugs. Sedation (including somnolence, drowsiness, etc.)

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and dizziness (including light-headedness and presyncope) were the most common AEs, while cognitive effects (e.g., memory and speech impairment) and blurred vision were also reported at doses of 15 to 25 mg of XEN1101. A higher incidence of moderate CNS AEs was reported with repeat dosing at 25 mg QD. Orthostatic hypotension (vasovagal reactions in association with blood draws) were seen in the first in human (FIH) study, but not in the TMS crossover study conducted at a different site. The most common adverse effects of XEN1101 in the TMS cross-over study were dizziness, somnolence and disturbance in attention (Premoli et al. 2019). The detailed safety profile of XEN1101 observed in the Phase I clinical studies is provided in the Investigator's Brochure. The Investigator will also monitor each participant for clinical and laboratory evidence for predefined adverse events of special interest (AESIs) throughout the participant's participation in this study. These events include disturbances in thinking and perception, urinary retention, cardiovascular changes (EKG changes), and ophthalmologic changes. Please see section 11.3 for more information regarding these events. Below we summarize the risks of the study drug and strategies to mitigate risk. In addition, please see section 5.4 "Safety Evaluation" for additional description of study safety evaluations.

Suicidality:
Antiepileptic drugs (AEDs), including ezogabine, have been found to increase the risk of suicidal thoughts or behavior in pooled analyses. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy) of 11 different AEDs showed that participants randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal thinking or behavior compared to participants randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated participants was 0.43% compared to 0.24% among 16,029 placebo-treated participants, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 participants treated. There were 4 suicides in drug-treated participants in the trials and none in placebo-treated participants, but the number is too small to allow any conclusion about drug effect on suicide.

Suicide ideation and behavior will be monitored during the length of the study through clinical assessments at screening and exit visits, and weekly during the treatment period. The Columbia Suicide Severity Rating Scale (C-SSRS) will also be conducted at each study visit to monitor suicidal ideation and behavior. If, at any point during the clinical trial, a participant will be assessed with a suicidal ideation with any intent or plan, as measured by a C-SSRS score of greater than 2 during the past week, a safety review will be performed by the site PI, or his designee. See section 5.4.4 "Safety Review" for additional information.

Potential for Unforeseen Risks:
In addition to the risks described above, there may be other risks associated with XEN1101 that are currently unknown.

Potential for Harms Unrelated to Study Drug:
The following additional sources of potential discomfort or harm could also occur:

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- Psychological Screening: Participants that meet exclusion criteria (e.g. positive pregnancy test) may become distressed when informed. All information will be shared in a private office with the door closed and a trained study team member will be available to offer information, support, and referral for any services indicated.
- Venous Puncture: Participants may experience minor discomfort or pain when a needle is used to draw blood. Bruising, infection, and dizziness are also common side effects. Risks of venipuncture are minimized by having experienced nursing personnel who will perform the procedure. Infection is avoided by adequate cleansing of the skin prior to intravascular line insertion.
- fMRI Scans: The fMRI procedure is very safe and exposes the study participants to minimal risk or discomfort. The MRI scanning involves the participant placing their head in a tube and some participants may experience a feeling of claustrophobia while in the scanner. However, a study investigator will be present for all scanning sessions in case of any unexpected complications. In addition, the participant will remain in verbal contact with a study investigator (via intercom) throughout the procedure so that they may communicate immediately any problems or express a desire to terminate the scan at any time.
- Questionnaires: Some participants may experience psychological distress when asked to answer personal questions about their emotions. In this case, experimenters will remind participants that they can refuse to answer any upsetting questions. Clinicians will also be available to meet with any distraught individuals.
- Privacy risks: There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk. Please refer to page 40 section “Data Collection, Retention and Monitoring” for more details.

To protect participants from unknown risks we will not allow participants to participate in the study if they have: 1) any clinically significant abnormality on the screening tests; 2) any clinically significant history of medical, psychiatric, or substance use-related disorder other than a mood and anxiety spectrum disorder; 3) excessive alcohol intake or unwillingness to stop alcohol consumption for the duration of the study; 4) taken any prescribed or not prescribed medication prohibited by the protocol within 30 days of the first study visit, or need to continue any of the above mentioned medications during the study. For more details on study eligibility, see section 6 “Participant Selection”.

Benefits Assessments:

Participants may not receive any direct benefit from participating in this study. There is a small possibility that we may detect an unrelated medical condition during the procedures conducted in this study that could have health benefits for some individuals. Some individuals may experience improvement in their symptoms through participation in the study, though some are likely to remain the same and some may get worse due to the effects of the medication or due to the natural course of their illness. The information obtained from this study may help improve the treatment of future patients with MDD or other mood disorders. Since the available treatments for patients with MDD have significant limitations (Trivedi et al., 2006), this study has

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the potential to take steps to address these limitations by: 1) establishing that KCNQ channel modulators are a safe and efficacious treatment for MDD; 2) exploring the impact of the drug on a discrete brain circuit for reward 3) test a potential new class of treatments for an important medical problem, with significant impact on patients and on society; 4) exploring the impact of KCNQ channel modulators on behavioral and clinical measures of anhedonia and depression.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of the current study is to examine the effect of the KCNQ2/3 channel opener XEN1101 compared to placebo on change in activation within the bilateral ventral striatum (VS) in participants with MDD and elevated anhedonia (indexed by a score of ≥ 20 on the Snaith-Hamilton Pleasure Scale [SHAPS]). Two treatment conditions in a parallel arm design will be: (1) XEN1101 20 mg capsules daily, or (2) matching daily placebo capsules. The effect of XEN1101 on the VS will be assessed through the utilization of the Incentive Flanker Task during a functional MRI scan.

3.2. Secondary Objectives

Secondary objectives are to assess the effect of XEN1101 compared to placebo on clinical measures of depression (as assessed primarily by the Montgomery–Åsberg Depression Rating Scale [MADRS]) and anhedonia (as assessed by the SHAPS).

3.3. **Exploratory Objectives**

Exploratory objectives are to explore the effect of treatment on the following measures:

- Symptoms of self-reported depression measured with the Quick Inventory of Depressive Symptomatology, Self-Report or QIDS-SR.
- Additional symptoms of anhedonia will be measured with the Temporal Experience of Pleasure Scale or TEPS, a self-report instrument assessing pleasure experience. The TEPS is scored with two sub-scores (consummatory and anticipatory).
- We will also explore changes in global illness improvement and severity through The Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression - Severity (CGI-S).
- In the same manner as the primary endpoint, fMRI activation in other regions of the reward cortico-striatal circuit will be measured during the gain cue of the IFT and contrasted with neutral cue at baseline and week 8 post-randomization.
- Behavioral task outcomes will be measured with the Probabilistic Reward Task or PRT to assess reward bias and the Stock market task to assess value signal and reward prediction errors.

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4. STUDY DESIGN

4.1. Study Overview

This is a proof of concept multi-site, phase II, double-blind randomized, parallel-arm, placebo-controlled clinical trial. Individuals with a primary diagnosis of major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) will be enrolled.

Each participant will be randomly assigned to one of the treatment arms in a 1:1 fashion under double-blind conditions; randomization will be under the direction of the coordinating center and stratified by center. Screening data will be reviewed to determine participant eligibility. Participants who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. Each participant will receive one of the two experimental treatments and will take a daily dose of study drug or placebo for 8 weeks. Evaluations will be taken at screening, baseline (week 0), weeks 1, 2, 4, 6, and 8 (primary outcome, end of treatment [EOT]), and at study exit. Please refer to **Table 3** "Schedule of Events."

The following treatment regimens will be used:

- Experimental treatment: XEN1101 10 mg capsules at the following doses; participants will be instructed to take two capsules once daily for a total daily dose of 20 mg. Participants who do not tolerate 20 mg daily may have their dose reduced to 10 mg daily.
- Placebo capsules

Total duration of participant participation be up to 18 weeks, including a screening period up to 6 weeks and a study exit visit to occur 4 weeks following discontinuation of the study drug.

Total duration of study enrollment is expected to be 24 months.

5. Criteria for evaluation

5.1. Primary Endpoint

The primary endpoint is the change in activation within the bilateral ventral striatum (VS) from baseline to week 8 post-randomization as measured by fMRI during the Incentive Flanker Task (IFT). VS activation for each participant will be calculated as a contrast between gain and neutral cues to model reward anticipation. The right and left VS will be averaged into a single bilateral region of interest as there are no laterality hypothesis regarding effect of treatment on the VS.

5.2. Secondary Endpoints

The trial has two secondary endpoints:

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- Change in depression severity as measured by the Montgomery-Asberg Depression Rating Scale or MADRS (Montgomery and Asberg, 1979) at baseline and 2-week intervals over 8 weeks from randomization.
- Change in clinical symptoms of anhedonia as measured by Snaith-Hamilton Pleasure Scale or SHAPS (Snaith et al, 1995) at baseline and 2-week intervals over 8 weeks from randomization.

5.3. Exploratory Endpoints

5.3.1. Clinical Outcomes

Symptoms of depression will be measured with the Quick Inventory of Depressive Symptomatology, Self-Report or QIDS-SR (Rush et al, 2003). The QIDS will be collected at baseline, weeks 2, 4, 6 and 8 post-randomization.

Symptoms of anhedonia will also be measured with the Temporal Experience of Pleasure Scale or TEPS (Gard et al, 2006), a self-report instrument assessing pleasure experience. The TEPS is scored with two sub-scores (consummatory and anticipatory). The TEPS will be collected at baseline, weeks 2, 4, 6 and 8 post-randomization.

We will explore changes in global illness improvement and severity through The Clinical Global Impression – Improvement (CGI-I) and Clinical Global Impression - Severity (CGI-S). The scales will be collected at baseline, weeks 2, 4, 6 and 8 post-randomization.

5.3.2. fMRI Activation within the Reward Circuit

In the same manner as the primary endpoint, fMRI activation in other regions of the reward cortico-striatal circuit (medial prefrontal cortex (mPFC), bilateral dorsal striatum (DS), and anterior cingulate cortex (ACC)), as well as whole-brain analyses, will be measured during the gain cue of the IFT and contrasted with neutral cue at baseline and week 8 post-randomization. Similarly, activation during the loss cues compared to neutral cues during the IFT task will be computed.

5.3.3. Behavioral Task Outcomes

Behavioral task outcomes will be measured with the Probabilistic Reward Task or PRT (Pizzagalli, 2008) to assess reward bias and the Stock market task (Gu et al, 2014) to assess value signal and reward prediction errors. These will be captured at both baseline and week 8 post-randomization.

During the PRT, participants must discriminate between two ambiguous stimuli, displayed rapidly on a computer screen, in order to receive a monetary reward. Unbeknownst to the participants, correct identification of one stimulus is reinforced three times more frequently than the other stimulus. Under these experimental circumstances, healthy participants reliably develop a response bias (that is, preference) for the stimulus that is reinforced more frequently, regardless

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of which stimulus was actually presented. Thus, reward responsiveness assessed in this task reflects the rapid shaping of future behavioral choices based on prior reinforcement experiences. Participants with MDD and healthy participants with elevated depressive symptoms fail to develop this biased response for the more frequently reinforced stimulus, and tend to respond similarly to both stimuli, reflecting decreased responsiveness to rewards.

The Stock market task is designed to delineate two distinct computationally defined learning signals: value signal (i.e. % gain or loss in market value) and reward prediction errors (RPE; positive if outcome is better than predicted, or negative if outcome is worse than predicted). The participant's task is to make sequential investment decisions. The use of this task will allow us to quantify reward behavior for the purpose of computational modeling. This outcome will be considered exploratory.

5.3.4. Other Exploratory Endpoints

The plasma concentration of XEN1101 and its metabolites will be determined at week 1 and week 8 and reported.

5.4. Safety Evaluations

Safety will be monitored by the evaluation of potential adverse events, clinical rating assessments, clinical laboratory test results, vital signs measurements, ECG, and physical examination. Below, we outline specific safety evaluations conducted as part of the study protocol. In addition to the procedures described above, the following procedures are performed as part of the study safety evaluations. Medical history, current and past physical and psychiatric history, venous blood sampling for clinical laboratory tests (comprehensive metabolic panel, CBC, TSH), vital signs, urine toxicology, pregnancy test (if applicable), fundoscopic examination, and ECG will be performed by qualified staff.

5.4.1. Adverse Events

The incidence and frequency of all anticipated and unanticipated serious and non-serious adverse events (AEs) that occur between randomization and 12 weeks after randomization will be determined. AE seriousness, severity/grade, relatedness and expectedness will be assessed by a study physician delegated under the protocol to carry out study procedures.The Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms will be recorded for each reported AE.

5.4.2. Clinical Safety Assessments

Monitoring for Suicidal Ideations or Behaviors: The Columbia-Suicide Severity Rating Scale or C-SSRS (Posner et al, 2007) will be collected as a safety endpoint for changes in suicidal ideation at baseline, weeks 1, 2, 4, 6, 8, and 12 post-randomization. If, at any point during the clinical trial, a participant is assessed with a suicidal ideation with any intent or plan, as measured by a C-SSRS

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score of greater than 2 since the last visit, the site PI, or his designee, will conduct a safety review. See section 5.4.4 “Safety Review” for additional information.

Monitoring for the Emergence of Psychosis: The Brief Psychiatric Rating Scale- 4 item (BPRS-4) will be used to assess acute behavioral changes indicative of psychosis including conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content (Overall and Gorham, 1962) at baseline, weeks 1, 2, 4, 6, 8, and 12 post-randomization. Should a participant indicate the emergence of psychosis throughout the course of the trial as measured by a BPRS-4 item score of greater than 2, the site PI, or his designee, will conduct a safety review. See section 5.4.4 “Safety Review” for additional information.

Monitoring for Urinary Retention: The American Urological Association Symptom Score Questionnaire (AUA) is an index used to determine the presence and severity of urinary retention symptoms. It will be measured at baseline, weeks 4, 8 and 12 post-randomization. If, at any point during the clinical trial following participant randomization, a participant scores greater than 7 on the AUA and this score marks an increase from baseline, the site PI, or his designee, will conduct a safety review. See section 5.4.4 “Safety Review” for additional information.

5.4.3. Other Assessments

Emergent assessments from clinical laboratory tests (comprehensive metabolic panel, complete blood count, and thyroid stimulating hormone), vital signs (temperature, heart rate, and blood pressure), electrocardiograms, ophthalmologic examinations, and physical examinations of the major body systems will be collected and reported.

5.4.4. Safety Review

If indicated, a safety review will consist of a separate review of safety and well-being of the participant by the site PI or his designee. This review will be documented by a Safety Review Form (SRF) that will be filed in the participant binder or the EDC and that will consist of a brief description of the case and of the event that triggered the review. Outcome of the review will be the decision whether to continue the participant at the current dose, dose adjust the participant to the lower dosage of 10mg daily, or discontinue the participant from the study drug (if this is the case, appropriate clinical care will be provided). In the eventuality the event satisfies the definition of an adverse event (AE) or of a serious adverse event (SAE), it will be reported accordingly. All safety reviews will be sent to the medical monitor for oversight. In the instance of an adverse event of special interest (AESI), the study team will follow procedures outlined in section 11.3 of the protocol. All AESIs and resolution per protocol will be reported to the medical monitor. See section 11.7 “Medical Monitoring” for additional detail on the role of the medical monitor.

6. PARTICIPANT SELECTION

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6.1. Study Population

Participants who meet DSM-5 criteria for major depressive disorder at the time of screening and meet the inclusion and exclusion criteria will be eligible for participation in this study.

Recruitment feasibility: The research plan calls for the randomization of n=60 participants ages 18-65 with a primary diagnosis of current MDD and significant anhedonia across the two performance sites (ISMMS and BCM) over a 24-month recruitment period, which is ~1.3 participants randomized per month per site. This is a feasible goal based on current participant flow at the two sites, and our demonstrated track record of enrollment at similar rates in prior studies recruiting from similar populations.

6.2. Inclusion Criteria

1. Written informed consent (and assent when applicable) obtained from participant
2. Ability for participant to comply with the requirements of the study as determined by the PI;
3. Men and women, age 18-65 years;
4. Participants must meet DSM-5 criteria for current depressive disorder (major depressive disorder [MDD]) in a major depressive episode (MDE) as determined by a study psychiatrist and confirmed using the Structured Clinical Interview for DSM-5 Research Version (SCID-5-RV);
5. Clinically significant anhedonia as determined by a SHAPS score ≥ 20 at screening;
6. Current illness severity is at least moderate, defined as a score of ≥4 on the CGI-S Scale;
7. If female of childbearing potential, must agree to use of a medically accepted form of contraception*, or else agree to abstinence until 3 months after the last dose of study drug.

6.3. Exclusion Criteria

1. A primary psychiatric diagnosis other than MDD as defined by DSM-5;
2. Has a history of schizophrenia or other psychotic disorder, major depressive disorder with psychotic features, or bipolar I or II disorder;
3. History of non-response to >4 adequate antidepressant trials in the current episode as determined by the Antidepressant Treatment Response Questionnaire (ATRQ);
4. History of non-response to electroconvulsive therapy in the current depressive episode;
5. A current diagnosis of depression with peripartum onset;
6. Diagnosis of a major neurocognitive disorder;
7. Meets criteria for a substance use disorder within the past 6 months, with the exception of nicotine use disorder;
8. Participant shows clinically significant retinal macular disease, or retinal pigment epithelium abnormality prior to randomization.
9. Male participants, if heterosexually active with partner who is female of childbearing potential, pregnant, or breastfeeding, who are unwilling to agree to barrier contraception for the treatment period and for at least 3 months after the last dose of study drug. Female partners of male participants who are unwilling to use at least one form of highly effective

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contraception starting at least one cycle prior to male participant study drug initiation until 6 months after the last dose of study drug.*

10. Female participants who are pregnant, breastfeeding, or may become pregnant, or unwilling to practice birth control during participation in the study or the 3 months following;*
11. Inability to swallow capsules;
12. Any contraindication to MRI including claustrophobia, any trauma or surgery which may have left magnetic material in the body, magnetic implants or pacemakers, and inability to lie still for 1 hour or more;
13. Positive urine toxicology screen for drugs of abuse at the time of screening**;
14. Use of any dis-allowed medication according to the study protocol***;
15. Serious and imminent risk of self-harm or violence as determined by the PI;
16. Extreme illness severity as defined by a CGI-S score ≥6;
17. Any current active suicidal ideation as measured by a Columbia Suicide Severity Rating Scale [C-SSRS] score of greater than 2 during the past month at the time of screening
18. History of suicide attempt in past 2 years;
19. Any unstable medical condition, including as follows;

    19.1. History of skin or retinal pigment epithelium abnormalities caused by ezogabine;
    19.2. Family history of sudden death of unknown cause;
    19.3. Clinically significant abnormalities of laboratory tests, physical examination, or ECG;
    19.4. History or presence of long QT syndrome;
    19.5. QT corrected by Fridericia's formula (QTcF) > 450 msec;
    19.6. Alanine transferase (ALT; SGPT) or aspartate transferase (AST; SGOT) levels >3 times the upper limit of normal (ULN) at screening;
20. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the participant or the quality of the data.

*Contraception Requirements
Female subjects must either be:

- Postmenopausal (as defined as amenorrhea for at least 12 months with no alternative medical cause for women aged 55 years or older, or amenorrhea for at least 12 months and confirmed by a follicle-stimulating hormone [FSH] result of ≥40 IU/L for women aged less than 55 years) or permanently sterile (permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy);
  OR
- Childbearing potential AND (if heterosexually active) agree to use at least 1 form of highly effective contraception as defined below, starting at least 1 menstrual cycle before the first dose of study drug, and continuing until at least 3 months after the last dose of the study drug.

Highly effective contraceptive methods for female subjects are as follows:

- Barrier method plus hormonal contraception

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  - The efficacy of hormonal contraceptives can be compromised by the co-administration of the study drug, therefore if combined or progesterone-only hormonal contraceptives are used, the subject must agree to use an additional barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm, or cervical cap with spermicide.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Male subjects:

- Male subjects, if heterosexually active with a female partner of childbearing potential, or a pregnant or breastfeeding partner, must agree to use barrier contraception (male condom) for the duration of the treatment period and for at least 3 months after the last dose of the study drug.
- Male subjects with female partners of childbearing potential must have that female partner use at least 1 form of highly effective contraception, as defined above, starting at least 1 menstrual cycle before (the male subject's) first dose of study drug and continuing until at least 3 months after their male partner's last dose of the study drug.
- Male subjects who have had a vasectomy.

**Participants with a positive urine drug screen for cannabinoids, barbiturates, opiates, or amphetamines may be allowed in the study provided that the drug was used for a documented, legitimate medical purpose and the use of such products has been discontinued (documented by a negative repeat test) prior to randomization.

***Potential participants will not be discontinued from medication for the purposes of this study. If a participant is taking a protocol dis-allowed medication at the time of screening, the participant may discontinue the medication under the supervision of their treating physician in the case that the participant is not benefiting from the medication or otherwise wishes to discontinue the medication. In no case will a dis-allowed medication be discontinued for the purpose of study participation if the participant is receiving clinical benefit from the medication.

7. Concurrent Medications

7.1. Allowed Medications and Treatments

Study participants are required to be free of antidepressant and other dis-allowed medication with CNS activity for a duration equivalent to 5 half-lives of the medication at the time of randomization. As needed (e.g., "PRN") use of non-benzodiazepine hypnotic agents (including zolpidem, zaleplon, eszopliclone, diphenhydramine, suvorexant, lemborexant, and ramelteon) or benzodiazepines not in excess of the equivalent of 2 mg of lorazepam daily will be allowed.

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Participants will be prohibited from taking as needed benzodiazepines or other as needed therapy with CNS activity on the day of study assessments. Participants receiving psychotherapy may continue to receive psychotherapy provided this therapy has been stable in terms of frequency for at least 2 months prior to screening and is expected to remain unchanged during the study treatment period. Between the primary outcome visit (week 8) and study exit visit (week 12), participants may be started on psychiatric medications as needed.

7.2. Prohibited Medications and Treatments

The following medications are not permitted for the duration of the study:

- Drugs of abuse or any prescribed or over-the-counter medication used in a manner that the Investigator considers indicative of abuse or dependence.
- Recreational or medicinal use of marijuana, cannabinoids and/or derivatives is not permitted
- Other investigational drug or device within five half-lives or 30 days prior to screening, whichever is longer
- Antidepressants
- Antipsychotics
- Anticonvulsant/Mood stabilizers
- Lithium
- Stimulants
- Opioids

See Table 4 “List of Prohibited Medications” for a complete list of all prohibited medications. The administrations of the cited medications will be considered a protocol violation. In the event that a participant is taking a prohibited medication at the time that consent is obtained, the participant will discuss with their treating physician if tapering from this medication is advised. While study physicians may discuss this process with the treating physician, any taper that takes place will be initiated and overseen by the treating physician. In the four weeks between primary outcome and study exit, however, participants may take any psychiatric medications indicated by their psychiatrist.

8. STUDY TREATMENTS

8.1. Method of Assigning Participants to Treatment Groups

Central randomization will be implemented in this study by the coordinating site. In total, N=60 eligible participants will be randomly assigned to XEN1101 (n=30) or placebo treatment (n=30) groups in a 1:1 ratio using a computer-generated randomization scheme developed by the coordinating site. Randomization will be stratified by clinical center and balanced across treatment groups using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the participant.

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8.2. Blinding

Participants who meet all entry criteria will be randomly assigned to one of the treatment arms, and assigned randomization numbers in consecutive order. The randomization list will be a computer-generated random-number list generated by the study statistician (who has no participant contact) at the coordinating site using a permuted block procedure and stratified by clinical center. The randomization list will be provided by the study statistician at the coordinating site to the research pharmacists at the coordinating and collaboration sites. Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or participants.

The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization code will be strictly controlled;
- Packaging and labeling of test and control treatments will be identical to maintain the blind;
- Investigators, study coordinators and all study personnel with study participant contact will remain blind to the treatment assignment.
- An unblinded data manager and statistician, who have no participant contact, will facilitate communications with the DSMB.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

Conditions Under Which the Study Blind May Be Broken

Unblinding by request of the PI or an Investigator should occur only in the event of an emergency or AE for which it is necessary to know the study drug assignment to determine an appropriate course of therapy for the participant. If the Investigator must identify the treatment assignment of an individual participant, the Investigator or qualified designee should request the treatment assignment from the research pharmacist. The Investigator is advised not to reveal the study drug assignment to other blinded site personnel.

It is anticipated that events that may trigger unblinding include:

- The adverse event is serious;
- The identity of the treatment assignment (e.g., drug or placebo) would be important to the evaluation and treatment of the adverse event; For example if a participant developed psychosis or suicidality, knowledge of the treatment assignment may influence the course of care;
- It will be potentially harmful to continue the study drug and to simultaneously treat the adverse event; For example if there is a risk of interaction between the study drug and a recommended treatment for the AE;

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Prior to unblinding, and if the situation allows, the Investigator should consult with the medical monitor. If this is impractical, the study team will provide medically appropriate care. The investigator will notify the medical monitor as soon as possible of any actions taken along with any unblinded information if unblinding occurs.

Medically necessary care should not be delayed for unblinding information (i.e., the Investigator should treat the participant based on the participant's signs/symptoms without waiting for the unblinding process to be completed). The Investigator must document the reason for breaking the blind within the EDC. Additionally, the Investigator should clearly explain the reasons for breaking the blind in the participant's source documents.

When a blind is broken, the participant will be withdrawn from the study drug. For participants who are unblinded and withdrawn from the study drug, an early exit visit should be completed as soon as possible.

Any reports related to this event submitted to regulatory agencies, including the IRB and DSMB, will be provided in a unblinded manner. The unblinded database manager will complete this submission so that blinding will be maintained for other personnel involved in the conduct of the study. The DSMB may request unblinded data at any time during the study.

8.3. Test and Control Formulation

XEN1101 is formulated as an immediate-release capsule filled with the micronized active pharmaceutical ingredient (API) XEN1101 (without excipients), suitable for oral administration.

XEN1101 will be supplied as opaque white (hydroxypropyl)methylcellulose (HPMC) capsules containing 10 mg XEN1101. The corresponding placebo drug product consists of identical-looking capsules filled with 10 mg of an inert material (microcrystalline cellulose). The IMP and placebo drug products will be packaged in sealed high-density polyethylene (HDPE) bottles.

The IMP and placebo drug products will be labeled in accordance with local laws and regulations.

8.3.1. Formulation of Test Product

XEN1101 is being developed by Xenon Pharmaceuticals Inc. for the treatment of focal epilepsy and is supplied as capsules filled with 10 mg of XEN1101 for oral administration. The capsules should be swallowed whole. XEN1101 is manufactured under cGMP according to currently established Specifications by Xenon Pharmaceuticals Inc.'s designated drug product manufacturer (Lonza, Tampa, FL, USA) and will be provided to the Research Pharmacies at both sites.

8.3.2. Formulation of Control Product

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The placebo drug product is supplied as capsules filled with 10 mg of microcrystalline cellulose for oral administration. The capsules should be swallowed whole. The placebo drug product is manufactured under cGMP according to currently established Specifications by Xenon Pharmaceuticals Inc.'s designated drug product manufacturer (Lonza, Tampa, FL, USA) and will be provided to the Research Pharmacies at both sites.

8.3.3. Packaging and Labeling

Study drug will be supplied by the research pharmacy at each site in the dosage prescribed by the PI or his designee (another study M.D. approved by the PI and the Institutional Review Board [IRB] for this role).

The drug product and placebo drug product will be packaged in sealed HDPE bottles.

The research pharmacy will generate the labels, and bottles will be labeled with an appropriate multi-language booklet, in compliance with applicable regulations for Investigational Drugs.

The following information, at a minimum, will be included on the labels:

- A statement indicating that the study drug is an investigational drug to be used only by a qualified Investigator (e.g., "for clinical trial use only")
- Study drug number
- Recommended storage conditions
- Name and address of the Sponsor
- Protocol number

8.4. Supply of Study Drug at the Site

XEN1101 will be provided by Xenon Pharmaceuticals and sent directly to the research pharmacy at each site. The initial study drug shipment will be shipped after site activation. Subsequent study drug shipments will be made after site request for resupply.

8.4.1. Dosage/Dosage Regimen

For the XEN1101 arm, participants will start at 20 mg (2 x 10 mg capsules) once daily (QD) at baseline and will remain at 20 mg QD until the end of treatment at visit 5 (week 8). If the 20 mg QD dosage is not tolerated, participants may reduce dosing to 10 mg QD dosage and will remain at 10 mg QD until the end of treatment at visit 5 (week 8). If participants continue to experience tolerability issues despite the dose reduction, they will be discontinued from study drug, but will remain in the study protocol.

Those assigned to receive placebo will receive capsules containing an inactive compound at a frequency comparable to those in active treatment (i.e. 2 capsules, 1 time per day). To assure the blindness of the trial, all placebo pills will look identical to XEN1101.

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8.4.2. Dispensing

The drug will be dispensed by the pharmacist of the research pharmacies of both study sites where it will be collected by study personnel. Only the research pharmacist at each site will know the true identity of the study pills for each participant.

8.4.3. Administration Instructions

At every study visit the participant will receive the study drug in bottles labeled with the protocol number, a treatment number, the name of the Sponsor, and directions for participant use and storage. The dosage will be prescribed by the PI or a study physician , according to the tolerability showed by the participant. The drug supply prescribed will be according to the length from the subsequent visits.

Participants will be instructed to take a single daily oral dose of either XEN1101 or placebo, at approximately the same time in the evening each day. As food enhances the absorption of XEN1101, it is recommended to take the study drug with the evening meal (e.g., either before, with or after the evening meal).

Participants will be instructed that if they miss a daily dose, to skip it and continue with the next dose as scheduled, and not to supplement a missed dose.

8.4.4. Storage

At the investigational site, the study drug must be stored at controlled ambient room temperature (15 °C to 25 °C, or 59 °F to 77 °F). While the study drug is being stored at the investigational site, excursions outside the temperature range must be recorded in the study documentation and reported to Xenon (or designee).

Participants will be instructed to store the study drug at ambient room temperature (15 °C to 25 °C, or 59 °F to 77 °F), protected from excessive heat or freezing and out of the reach and sight of children.

8.5. Study Drug Accountability

An accurate and current accounting of the dispensing of study drug for each participant will be maintained on an ongoing basis by a member of the study site staff. The investigational site must keep an accurate inventory of study drug shipments received and the amount of study drug dispensed per participant on the Investigational Drug Accountability Record. At the end of the study, a full reconciliation of drug inventory will be performed. After a full reconciliation, any unused study drug will be destroyed by study personnel (if the site has the capability to do so, in accordance with applicable regulations) or sent to Xenon or a designee for subsequent destruction. If no study drug remains, this will be indicated in the drug accountability log.

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8.6. Measures of Treatment Compliance

Subsequent to randomization, study participants are provided with study drug or placebo in identical packaging and sufficient medication to reach the next visit. Adherence to study drug will be measured throughout the study using pill count, participant diary, participant report, and drug plasmatic levels. Participants will be asked to keep a participant diary noting the date and time they take the study drug and any adverse effects. They will be asked to bring all used and unused study drug capsules and associated containers to on site study visits. A study team member will count the number of returned pills and record the number on the "Pill tracking log".

9. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is summarized in Table 3.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the participant.

9.1. Clinical Assessments

Concomitant Medications: All concomitant medication and concurrent therapies will be documented at screening and at each study visit, and at early termination when possible. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Demographics: Demographic information (date of birth, gender, race/ethnicity) will be recorded at screening.

Medical History: Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at screening.

Physical Examination: A complete physical and neurological examination, including non-dilated ophthalmoscopy exam, will be performed by qualified staff (MD, NP, RN, or PA) at screening, baseline (week 0), visit 1 (week 1), visit 2 (week 2), visit 3 (week 4), primary outcome (week 8), and study exit (week 12). New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit. If a novel adverse event is found at study exit, participants will be followed for up to 30 days or until resolved. Any potential retinal changes noted during a non-dilated physical exam will be verified by a staff ophthalmologist.

Dilated Fundoscopic exam: A dilated fundoscopic exam will be performed at study screening and study exit (week 12) by a study ophthalmologist. This exam may also be performed to verify suspected retinal changes throughout the course of the study.

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Vital Signs: Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at screening, baseline (week 0), visit 1 (week 1), and the primary outcome (week 8). Vital signs may be repeated at study exit (week 12) if clinically significant abnormal laboratory values are found at the primary outcome (week 8). Orthostatic blood pressure will also be taken at screening, baseline (week 0), visit 1 (week 1), visit 2 (week 2), visit 3 (week 4), visit 4 (week 6), primary outcome (week 8) and study exit (week 12).

Electrocardiogram: An electrocardiogram (ECG) will be performed at screening, visit 2 (week 2), at the primary outcome (week 8), and at the study exit visit (week 12).

9.2. Clinical Measures

Screening procedures (V-1, Week -6 – 0)

Structured Clinical Interview for DSM-5 (SCID-5). The Structured Clinical Interview for DSM-5 (First et al. 2015) is a semi-structured interview guide for making DSM-5 diagnoses. It includes an overview to obtain information about demographics, work history, chief complaint, history of present illness, past history, treatment history, and current functioning. The main body of SCID-5 includes 9 modules that are designed to diagnose 51 mental illnesses in all. During the study screening period, the SCID-5 will be administered by a trained study team member who has completed SCID-5-RV training and who is familiar with the DSM-5 classification and diagnostic criteria. The current study will utilize the most comprehensive version of the SCID-5, the SCID-5-Research Version (RV), which contains more disorders than the Clinician Version and includes all of the relevant subtypes, severity, and course specifiers. An important feature of the SCID-5-RV is its customizability, allowing the instrument to be tailored to meet the requirements of a particular study. The SCID-5-RV comes in a standard "core" configuration that includes the disorders most researchers are likely to assess routinely for most studies, as well as in an “enhanced” configuration that includes a number of optional disorders, in addition to the disorders from the "core" configuration.

Antidepressant Treatment History Questionnaire (ATRQ) (Chandler et al. 2010): is a self-rated scale used to determine treatment resistance in major depressive disorder (MDD) during the current episode. The ATRQ defines 6 weeks as an adequate duration of treatment and provides specific operational criteria for adequate dosage for each of the most commonly used antidepressant medications.

Childhood Trauma Questionnaire (CTQ): The CTQ (Bernstein et al. 2003) is a 28 item self-report questionnaire that is used to evaluate and record a history of childhood abuse and neglect. Each item is scored on a 5-point likert scale from “never true” to “very often true”. Scores are determined based on five scales; physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect.

Traumatic Life Events Questionnaire (TLEQ): The TLEQ (Kubany et al. 2000) is a self-report questionnaire that assesses the frequency and severity of traumatic experiences in adulthood.

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This questionnaire consists of a list of 22 behaviorally descriptive traumatic events and an additional "other" category with examples. Once an event is endorsed, the item is coded for frequency ("never," "once," "twice," "3 times," "4 times," "5 times," and "more than 5 times").

Snaith-Hamilton Pleasure Scale (SHAPS): The SHAPS (Snaith et al. 1995) is a well-validated 14-item self-report questionnaire commonly used to assess anhedonia. Each item on the SHAPS is worded so that lower scores indicate greater pleasure capacity. A total score can be derived by summing the responses to each item. Items answered with "strongly agree" are coded as "1", while a "strongly disagree" response was assigned a score of "4." Total scores on the SHAPS can range from 14 to 56, with higher scores corresponding to higher levels of anhedonia.

Clinical Global Impression - Severity (CGI-S): this is a widely administered clinician rated global measure of participant overall illness severity. Participants are rated on a 1-7 scale where 1 corresponds to "Normal, Not at All Ill", 2 is "Borderline Mentally Ill", the anchor for 3 is "Mildly Ill", the anchor for 4 is "Moderately Ill", 5 is "Markedly Ill", 6 is "Severely Ill", and 7 is "Among the Most Extremely Ill Participants".

Columbia-Suicide Severity Rating Scale (C-SSRS): The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2007) is a comprehensive, semi-structured interview that uniquely measures the full spectrum of suicidality including passive and active suicidal ideation, suicidal intent as well as suicidal behaviors. Participants will be assessed at every visit with the CSSRS by a qualified rater. Study participants will meet with a study clinician at each study visit, which will include a review of the C-SSRS. Any participant with an increase in suicidality and all those participants found to have a plan or intent will undergo thorough assessment by the study psychiatrist. If, at any point during the clinical trial, a participants will be assessed by the study clinician with a suicidal ideation with any intent or plan, as measured by a C-SSRS score of greater than 2 during the past week, the site PI, or his designee, will conduct a safety review. For more details regarding the safety review procedures, please refer to section 5.4 "Safety evaluation".

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Snaith-Hamilton Pleasure Scale (SHAPS): See above for description.

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

Temporal Experience of Pleasure Scale (TEPS): The TEPS is an 18-item self-report measurement of anhedonia which consists of a series of statements that must be rated according to how accurate they are for the individual (Gard et al. 2006). The scale produces two sub-scores that differentiate the role of anticipatory pleasure ('wanting') from consummatory pleasure ('liking'). The anticipatory sub-score (TEPS-ant) is derived of 10 items while the consummatory sub-score (TEPS-cons) is derived from 8 items.

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

The Brief Psychiatric Rating Scale- 4 item (BPRS-4) is used to assess acute behavioral changes during the administrations (Overall and Gorham, 1962). Four key BPRS items for the positive (+) symptoms of psychosis will be used: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content.

Clinical Global Impression - Severity (CGI-S): See above for description.

Clinical Global Impression - Improvement (CGI-I): this is a widely administered clinician rated global measure of the degree of improvement from the initial assessment in participant overall illness severity. Participants are rated on a 1-7 scale where 1 corresponds to “Very Much Improved”, 2 is “Much Improved”, the anchor for 3 is “Minimally Improved”, the anchor for 4 is “No Change”, 5 is “Minimally Worse”, 6 is “Much Worse”, and 7 is “Very Much Worse”.

The American Urological Association Symptom Score Questionnaire (AUA): this is a symptom index used to determine the presence and severity of urinary retention symptoms. This questionnaire includes seven questions, each assessing a different aspect of urinary output (incomplete emptying, frequency, intermittency, urgency, weak-stream, straining, and nocturia). Each question is rated on a 6-point Likert scale of 0: “none”, 1: “less and 1 time in 5”, 2: “less than half the time”, 3: “about half the time”, 4: “more than half the time”, or 5: “almost always”. The total symptom score is obtained by summing the scores for each of the seven questions. A score of 0 to 7 indicates mild symptom severity, 8 to 19 indicates medium symptom severity, and 20 to 35 indicates severe symptoms.

Columbia-Suicide Severity Rating Scale (C-SSRS): See above for description.

9.3. Behavioral Computer Tasks

Probabilistic Reward Task (PRT): This 25-min task is presented on a 17” PC monitor using E-Prime (version 1.1; Psychology Software Tools, Inc, Pittsburgh, PA). Stimuli consist of simple cartoon faces presented in the center of the monitor. At the beginning of the trial, the face has no mouth. After a given delay, either a straight mouth of 11.5 mm (“short mouth”) or 13 mm (“long mouth”) is presented for 100 ms. On each trial, participants are instructed to press an appropriate button to decide whether a long or small mouth had been presented. Unbeknownst to participants, correct identification of one stimulus (the “rich stimulus”) is rewarded three times more frequently (“Correct! You won 20 cents”) than the other (“lean”) stimulus. In healthy controls, this reinforcement schedule leads to a response bias (i.e., a preference for the more frequently rewarded stimulus). The task consists of three 100-trial blocks, and the degree of response bias toward the more frequently reinforced stimulus is used for operationalizing sensitivity to reward. An index of reward learning across the task is then computed by subtracting the total response bias in the first block from the total response bias in the last block. Stimulus exposure (100 ms)

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and the difference between mouth sizes (11.5 vs. 13 mm) are identical to those in prior studies using this paradigm (Pizzagalli et al. 2008; Pizzagalli, Jahn, and O'Shea 2005; Vrieze et al. 2013) and were selected to achieve optimal psychometric properties (e.g., overall hit rates of 75-85%).

The Stock Market Task: This task was designed to delineate two distinct computationally defined learning signals: value signal (i.e. % gain or loss in market value) versus reward prediction errors (RPE; positive if outcome is better than predicted, or negative if outcome is worse than predicted). The participant's task is to make sequential investment decisions. The task lasts 10-27 min (average 17.5 min) depending on the participant's reaction time (Gu et al. 2014). The participant is endowed with 100 monetary units to invest. At each time point t, the participant makes an investment decision bt (0~100% of current portfolio). The market price pt is then revealed with two possible directions of outcomes (increase or decrease), and the participant's gain or loss will be displayed. There are a total of 10 markets and the participant makes 20 choices in each market.

9.4. Primary Outcome Measure: Neuroimaging Assessments

fMRI Task Description: The current proposal will implement a variation of the monetary incentive delay (MID) task, the incentive flanker task (IFT). The IFT incorporates a longer mean cue time, jittered cue time, and catch trials, all features that facilitate differentiation between reward expectancy and reward responsiveness (Stern et al., 2011), though data should be comparable to that obtained from the MID for purposes of comparison (thereby facilitating the NIH common data elements initiative). We have demonstrated in our laboratory that the IFT robustly engages the cortico-striatal reward circuit. During the flanker conflict portion of the task, participants are instructed to press the left response button for target letters S/K and the right response button for letters H/C (letter assignment is counterbalanced across participants). Target letters are flanked by letters representing same or different button presses. Cues presented prior to letter stimuli (2-6 s) designate the monetary value for each trial: (1) "gain" cues indicate that participants earn 50 cents with a correct response (and fail to gain with an error); (2) "loss" cues indicate that participants can avoid a loss of 50 cents with a correct response (and lose money with an error); (3) "neutral" cues indicate that no money is at stake. Two-thirds of all cues will be followed by the letter stimuli. Immediately after the response, outcome feedback is presented for 2 s, followed by a blank inter-trial interval (ITI) for 2–6s before the next trial begins with a new cue. One-third of cues will be followed by a blank screen for 2s ("catch" trials), which will break co-linearity between the cue and feedback, allowing differentiation of brain activity related to expectancy and feedback response despite the slow hemodynamic response of the Blood-Oxygen-Level-Dependent (BOLD) signal. Even though BOLD signals to the button press response and outcome are not distinguishable in the current paradigm, comparisons between gain, loss, and null outcomes will subtract out brain activity related to motor responses occurring in each condition.

Scan Acquisition: All scans will be conducted on 3 Tesla MRI systems. Both sites (ISMMS and BCM) have a 3T whole body MRI scanner. The 3T scanner at Mount Sinai is a Siemens Magnetom scanner and the 3T scanner at Baylor is a Siemens Terra. The same head coil, a Nova Medical 32-

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channel (1 channel transmit / 32 channel receive), is being used at both sites. MR compatible video projection system with vision correction lenses, high quality headphones and a button box will be used for fMRI task presentation and response recording. Physiological monitoring is performed and digitally recorded during all scans. Detailed procedures for inter-site harmonization and QA procedures will be provided in an SOP.

fMRI Task Processing: Prior to analyzing imaging data, task behavioral data including reaction time (RT) and accuracy in response to flanker stimuli will be analyzed using ANCOVAs (including site, and any potential confounds) to examine main effects and interactions of treatment condition and cue type on reaction time and accuracy. fMRI data will undergo preprocessing using a combination of AFNI, FSL, and Advanced Normalization Tools (ANTs), including despiking, motion correction, alignment to anatomical image (using boundary-based registration), intensity normalization, smoothing (FWHM = 5mm), and warping to standard space. Motion and intensity outliers will be regressed out of the data. Following preprocessing, we will first conduct participant-level (also called 'first-level') analyses. As is the norm in the field, participant-level analyses conduct multiple linear regressions for each participant whereby the BOLD signal is predicted from a series of categorical regressors specifying the presence or absence of the conditions of interest across the full time series. As an example, in a trial where a cue is shown for 4 seconds followed by an outcome for two seconds, followed by another cue for 4 seconds, the cue regressor would be coded "1" (present) for the first and last 4 timepoints (in seconds) and "0" (absent) for the 2 middle timepoints where the outcome was shown. For each participant, regressions are performed within a standardized neuroimaging analysis software (such as Statistical Parametric Mapping, FSL, or AFNI), producing a single beta weight for each regressor reflecting the relationship between the presence/absence of condition of interest and BOLD signal at each voxel in the brain. For all analyses, the predicted BOLD signal is convolved with a standard hemodynamic response function (hrf) to model the slow rise and fall of the hemodynamic response in the brain. For each participant, the beta weights are then linearly combined to create contrasts (gain > neutral cue contrast, the primary contrast of interest for this study, is the beta weight for gain cue minus beta weight for neutral cue). This contrast represents the mental construct of reward anticipation.

Resting State fMRI (R-fMRI): Approximately 10 minutes worth of resting state fMRI data will be collected at both sites, pre- and post-treatment. Participants will be instructed to rest, eyes open and fixed on a central fixation cross, and to try to remain as still as possible. R-fMRI data will be examined primarily as an exploratory aim and additionally contributes to the common data element initiative. As there are a number of serious, potential confounds to the analysis of R-fMRI, advanced processing and analytic methods will be employed, including the use of robust artifact detection and removal (Pruim et al., 2015). We will conduct targeted analysis to explore whether treatment alters connectivity and network patterns with known abnormalities and that are specifically impacted by our treatment (e.g., fronto-striatal connectivity implicated in reward; see Heller et al., 2013).

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9.5. Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), seriousness, severity/grade, expectedness, outcome, treatments administered and relation to study drug will be recorded on the case report form (CRF). Please refer to section 11 “Adverse experience reporting and documentation” for more details.

9.6. Clinical Laboratory Measurements

Hematology and Blood Chemistry Profile: Blood will be obtained at screening and primary outcome (week 8) and sent to each site’s clinical hematology lab for a Hemoglobin, Hematocrit, Electrolytes, Metabolic Panel, Thyroid Function Tests, Hepatic and Renal Function Tests. A complete blood count with differential will be performed at screening, baseline (week 0), visit 3 (week 4), and primary outcome (week 8). Clinical labs may be repeated at study exit (week 12) if a clinically significant abnormal finding is found at the primary outcome visit (week 8).

Pregnancy Test: A urine pregnancy test will be obtained from female participants who are of childbearing age prior to their participation in the study (screening visit), at baseline (week 0), Visit 1 (week 1), visit 2 (week 2), visit 3 (week 4), visit 4 (week 6), and at the end of treatment/primary outcome visit (week 8).

Urinalysis and Urine Toxicology: Urine will be obtained and each site’s clinical laboratory for determination of color, urine specific gravity, osmolality, cellules, proteins and bacteria prior to their participation in the study (screening visit) and at primary outcome visit (week 8). A urine toxicology screen for drugs of abuse will be performed at screening, baseline (week 0), and end of treatment/primary outcome visit (week 8). Clinical labs may be repeated at study exit (week 12) if a clinically significant abnormal finding is found at the primary outcome visit (week 8).

9.7. Pharmacokinetics Measurements

Blood samples for determination of plasmatic concentrations of XEN1101 and its metabolites will be collected at visit 1 (week 1) and the end of treatment visit/primary outcome (week 8). These samples will be handled, processed, and couriered in accordance with applicable state, federal, and international regulations. Blood samples for XEN1101 plasma concentrations will be collected, processed and stored at each site (at -20 or -80°C), prior to shipment on dry ice to Xenon’s designated bioanalytical laboratory for analysis (York Bioanalytical Services, UK). Given that the results of these analyses could unblind study team members, only the unblinded database manager or statistician will have access to this information until the study is complete and the database is locked.

10. EVALUATIONS BY VISIT

It is anticipated that all study visits specified in the protocol will occur in person. However, in the context of the COVID-19 pandemic and to increase feasibility and adherence to the protocol,

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certain study procedures may occur via an approved remote platform that conforms to the individual policies of the study sites and all applicable laws and regulations. Please see section 17.2 “Remote Procedures” for additional information on which procedures may be completed remotely.

10.1. Screening Visit (V-1, Week -6 – 0)

1. Review the study with the participant and obtain written informed consent and HIPAA authorization.
2. Review inclusion and exclusion criteria.
3. Assign the participant a unique screening number.
4. Record demographics data.
5. Perform a clinical interview.
6. Record medical, psychiatric, medication and treatment history, diagnosis date, and prior treatments.
7. Record concomitant medications and tapering of prohibited medications (if applicable).
8. Perform self and clinician administered ratings scale:
   - SCID-5-RV
   - CGI-S
   - CSSR-S – Lifetime / Past month
   - SHAPS
   - ATRQ
   - CTQ
   - TLEQ
9. Perform a complete physical examination.
10. Perform and record vital signs (including orthostatic blood pressure measurement)
11. Perform an ECG.
12. Collect urine for urinalysis, urine toxicology and pregnancy test (female participants who are of childbearing age).
13. Collect blood for clinical laboratory tests
14. Perform a dilated fundoscopic exam
15. Schedule participant for Baseline (Visit 0) within 6 weeks of Screening.

Note: The screening visit may occur on up to three separate days. The whole procedures will be completed before the randomization day and within six weeks of the first screening visit. Screening measures may be completed under a separate screening protocol at each site. As long as the assessments are completed within six weeks of the signing of consent for this protocol, the screening measures will not be repeated. Participants who are deemed screen fails may be re-screened at a later date, based on PI discretion. If re-screened, participants will repeat all screening procedures.

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10.2. Baseline (V0, Week 0)

1. Obtain interval medical history.
2. Record changes to concomitant medications.
3. Collect urine for toxicology and pregnancy test (female participants who are of childbearing age)
4. Collect blood for clinical laboratory tests
5. Record vital signs (including orthostatic blood pressure measurement)
6. Perform self and clinician administered ratings scale:
   - MADRS
   - CSSRS-Since Last Visit
   - CGI-S
   - CGI-I
   - SHAPS
   - TEPS
   - QIDS-SR
   - BPRS-4
   - AUA
7. Perform a complete physical examination
8. Perform the PRT
9. Perform the Stock Task
10. Complete neuroimaging procedures
11. Randomize of the participant
12. Illustrate drug administration and participant diary
13. Dispense study drug/placebo

Note: The Baseline/Randomization Visit should take place within six-weeks of the date that the participant signed consent for this study. The Baseline/Randomization Visit may occur on up to two separate days within 5 business days of each other. The neuroimaging procedures must be completed before the participant is randomized. Neuroimaging procedures should occur in the morning at each site to enhance standardization across sites.

10.3. Visit 1 (Week 1)

1. Obtain interval medical history.
2. Record any AEs and review participant diary for adverse experiences and dosing compliance.
3. Record changes to concomitant medications.
4. Record vital signs (including orthostatic blood pressure measurement)
5. Collect urine for a pregnancy test, (female participants who are of childbearing age)
6. Perform self and clinician administered ratings scale:
   - CSSRS-Since Last Visit
   - BPRS-4

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7. Collect venous blood samples for PK analysis
8. Perform a physical examination
9. Dispense study drug/placebo

10.4. Visit 2 (Week 2)

1. Obtain interval medical history.
2. Record any AEs and review participant diary for adverse experiences and dosing compliance.
3. Record changes to concomitant medications.
4. Record vital signs (including orthostatic blood pressure)
5. Collect urine for a pregnancy test, (female participants who are of childbearing age)
6. Perform self and clinician administered ratings scale:
   - MADRS
   - CSSRS-Since Last Visit
   - CGI-S
   - CGI-I
   - SHAPS
   - TEPS
   - QIDS-SR
   - BPRS-4
7. Perform an ECG
8. Perform a physical examination
9. Dispense study drug/placebo
10. Approximately one week following this visit (i.e. halfway to the next in person visit), study coordinators will contact the participant to inquire if they are having any problems related to the study drug. The study coordinator will complete a phone check in form that will record any new medical problems or general tolerability issues. A request by the study participants or any safety concern will trigger a follow up phone call assessment by a study physician. At physician's discretion, an un-schedule in-person or remote telehealth visit will be performed.

10.5. Visit 3 (Week 4)

10. Obtain interval medical history.
11. Record any AEs and review participant diary for adverse experiences and dosing compliance.
12. Record changes to concomitant medications.
13. Record vital signs (including orthostatic blood pressure)
14. Collect urine for a pregnancy test, (female participants who are of childbearing age)
15. Perform self and clinician administered ratings scale:
    - MADRS
    - CSSRS-Since Last Visit

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- CGI-S
- CGI-I
- SHAPS
- TEPS
- QIDS-SR
- AUA
- BPRS-4

16. Perform a physical examination
17. Collect blood for clinical laboratory tests
18. Dispense study drug/placebo
19. Approximately one week following this visit (i.e. halfway to the next in person visit), study coordinators will contact the participant to enquire if they are having any problems related to the study drug. The study coordinator will complete a phone check in form that will record any new medical problems or general tolerability issues. A request by the study participants or any safety concern will trigger a follow up phone call assessment by a study physician. At physician's discretion, an un-scheduled in-person or remote telehealth visit will be performed.

10.6. Visit 4 (Week 6)

1. Obtain interval medical history.
2. Record any AEs and review participant diary for adverse experiences and dosing compliance.
3. Record changes to concomitant medications.
4. Record vital signs (including orthostatic blood pressure)
5. Collect urine for a pregnancy test, (female participants who are of childbearing age)
6. Perform self and clinician administered ratings scale:
   - MADRS
   - CSSRS-Since Last Visit
   - CGI-S
   - CGI-I
   - SHAPS
   - TEPS
   - QIDS-SR
   - BPRS-4
7. Dispense study drug/placebo
8. Approximately one week following this visit (i.e. halfway to the next in person visit), study coordinators will contact the participant to enquire if they are having any problems related to the study drug. The study coordinator will complete a phone check in form that will record any new medical problems or general tolerability issues. A request by the study participants or any safety concern will trigger a follow up phone call assessment by a study physician. At physician's discretion, an un-schedule in-person or remote telehealth visit will

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be performed.

Note: Study Visits 1, 2, 3, and 4 are due to take place 1, 2, 4, and 6 weeks after the baseline visit (week 0) respectively. To allow for scheduling feasibility, Visits 1-4 can take place within 3 days before or after the scheduled visit.

10.7. Visit 5 (End of Treatment/Primary outcome visit; Week 8)

1. Obtain interval medical history.
2. Record any AEs and changes in concomitant medications and review participant diary for adverse experiences and dosing compliance.
3. Record vital signs (including orthostatic blood pressure)
4. Collect urine for toxicology, urinalysis and pregnancy test (female participants who are of childbearing age)
5. Perform self and clinician administered ratings scale:
   - MADRS
   - CSSRS-Since Last Visit
   - CGI-S
   - CGI-I
   - SHAPS
   - TEPS
   - QIDS-SR
   - AUABPRS-4
6. Perform the PRT
7. Perform the Stock Task
8. Collect venous blood samples for clinical laboratory tests and PK analysis
9. Complete neuroimaging procedures
10. Perform a physical examination
11. Perform an ECG
12. A clinician will meet with the participant to discuss the end of treatment plan and provide a clinical referral, if needed.

Note: This visit may occur on up to two separate visits. These visits should be within 3 days of each other.

10.8. Visit 6 (Study Exit Visit; Week 12)

1. Record any AEs.
2. Record changes to concomitant medications and review participant diary for adverse experiences.
3. Record vital signs (including orthostatic blood pressure)
4. Perform self and clinician administered ratings scale:
   - CSSRS-Since Last Visit

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- AUA
- BPRS-4

5. Perform a physical examination
6. Perform dilated fundoscopic exam
7. Perform an ECG
8. Collect blood for clinical laboratory tests and PK analysis*
9. Collect urine for urinalysis*

Note: The exit visit may occur on up to three separate days, between 4 week and 5 weeks from the end of treatment visit (week 8). The participant will be considered exited from the study when all the procedures listed above will be completed.

* Clinical safety data (i.e. urinalysis, blood draws, etc.) may be repeated at this visit if a clinically significant abnormal value is found during the primary outcome visit.

10.9. Study Procedures for Early Exit Visit

1. Record any AEs.
2. Record changes to concomitant medications and review participant diary for adverse experiences and dosing compliance.
3. Record vital signs (including orthostatic blood pressure)
4. Perform self and clinician administered ratings scale:
   - CSSRS-Since Last Visit
   - MADRS
   - CGI-I
   - CGI-S
   - SHAPS
   - TEPS
   - QIDS-SR
   - AUA
   - BPRS-4
5. Collect urine for urinalysis and pregnancy test (applies to women of child-bearing potential only)
6. Collect blood for clinical laboratory tests and PK analysis
7. Perform an ECG
8. Perform a physical examination
9. Perform the PRT
10. Perform the Stock Task
11. Complete the neuroimaging procedures
12. Perform dilated fundoscopic exam

Note: These procedures will be performed for early withdrawal visits that take place before completion of the primary outcome/end of treatment visit (week 8). Capturing outcome data

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for participants who do not complete the full study protocol will allow a more precise estimate of the treatment effect. Clinical safety data (i.e. urinalysis, blood draws, etc.) may also be repeated at this visit if a clinically significant abnormal value is found.

10.10. Unscheduled visits.....

If clinically indicated, participants may complete remote or in-person unscheduled visits to meet with a study physician. All associated documentation will be kept in the participant's participant record.

11. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1. Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a study participant administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

Any condition, laboratory abnormality, or physical finding with an onset date prior to the participant signing consent for study participation is considered to be pre-existing in nature and part of the participant's medical history and will not be recorded as AEs.

AE Expectedness

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered "unexpected".

AE Severity

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Separate tabulations and listings will be produced for related adverse events, serious adverse events, discontinuation due to adverse events and events of at least grade 3 severity.

List criteria for AEs according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (September 2020) should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the

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abovementioned criteria, the guidelines shown in Table 1 below should be used to grade severity. Notably, the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The participant may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The participant is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the participant's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unlikely	An event that does not follow a reasonable temporal sequence from administration of the Investigational Product, and that could readily have been produced by a number of other factors.

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Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2. Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life threatening experience defined as any adverse experience that places the participant, in the view of the treating physician, at immediate risk of death at the time of occurrence; i.e, it does not include a reaction that, had it occurred in a more severe form, might have caused death.
3. Requires inpatient hospitalization or prolongation of an existing hospitalization (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery)
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly/birth defect in the offspring of an exposed participant
6. Important medical events that may not result in death, be life threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7. Any death occurring within 30 days of the participant receiving study drug, regardless of the participant having discontinued from the protocol, must be reported as an SAE.

11.3. Adverse Events of Special Interest (AESI)

The Investigator will monitor each participant for clinical and laboratory evidence for predefined adverse events of special interest (AESIs) throughout their participation in this study.

The Investigator will assess and record any additional information on any AESIs in detail on an AE form, which must be submitted within the timeframe established for data entry. The Investigator will determine whether in his/her clinical judgement an AE is or is not an example of the relevant AESI category (i.e., disturbances in thinking and perception, bladder and urethral symptoms, cardiovascular changes, ophthalmologic changes). In addition, AESIs must be recorded in the eCRF.

These events can be either serious or non-serious, according to the criteria outlined in Section 11.2. These events can also be rated mild, moderate, or severe according to the criteria outlined in Section 11.1.

Should any AESI meet criteria for an SAE as defined by section 11.2, the participant will discontinue study drug. In addition, non-serious but severe AEs will lead to the discontinuation of the study drug. If feasible and safe, participants who experience adverse events will continue to be followed until study completion.

In the instance of an AESI, the study team will follow procedures outlined in this section of the protocol. All AESIs and resolution per protocol will be reported to the medical monitor for review.

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To facilitate their examination, clinically relevant treatment emergent AEs of special interest will be grouped separately into categories including AEs suggestive of dissociation; suggestive of sedation; or suggestive of drug abuse, dependence, or withdrawal.

For this study, AESIs include the following:

1) Adverse events suggestive of disturbances in thinking and perception including the following:
   - AEs that map to the following high level MedDRA terms:
     - Delusional symptoms
     - Hallucinations (excl sleep-related)
     - Perception disturbances NEC
     - Thinking disturbances
   - Elevations of BPRS score will be considered an adverse event as defined below:
     - Any item on the BPRS-4 > 2 (lowest score=1) will be coded as an AE of special interest and a safety review should be completed.
     - Any item on the BPRS-4 > 3 will lead to the discontinuation of study drug.
2) Adverse events suggestive of urinary retention including the following:
   - AEs that map to the high level MedDRA terms of Bladder and Urethral Symptoms. Any bladder or urethral symptom with an onset date prior to participant randomization is considered to be pre-existing in nature and part of the participant's medical history, and thus will not be recorded as an AE or AESI.
   - Elevations of AUA score from baseline will also be considered an adverse event as defined below:
     - A total score on the AUA-4 > 7 (lowest score = 0) that also marks an increase from baseline will be coded as an AE of special interest and a safety review should be completed.
     - A total score on the AUA-4 > 19 that also marks an increase from baseline will lead to the discontinuation of study drug.
3) Adverse events suggestive of cardiovascular changes including the following:
   - AEs that map to the following system organ class MedDRA term:
     - Cardiac Disorders, including:
       - Cardiac arrhythmias
       - Cardiac disorders, signs and symptoms NEC
       - Cardiac valve disorders
       - Coronary artery disorders

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- Heart failures
- Myocardial disorders
- Pericardial disorders

- An ECG result that meets one of the following criteria will be deemed an AESI and will lead to the early discontinuation of study drug:
  - An ECG that is deemed clinically significant by the investigator or medical monitor
  - An ECG result indicating a QTcF (QT corrected by Fridericia's formula) > 500 ms
  - An ECG result indicating a QT interval increase of > 60ms

4) Adverse events suggestive of ophthalmologic changes including the following:

- AEs that map to the high level group term MedDRA term of Ocular structural change, deposit and degeneration NEC including:
  - Choroid and vitreous structural change, deposit and degeneration
  - Optic disc abnormalities NEC
  - Orbital structural change, deposit and degeneration
  - Retinal structural change, deposit and degeneration
  - Scleral structural change, deposit and degeneration
  - Structural change, deposit and degeneration of eye NEC
- Any retinal change on fundoscopic exam indicating retinal changes similar to those seen in retinal pigment dystrophies;
  - This will be recorded as an AESI and the participant will be discontinued from the study drug.

11.4. AE/SAE Reporting Procedures

To IRB and PI (Sponsor-Investigator)
Any AE must be recoded on the appropriate CRF/eCRF. All AE/SAEs that are considered related to study drug must be followed to resolution or stabilization if improvement is not expected. AE/SAEs that completely resolve and then recur should be recorded as a new AE/SAE. AE/SAEs that are considered related to study drug and continuing at 30 days post-last dose should have a comment in the source documents by the site PI that the event has stabilized or is not expected to improve.

Any SAE occurring during the study period (beginning with informed consent and lasting until 30 days after the last dose of study drug) must be immediately reported no later than **3 business days** after learning of an SAE or AESI to the Study PI and IRB.

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All AE/SAEs with an onset date after the participant signs consent for study participation must be reported to the IRB at the time of annual renewal. Details of the event must include seriousness, severity, expectedness, relationship to study drug, duration, action taken, and outcome.

All AE/SAEs that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the PI, IRB, and DSMB as detailed below in Section 11.5 "Unanticipated Problem Reporting".

To Xenon Pharmaceuticals

While Dr. Murrough will serve as the Sponsor-Investigator for this study under an IND, Dr. Murrough will report SAEs, AESIs, UPs, and SUSARs to Xenon Pharmaceuticals within timeframe outlined herein for reporting to Sponsor. The Sponsor-Investigator will also provide bi-annual reports to Xenon Pharmaceuticals detailing cumulative AEs, AESIs, SAEs, UPs, and participant enrollment. Study treatment assignments will be masked in any reports to Xenon Pharmaceuticals.

To NIMH DSMB

All AEs, SAEs, and AESIs will be reported to the NIMH DSMB in data reports prepared three times annually. Details of the event must include the AE, severity, expectedness, relationship to study drug, duration (start/ stop date), action taken, and outcome.

In addition, SAEs that include all deaths and immediately life-threatening events, whether related or unrelated, will be reported to the NIH DSMB within **5 business days** of the site PI awareness of the event.

SAEs that are unexpected and at least probably related to study participation and AESIs that also meet the definition of a SAE will be reported to the NIH DSMB **within 10 days.**

For all AEs and SAEs that are deemed expected and/or unrelated to the study, or AESIs, a summary will be submitted to the NIMH DSMB with the tri-annual progress report. All AE/SAEs that are considered related to study drug must be followed to resolution or stabilization, if improvement is not expected. AE/SAEs that completely resolve and then recur should be recorded as a new AE/SAE. AE/SAEs that are considered related to study drug and continuing at 30 days post-last dose should have a comment in the source documents by the PI that the event has stabilized or is not expected to improve. Other supporting documentation of the event may be requested by the DSMB/NIMH and should be provided as soon as possible.

Any suspension or termination of approval will include a statement of the reason(s) for the action and will be reported promptly to the NIMH DSMB within **3 business days** of receipt.

To FDA

A report on the MedWatch 3500A form must be sent to the FDA when the event is:

1. serious unexpected suspected reaction (the investigator judges there is evidence to suggest a causal relationship);



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2. findings from other clinical, animal, or in-vitro studies that suggest significant human risk and
3. a clinically important increase in the rate of a serious suspected adverse reaction no later than 15 days after determining that the information qualifies for reporting.

The relevant health authorities will be notified of any unexpected serious adverse reactions (SUSARs) within the required reporting timelines (within **7 calendar days** for fatal and life-threatening SUSARs, or **15 calendar days** for all other SUSARs).

Pregnancy

Participants will be asked to immediately inform the study team and her doctor if any of the following occur:

- She becomes pregnant while taking the study drug
- She misses her menstrual period, or experiences unusual menstrual bleeding
- She stops using birth control
- She thinks, FOR ANY REASON, that she may be pregnant

Pregnancies occurring while the participant is participating in the study or within 30 days after the participant's administration of study drug are considered expedited reportable events. The study drug is to be discontinued immediately and the participant instructed to return any drug to the Investigator. The participant will be exited from the study and the collection of pregnancy outcome data will not be mandated. The pregnancy will be considered an immediately reportable event and will be reported to the DSMB and the study PI/Sponsor within **5 business days** of the site PI becoming aware of the event. The event will also be reported to the site local IRB within **5 business days** or following the local IRB regulations, whichever is more conservative.

11.5. Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UP.

11.6. Unanticipated Problem Reporting

It is the site investigator's responsibility to report UPs to the PI, DSMB/NIMH, and IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB, DSMB/NIMH, and to the PI/Sponsor within **3 business days** of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB, the DSMB/NIMH, and to the PI/Sponsor within **2 weeks** of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within **one month** of the IRB's receipt of the report of the problem from the investigator.

11.7. Medical Monitoring

Dr. Dan Iosifescu, MD is the medical monitor for the study. Dr. Iosifescu is a Board-certified psychiatric and clinical investigator with over a decade of experience in clinical trials of psychopharmacological agents in depression and other mood disorders. The medical monitor for this study will act as a safety officer who is separate from the study team and will assist the study Sponsor/PI in ensuring the quality of the medical monitoring during the study.

All SAEs, UPs, AESIs, and major (serious) protocol deviations will be sent to Dr. Iosifescu for review within **three business days** of site awareness. Dr. Iosifescu will also review all safety reviews performed by the study team and participate in shared decision making to support the PI in ensuring the safety of study participants. Dr. Iosifescu will provide feedback as to whether any

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action should be taken in regards to a participant in the trial, including if unblinding is required to facilitate a participant's treatment, though all final decisions are up to PI discretion.

Due to the close ongoing communication and reporting between the study team and the medical monitor, the medical monitor will remain blinded to treatment of participants to reduce bias and ensure study integrity, except in cases meeting unblinding criteria, as described in section 8.2 Blinding: "Conditions Under Which the Study Blind May be Broken."

Medical Monitor Contact Information:

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12. PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Bodies with the authorities to suspend or terminate the study include the NIMH, DSMB, FDA, and IRB. In addition, if at any time the study PI determines that there is sufficient need to terminate or suspend the study they may do so. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to NIMH, FDA, DSMB, and the IRB.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the involved regulatory authorities.

The following occurrence will require DSMB review:

Administration of study agent will be halted when **three severe AEs determined to be "probably related"** are identified. When this occurs, the site will stop accepting new study participants. The PI will inform the DSMB members within **5 business days** of this occurrence and will provide the DSMB with AE listing reports. The DSMB will provide recommendations for proceeding with the study to the PI. The PI will inform the FDA and IRB of the temporary halt and the disposition of the study.

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13. DISCONTINUATION AND REPLACEMENT OF PARTICIPANTS

13.1. Early Discontinuation of Study Drug

A participant may be discontinued from study treatment at any time if the participant, the investigator, or the Sponsor feels that it is not in the participant's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Participant withdrawal of consent
- Participant is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the participant to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)

For participants who are lost to follow up, it may not be possible to complete early discontinuation procedures. For participants who wish to withdraw consent, they will be asked to do so in writing following the completing of an early discontinuation visit. Some participants may not agree and wish to withdraw consent immediately in which case these early discontinuation procedures may not occur. Reasonable attempts will be made by the investigator to provide a reason for participant discontinuation from study treatment.

13.2. Withdrawal of Participants from the Study

A participant may be withdrawn from the study at any time if the participant or the investigator-sponsor feels that it is not in the participant's best interest to continue. All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for participant withdrawals. The reason for the participant's withdrawal from the study will be specified in the participant's source documents. As noted above, participants who discontinue study treatment early (i.e., they withdraw prior to Visit 6) should have an early discontinuation visit. Refer to Section 10. Evaluations by Visit for early termination procedures.

13.3. Replacement of Participants

Participants who withdraw from the study treatment will not be replaced.

14. PROTOCOL DEVIATIONS

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A Protocol Deviation (PD) is defined as any change, divergence, or departure from the IRB-approved study procedures in a research protocol.

In the present study, protocol deviations will be classified as either minor (non-serious) deviations or major (serious) deviations according to the definitions listed below:

Minor Protocol Deviations:
A minor protocol deviation occurs when accidental or unintentional changes are made to the research protocol (or non-compliance with the protocol) that does not increase risk or decrease benefit to participants, or does not have a significant effect on the participant's rights, safety or welfare; and/or on the integrity of the primary outcome data. Deviations may result from the action of the participant, researcher, or research staff.

A minor protocol deviation may be due to the research participant's non-adherence, or an unintentional change to or non-compliance with the research protocol on the part of a researcher. Examples of a minor protocol deviation include:

- A study visit held out of window
- Failure to collect an ancillary self-report questionnaire

Major Protocol Deviations:
A major protocol deviation, also referred to as a protocol violation,occurs when accidental or unintentional changes are made to (or non-compliance occurs with) the IRB approved protocol without prior sponsor and IRB approval that increases risk or decreases benefit to participants, affects the participant's rights, eligibility, safety, or welfare, or the integrity of the primary outcome data. Examples of major protocol deviations include (but are not limited to):

- Failure to obtain valid informed consent
- Loss of laptop computer that contained identifiable, private information about participants
- Accidental distribution of incorrect study drug or dose
- Randomizing a participant who does not meet inclusion/exclusion criteria
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a major protocol deviation. The PI will determine if a major protocol deviation will result in withdrawal of a participant.

When a protocol deviation occurs, it will be discussed with the Site PI and a Protocol Deviation Form detailing the deviation will be generated. This form will be signed by a the PI or delegated co-investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files. A major protocol deviation that has the potential to impact participant safety will be reported to the IRB, DSMB and study sponsor, within 3 business days of site awareness.

15. DATA SAFETY MONITORING PLAN

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A Data and Safety Monitoring Board (DSMB) will be created by the NIMH as an independent body charged with ensuring that the safety of study participants is protected and that the scientific goals of the study are being met. The DSMB conducts a review of all adverse events at least three times yearly, and reports their findings to the study PIs, who will inform their respective IRBs regarding the findings. The DSMB will be organized in compliance with the NIMH Charter, to ensure the safety of study participants and the integrity of the data collected in the projects. To achieve this goal, the DSMB will perform an ongoing evaluation of the overall clinical outcomes and the safety of participants participating in the clinical trial. The DSMB will also review any proposed amendments to the study protocol, perform expedited monitoring of immediately reportable serious adverse events, perform ongoing monitoring of all other AEs and SAEs, as well as drop-outs, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study participants, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The researchers will ensure participant privacy and research data confidentiality, and the DSMB through its review activities will provide support for the process. The DSMB will remain extrinsic to the study's infrastructure.

Please see Protocol Appendix for NIMH **DSMB Charter** for additional details.

16. CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). See separate clinical monitoring plan (CMP) for full details. The main features are below.

- Monitoring for this study will be performed by NIMH Clinical Research Education, Support and Training Program (CREST) monitors.
- Monitoring will be conducted either on-site or remotely, throughout the study, and involve targeted data verification of key data variables
- The site PI will be provided copies of monitoring reports within 10 days of visit and will be provided to the NIMH DSMB liaison within 30 days of the visit.
- Details of clinical site monitoring are documented in the CMP. The CMP describes who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe the site's quality management.

17. STATISTICAL METHODS AND CONSIDERATIONS

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17.1. Study Populations to be Analyzed

Screened Population: The Screened population will consist of all participants who signed a consent form and evaluated for eligibility at the screening visit. The Screened population will be used for participant disposition display only.

Intent-to-Treat (ITT) Population: The ITT population will consist of all randomized participants grouped by their assignment at randomization, regardless of whether they received the assigned treatment or completed the trial. The ITT population will be used for all efficacy analyses and presentation of participant and baseline characteristics.

All Available Data Population**:** The All Available Data population will consist of all randomized participants who contribute at least one data point to the analysis. The All Available Data population will be used in the analysis of longitudinal secondary and exploratory endpoints in the event that participants are missing all baseline and follow-up assessments for whatever reason.

Safety Population: The Safety population, defined as all randomized participants who received at least one dose of the study drug (XEN1101 or placebo), will be used to present the safety summaries by the actual treatment received.

17.2. **Statistical Methods**

Study day will be calculated from the reference start date and will be used to show the study days of assessments and events. Reference start date is defined as the date of randomization unless otherwise specified.

All data will be presented by treatment group as well as for the whole sample. For all baseline, demographic and efficacy variables, data will be summarized and analyzed by randomized treatment group as per ITT.

In summary tables of normally distributed continuous variables, the following descriptive statistics will be used: minimum and maximum, mean, and standard deviation. In summary tables of non-normally distributed variables data will be presented using the minimum, maximum, median and lower and upper quartiles.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of participants within the randomization group unless otherwise specified.

Rates of events will be calculated as the ratio of the total number of events recorded divided by the total participant-time in study (e.g., months or days). Total participant-time will be calculated by summing the time that participants were at risk for a specific event from the time they were randomized in the study until study exit. Rates and 95% confidence intervals will be reported.

For any variable measured at multiple points in time, change from baseline will be calculated as the difference between the value of the variable at a specific point in time (e.g. 5 weeks) minus the baseline value. Relative change from baseline will be calculated as the value of a parameter

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at a specific point in time minus the baseline value of the parameter divided by the baseline value of the parameter. Percent change will be calculated as the relative change multiplied by 100.

Hypothesis testing will be conducted at the 0.10 two-sided significance level for the primary and secondary efficacy endpoints. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (for example to a logarithmic scale) to satisfy model assumptions such as normally distributed residuals with constant variance, or the application of non-parametric techniques.

Additional ad-hoc analyses may be conducted as deemed appropriate.

All statistical analysis will be performed using SAS V9.4 or higher.

17.3. **Missing Data**

Missing values will be imputed using multiple imputation (Groenwald, 2014; Little 2012; Little 2015) for the primary outcome.

17.3.1. Missing values for the primary outcome

Missing outcome values for the primary endpoint analysis will be imputed. For the primary endpoint, missing data can be the result of participant refusal, missed visit, or study dropout (withdrawal, lost to follow-up). Missing data due to participant refusal or missed visits are assumed to be missing at random (MAR). Study dropout is also assumed to be MAR.

17.3.2. Missing values for the secondary and exploratory outcomes

Missing outcome values for the secondary and exploratory endpoints will not be imputed.

17.3.3. Sensitivity analysis

Sensitivity analyses will be conducted to investigate possible violations of the *MAR* assumption for the primary endpoint. In order to understand the extent of the violations to the MAR assumption, we will employ a 'tipping point' approach (Yan 2009; Yuan 2013). When the data is missing not at random (MNAR), sensitivity analyses using the tipping point approach will allow re-analyzing the data with a shift parameter using user supplied values added to the imputed values for observations in the XEN1101 group in each imputed dataset. This will allow seeing how the estimates change under the MNAR assumption. Tipping point analyses can then be used to quantify the potential bias required among unobserved data to render the results from current data statistically non-significant at the two-sided 0.10 level.

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If the tipping point analyses shows questionable MAR then the data is potentially MNAR, and we will not be able to impute missing values in the same way. However, we could impute under MNAR using a pattern mixture model framework (Little and Rubin, 2002) and then imputing under the MNAR assumption using either a delta-adjusted pattern imputation or fully conditional specification.

17.4. **Participant Characteristics**

17.4.1. Participant Disposition

The participant disposition table will summarize participants' characteristics by randomization group and overall.

- The number (%) of participants randomized
- The number (%) of participants withdrawn or lost to follow-up by the primary outcome visit (week 8)
- The number (%) of participants withdrawn or lost to follow-up by the study exit visit (week 12)

The number (%) of participants who complete and withdraw/lost to follow-up from the study and the primary reason for withdrawal will be summarized by randomization group and overall for all participants.

17.4.2. Protocol Deviations

Major and minor protocol deviations are defined as deviations from the procedures outlined in protocol section 15 "Protocol Deviations".

17.4.3. Demographic Characteristics

Demographic and baseline characteristics data including age, gender, race, and ethnicity will be summarized using summary statistics for continuous variables or by group frequencies and percentages for categorical variables, as appropriate.

17.5. **Efficacy Analysis**

17.5.1. Sample Size Estimation

In order to compare the effect of XEN1101 compared to placebo, we will use prior estimates of ventral striatum, the primary outcome, from the R61 trial with ezogabine and placebo of the mean difference between baseline and week 5 for ezogabine of 0.323 and for placebo of -0.1395. We assumed the variance of the random intercept of 0.1352 and residual variance of 0.3646. Using a random intercept model and assuming power of ≥80% and two-sided significance level of 0.10, for n=25 per group, we would be able to detect a difference between placebo and XEN1101 of 0.4 to 0.6, which is close to prior study estimates of 0.5. In addition, in order to handle uncertainties in recruitment at each site or at least a 20% dropout rate with 25

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subjects/group, we will plan to enroll a total of 60 subjects or 30 subjects/group and be well powered to detect this difference.

17.5.2. Analysis of Primary Endpoint

The primary endpoint is the change in activation of the bilateral VS, a region of the rewards circuit in the brain. A mixed model with random intercept will be used to compare change in bilateral VS from baseline to week 8 between XEN1101 and placebo. The covariates in the model will include treatment, time and an interaction between treatment and time. Due to the small sample size, no additional covariates will be included. The analyses will be conducted at a two-sided 0.10 level of significance in the ITT population.

Although randomization is stratified by site, the primary endpoint analysis will be of the pooled dataset. Site-specific treatment effect estimates will be provided descriptively.

17.5.3. Analysis of Secondary Endpoints

For the secondary measures, changes in MADRS and SHAPS over time across baseline, weeks 2, 4, 6, and 8 will be compared between randomization groups using a mixed model with random intercept and possibly random slope model. The analyses will be conducted at a two-sided 0.10 significance level in the ITT population. Given the early phase exploratory nature of the study there will be no adjustment for multiplicity.

17.5.4. Analysis of Exploratory Endpoints

Results from the exploratory analyses will be treated solely as hypothesis generating. No formal hypothesis testing will be performed and only point estimates and confidence intervals at the 90% confidence level will be reported in the ITT population.

Changes in QIDS-SR, TEPS, CGI-I and CGI-S over time across baseline, weeks 2, 4, 6 and 8 will be compared between randomization groups using a mixed model with random intercept and possibly random slope, similar to the analysis of the secondary outcomes.

Changes in behavioral task outcomes, measured by the Probabilistic Reward Task and the Stock market task and changes in fMRI activation in other regions of the brain, all at baseline and week 8, will also each be compared between randomization groups using a mixed model with random intercept, similar to the analysis of the primary outcome.

For pharmacokinetics evaluation of plasma XEN1101 concentrations, we will assess these descriptively by means and standard deviations or medians and interquartile ranges among participants in the XEN1101 group at week 1 and week 8.

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17.6. **Safety Analysis**

All adverse events in this study will be analyzed from the time of randomization. All adverse events will be analyzed using the safety population. AEs will be mapped to the MedDRA coding system and presented by System Organ Class, MedDRA Preferred Term and treatment**.** The number and percentage of participants with an AE or serious AE will be presented over the course of the trial. In addition, protocol defined AEs of special interest (AESI) will be tabulated and presented over the course of the trial. For the incidence count, a participant will be counted only once for a specific MedDRA Preferred Term, although a MedDRA Preferred Term might be recorded more than once for a particular participant. The number and rate of each AE will also be presented.

The C-SSRS, BPRS-4, and the AUA scales are considered safety measures in this trial. Each scale generates a continuous score which will be summarized as mean and variance at each visit at which they are measured. In addition, each score will be reviewed for safety. The C-SSRS has 10 categories, where each item is binary as yes/no and an overall score can be created from the 10 categories. A C-SSRS score greater than 2 will trigger a safety review. The BPRS-4 is 4 items scored from 1 to 7. Any BPRS-4 item greater than 2 will lead to a safety review and a BPRS-4 item greater than a 3 will lead to participant discontinuation of study product. The AUA is 7 items scored between 0 and 5. A total AUA score greater than 7 that marks an increase from baseline will lead to a safety review and a total AUA score greater than 19 that marks an increase from baseline will lead to participant discontinuation of study product.

Ongoing emergent clinically significant abnormalities in laboratory results, vital signs measurements, electrocardiograms, ophthalmologic changes and physical exams will be reported and evaluated on a case by case basis.

17.7. **Interim Analysis**

There is no planned interim analysis for this study.

18. DDATA COLLECTION, RETENTION AND MONITORING

18.1. Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each participant treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a participant's visit into the protocol-specific electronic Case Report Form (eCRF) or paper source document when the information corresponding to that visit is available. Participants will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee) but will be identified by a site number and a participant number.

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For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

18.2. Remote Procedures

In light of the COVID-19 pandemic, the study team has elected to allow that some study procedures be completed remotely. Questionnaires may be completed via a Redcap survey link to be emailed by the study team to the email provided, rating scales may be completed via a HIPAA compliant video platform, and physician forms may be completed via a HIPAA compliant video platform. In addition, consent may be obtained via a HIPAA compliant video platform with signatures captured via electronic case report form in REDCap.

18.3. Data Management Procedures

The data will be entered into a CRF in the developed electronic data capture (EDC) system. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

18.4. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. For EDC studies: Queries are entered, tracked, and resolved through the EDC system directly. For paper studies: Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution.

The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

18.5. Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

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Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., DSMB reports and final statistical analysis), data for analysis is locked and cleaned per established procedures.

18.6. Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A de-identified dataset will be made available to Xenon Pharmaceuticals. A file for each participant must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that participant. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (participant files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) will be kept secured for a minimum period of seven years following study completion.

18.7. Monitoring

Monitoring visits will be conducted according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator-sponsor grants permission to the monitors and appropriate regulatory authorities to conduct remote or on-site monitoring and/or auditing of all appropriate study documentation.

18.8. Participant Confidentiality

In order to maintain participant confidentiality, only a site number and a participant number will identify all study participants on CRFs and other documentation.

19. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), OHRP regulations (45 CFR 46), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number only. All study records will be kept in a locked file cabinet and code sheets linking a participant's name to a participant identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (Health Insurance Portability and Accountability Act of 1996).

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19.1. Protocol Amendments

Any amendment to the protocol will be written by Dr. James Murrough. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to participants. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately, provided the IRBs and DSMB are notified within five working days.

19.2. Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning participant recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB unconditional approval statement will be transmitted by the Investigator-sponsor to all study site PIs or designees prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the participants of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

19.3. Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Participants (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A, 45 CFR 46, CFR 46.116,) the Health Insurance Portability and Accountability Act (HIPAA), and local regulations.

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The Investigator-sponsor will prepare the informed consent form, assent and HIPAA authorization. The consent form generated by the Investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The investigator will send an IRB-approved copy of the Informed Consent Form to Xenon Pharmaceuticals.

A properly executed, written, informed consent will be obtained from each participant prior to entering the participant into the trial. Information should be given in both oral and written form and participants must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the participant will also be obtained. If a participant is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the participant. A copy of the signed consent form (and assent) will be given to the participant and the original will be maintained with the participant's records.

19.4. Publications and Data Sharing

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Investigator-Sponsor, participating institutions, and Xenon Pharmaceuticals. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials"; for trials of drugs and biologics, this entails controlled, clinical investigations, other than Phase 1 studies, of a product participant to FDA regulation.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA and the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information.

All the data from this trial will be recorded in the National Database for Clinical Trials Related to Mental Illness (NDCT), an informatics platform for the sharing of human participants' data from all clinical trials funded by the National Institute of Mental Health (NIMH).

The data repository is accessible only to qualified investigators and all participant data will be de-identified and not linkable directly to the study participant. None of the personally identifiable information (PII) will be exposed and each participant will be identified with a Global Unique

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Identifier (GUID). All participants will be assigned a GUID by the Data Management Center (DMC) for this study. The following information will be collected and entered into the study database to generate a GUID: First name, Last name, Middle name (if applicable), Month of birth, Day of birth, Year of birth, Physical sex at birth, and Name of city/municipality of birth. Once the GUID is generated, all personal information will be deleted from the study database.

During and after study conclusion, qualified study team members will send de-identified information of study participants to the NDCT. The de-identified study data will be accessible for research purposes to other researchers nationwide under the supervision of the NIMH that will regulate and supervise the access to study data in order to minimize the risks to participants' privacy. NDCT data could also be used by NIMH to report to Congress and on its web site. For more information on NDCT, please refer to http://ndct.nimh.gov.

19.5. Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of participants.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Investigator-Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Investigator-Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 and 45 CFR 46 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB, DSMB, the FDA, and the Investigator-Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to participants or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the participants.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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20. APPENDIX

20.1. Table 3. Schedule of Events

Study Phase	Screening	Double-Blind Treatment Period (Weekly Study Visits)								Primary Outcome	Study Exit	Unscheduled
Study Visit	V-1	V0 [e]	V1	V2		V3		V4		V5	V6	
Week	-6 - 0	0	1	2	3	4	5	6	7	8	12	
Screening												
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Demographics	x											
Medical History	x	x	x	x		x		x		x	x	
Family Psychiatric History	x											
Antidepressant Treatment Response Questionnaire	x											
Edinburg Handedness Inventory	x											
SCID-5-RV	x											
CTQ	x											
TLEQ	x											
Study drug/Placebo administration												
Randomization		x										
XEN1101/Placebo Treatment		x	x	x	x	x	x	x	x	x		
Safety assessments, concomitant medication and compliance monitoring												
Concomitant Medication	x	x	x	x		x		x		x	x	x
Dilated Fundoscopic Exam	x										x	
Physical Exam	x	x	x	x		x				x	x	x
Vital Signs	x	x	x	x		x		x		x	x*	x
Laboratory Tests [a]	x	x				x				x	x*	x
ECG	x			x						x	x	x
U-Toxicology	x	x								x		
Pregnancy Test	x	x	x	x		x		x		x		x
Adverse Events Monitoring	x	x	x	x	x	x	x	x	x	x	x	x
C-SSRS [f]	x	x	x	x		x		x		x	x	
BPRS-4		x	x	x		x		x		x	x	
AUA Symptom Questionnaire		x				x				x	x	
Medication Compliance [b]		x	x	x		x		x		x	x	
Clinical efficacy assessments												
CGI-S [c]; CGI-I	x	x		x		x		x		x		
MADRS [c]		x		x		x		x		x		
SHAPS [c]	x	x		x		x		x		x		
TEPS		x		x		x		x		x		
[illegible]-SR		x		x		x		x		x		

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Behavioral efficacy assessments												
PRT		x								x		
Stock Market Task		x								x		
Pharmacokinetics												
XEN1101 blood level			x							x		
Biomarkers												
Neuroimaging [d]		x								x		

Note: Study visits 1-5 may occur 3 days before or after the scheduled visit.

[a] Clinical laboratory tests include chemistry, complete blood count, liver function tests, and thyroid-stimulating hormone levels (see protocol for details); [b] Compliance will be assessed by participant report, pill count and serum drug levels; [c] SHAPS score ≥ 20 and CGI-S score ≥ 4 required for inclusion; [d] Neuroimaging acquisition includes a high resolution T1 anatomical scan and BOLD acquisitions for resting state functional connectivity (rs-fMRI) and task-activation fMRI during the incentive flanker task (IFT); [e] Baseline assessment; [f] Performed as lifetime and past month at screening and since list visit at all following visits.

* These assessments will only be completed if a clinically significant abnormal value is found during the primary outcome visit.

Abbreviations: BPRS-4, Brief Psychotic Rating Scale – 4 item; CTQ, Childhood Trauma Questionnaire, C-SSRS, Columbia-Suicide Severity Rating Scale; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; ECG, Electrocardiogram; fMRI, functional Magnetic Resonance Imaging; MADRS, Montgomery-Asberg Depression Rating Scale; PRT, Probabilistic Reward Task; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report; SHAPS, Snaith-Hamilton Pleasure Scale; TEPS, Temporal Experience of Pleasure Scale; TLEQ, Traumatic Life Events Questionnaire.

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20.2. Table 4. List of Prohibited Medications*

Antidepressants					
Generic	**Trade name**				
Clomipramine	Anafranil (SR)	Placil			
Sertraline	Zoloft	Lustral			
Citalopram	Celexa				
Escitalopram	Lexapro	Cipralex			
Fluoxetine	Prozac				
Fluvoxamine	Luvox				
Duloxetine	Cymbalta				
Mirtazapine	Remeron	Remeron SolTab			
Paroxetine	Paxil	Seroxat			
Venlafaxine	Effexor				
Desvenlafaxine	Pristiq				
Levomilnacipran	Fetzima				
Tofenacin	Elamol	Tofacine			
Doxepine	Sinequan				
Desipramine	Norpramin	Pertofran			
Imipramine	Apo-Imipramine	Norfranil	Janimine	Novopramine	Impril
Mianserine	Tolvon				
Nefazodone	Dutonin	Serzone			
Protriptyline	Triptil	Vivactil	Concordin		
Reboxetine	Edronax				
Isocarboxazid	Marplan				
Phenelzine	Nardil				
Tranylcypromine	Parnate				
Selegiline	Deprenyl	Eldepryl	Emsam		
Centrally active sedating antihistamines					
Generic	**Trade name**				
Azelastine HCl	Astelin	Optivar			
Dimenhydrinate	Dramamine				
Hydroxyzine HCl	Atarax	Vistaril			
Levocabastine	Livostin				
Methdilazine					
Promethazine	Phenergan	Anergan	Pentazine	Phenazine	
	Phencen	Phenerzine	Phenoject	Pro-50	
	Promacot	Pro-Med 50	Promet	Prorex	
	Prothazine	Shogan	V-Gan-50		
Trimeprazine					
Antipsychotics					
Generic	**Trade name**				
Aripiprazole	Abilify				
Chlorpromazine	Chlorpromanyl	Largactil	Novo-Chlorpromazine	Thorazine	
Clozapine	Clozaril				
Fluphenazine decanoate	Modecate	Prolixin Decanoate			
Fluphenazine enanthate	Moditen Enanthate	Prolixin	Enanthate		
Fluphenazine HCl	Anatensol				
Haloperidol	Haldol	Dozic	Peridol	Serenace	
Lurasidone	Latuda				
Loxapine	Loxapac				
Mesoridazine Besylate	Serentil				
Molindone	Moban				
Olanzapine	Zyprexa				
Prochloperazine	Compazine				
Quetiapine Fumarate	Seroquel				
Risperidone	Risperdal				
Thioridazine HCl	Phenothiazines	Serentil	Prolixin	Thorazine	
	Mellaril	Trilaton	Vesprin		
Thiothixene	Navane				
Ziprasidone	Geodon				

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Psychotropics miscellaneous				
Generic	**Trade name**			
Lithium	Camcolit	Carbolith	Duralith	Eskalith
	Lituane	Lithicarb	Lithizine	Lithobid
	Lithonate	Lithotabs	Priadel	Cibalith-S
Modafinil	Provigil			
R-modafinil	Nuvigil	Armodafinil		
Phenelzine sulfate	Nardil			
Sodium oxybate	Xyrem			
Stimulants				
Dextroamphetamine	Dextrostat	Ferndex		
Amphetamine/dextroamphetamine	Adderall	Benzedrine		
Methamphetamine	Methedrone	Desoxyn	Gradumet	
Methylphenidate	Ritalin	Metadate	Methylin	Concerta

Dopaminergic agents (e.g. levodopa, pramipexole,)				
Generic	Trade name			
Levodopa	Sinemet			
Pramipexole	Mirapex			
Ropinorole	Requip			
Rotigotine	Neupro			
Anti-Seizure Medications				
Generic	Trade name			
Gabapentin	Neurontin			
Valproic Acid	Depakote			
Carbamazepine	Tegretol			
Lamotrigine	Lamictal			
Pregabalin	Lyrica			
Phenytoin	Phenytek	Dilantin Infatabs	Dilantin Kapseal	
Opioids				
Generic	Trade name			
Buprenorphine	Suboxone			
Dihydrocodeinone	Vicodin			
Methadone	Methadone			
Morphine	Morphine			
Oxycodone	Oxycontin			
Tramadol	Ultram			
(Dextro)propoxyphene	Darvon			
Meperidine	Demerol			

* In addition to specific medications listed, the following classes of medication are prohibited: (1) antidepressant medication, including natural products/supplements e.g., St John's wort, (2) antipsychotic medication, (3) anticonvulsant/mood stabilizer medications, (4) lithium, (5) stimulant medication. Hypnotic medications used PRN are allowed (including zolpidem, zaleplon, eszopliclone, diphenhydramine, suvorexant, and ramelteon) except within 24 hours of the baseline and primary outcome fMRI and behavioral assessments. Benzodiazepine medications used PRN (not to exceed 2 mg of lorazepam equivalents daily) except within 24 hours of the baseline and primary outcome fMRI and behavioral assessments.

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