PROTOCOL

A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder

Sponsor:	Xenon Pharmaceuticals Inc. 200-3650 Gilmore Way Burnaby, BC V5G 4W8 Canada
Study Number:	XPF-008-204
[redacted]	[redacted]
Compound:	XEN1101
Date:	10 March 2022 **Version:** 3.0

CONFIDENTIALITY STATEMENT

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without prior written authorization from Xenon Pharmaceuticals Inc. or its affiliates.

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the protocol, the International Council for Harmonisation Guidelines for Good Clinical Practice (ICH-GCP), and applicable regulatory requirements.

The protocol, informed consent forms(s), recruitment materials, and all subject materials will be submitted to the Ethics Committee/Institutional Review Board (EC/IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the EC/IRB before the changes are implemented. In addition, all changes to the consent form will be EC/IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

SPONSOR APPROVAL

STUDY TITLE: A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

SIGNATURES:

[redacted]

[redacted]

[redacted]

Signature Manifest

[redacted]

Title: Protocol XPF-008-204 Version 3.0 10 March 2022

Effective Date: 14 Mar 2022

All dates and times are in Pacific Time.

Protocol XPF-008-204 Version 3.0 10 March 2022

Approval

[redacted]

INVESTIGATOR AGREEMENT

STUDY TITLE: A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder

By signing below, I agree that:

I have read this protocol. I approve this document, and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Xenon Pharmaceuticals Inc. (Xenon) to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the investigational product and study procedures. I will let them know that this information is confidential and proprietary to Xenon and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Xenon, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with applicable local regulations, Ethics Committee/Institutional Review Board regulations, and International Council for Harmonisation Guidelines for Good Clinical Practice (ICH-GCP).

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE 2
SPONSOR APPROVAL 3
INVESTIGATOR AGREEMENT 4
PROTOCOL VERSION HISTORY 10
LIST OF ABBREVIATIONS 11
1. PROTOCOL SUMMARY 14
1.1. Synopsis 14
1.2. Schema 22
2. INTRODUCTION 22
2.1. Study Rationale 22
2.2. Background 23
2.3. Benefit-Risk Assessment 25
2.3.1. Potential for Harm Related to Study Drug 25
2.3.2. Suicidality 25
2.3.3. Activation of Mania/Hypomania: 26
2.3.4. Potential for Unforeseen Risks 26
2.3.5. Potential for Harm Unrelated to Study Drug 26
2.3.6. Potential Benefits Related to Study Drug and Study Participation 26
3. OBJECTIVES AND ENDPOINTS 27
4. STUDY DESIGN 28
4.1. Overall Design 28
4.2. Scientific Rationale for Study Design 29
4.3. Justification for Dose 29
4.4. End of Study Definition 30
5. STUDY POPULATION 30
5.1. Inclusion Criteria 30
5.2. Exclusion Criteria 31
5.3. Eligibility Confirmation 33
5.4. Contraception Requirements 33
5.4.1. Exposure to Partners During the Study 34
5.4.2. Sperm or Ova Donation 34

5.4.3. Pregnancy 35
5.5. Lifestyle Considerations 35
5.6. Screen Failures 35
6. STUDY INTERVENTION 35
6.1. Description of Study Drug 35
6.2. Dosing and Administration 35
6.3. Preparation, Handling, Storage, and Accountability 36
6.3.1. Acquisition and Accountability 36
6.3.2. Formulation, Appearance, Packaging, and Labeling 37
6.3.3. Product Storage and Stability 37
6.4. Randomization and Blinding 37
6.5. Study Drug Compliance 38
6.6. Concomitant Therapy 38
6.6.1. Prohibited Medications and Procedures 38
6.6.2. Permitted Medications and Interventions 38
7. WITHDRAWAL CRITERIA 38
7.1.1. Discontinuation of Study Medication 38
7.1.2. Subject Discontinuation/Withdrawal From the Study 39
7.1.3. Procedures Following Early Treatment Discontinuation/Withdrawal 40
7.1.4. Lost to Follow-up 40
8. STUDY ASSESSMENTS AND PROCEDURES 40
8.1. Procedures 40
8.2. Clinical Assessments 45
8.2.1. Demographics 45
8.2.2. Medical and Psychiatric History 45
8.2.3. Concomitant Medications 45
8.2.4. MINI (Version 7.0.2) 45
8.2.5. ATRQ 45
8.3. Efficacy Assessments 45
8.3.1. MADRS 45
8.3.2. SHAPS 45
8.3.3. BAI 46
8.3.4. HAM-D17 46

8.3.5. QIDS-SR 46
8.3.6. CGI-S 46
8.3.7. CGI-I 46
8.3.8. PGI-I 46
8.3.9. Biometric Device for Monitoring Activity and Sleep 47
8.4. Safety, PK, and Other Assessments 47
8.4.1. Physical Exams 47
[redacted]
8.4.3. Vital Signs, Height, Weight, and BMI 47
8.4.4. ECG (12-Lead) 47
8.4.5. Urological Symptoms as Measured by the AUA Symptom Index 48
8.4.6. Clinical Laboratory Tests 48
8.4.7. Suicide Risk as Assessed by the C-SSRS 50
8.4.8. Withdrawal Symptoms as Assessed by the CIWA-B 50
8.4.9. PK Blood Samples 50
8.5. AEs and SAEs 50
8.5.1. Definition of AEs 50
8.5.2. Definition of SAEs 51
8.5.3. Classification of an AE 52
8.5.3.1. Severity of Event 52
8.5.3.2. Causal Relationship to Study Drug 52
8.5.3.3. Expectedness 53
8.5.3.4. Time Period and Frequency of Event Assessment and Follow-up 53
8.5.3.5. AE Reporting 54
8.5.3.6. SAE Reporting 54
8.5.3.7. Reporting Events to Subjects 55
8.5.3.8. Reporting Pregnancy 55
8.5.3.9. Special Situation Reports 56
9. STATISTICAL CONSIDERATIONS 57
9.1. Statistical Hypothesis 57
9.1.1. Primary Hypothesis 57
9.1.2. Secondary Hypotheses 57
9.2. Multiplicity Adjustment 57

9.3. Populations for Analysis 57
9.4. Statistical Analysis 58
9.4.1. Primary Endpoint 58
9.4.2. Secondary Endpoints 59
9.4.3. Exploratory Endpoints 59
9.4.4. Safety Analysis 59
9.4.4.1. AEs 59
9.4.4.2. Clinical Laboratory Findings 59
9.4.4.3. ECGs 59
9.4.4.4. C-SSRS 59
9.4.4.5. Vital Signs 60
9.4.4.6. AUA Symptoms Index 60
9.4.4.7. CIWA-B 60
9.5. Sample Size Determination 60
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 61
10.1. Regulatory, Ethical, and Study Oversight Considerations 61
10.1.1. Informed Consent Process 61
10.1.1.1. Consent/Assent Provided to Subjects 61
10.1.1.2. Consent Procedures and Documentation 61
10.1.2. Study Discontinuation and Closure 62
10.1.3. Confidentiality and Privacy 62
10.1.4. Future Use of Stored Specimens and Data 63
10.1.5. Safety Oversight 63
10.1.6. Clinical Monitoring 63
10.1.7. Quality Assurance and Quality Control 64
10.1.8. Data Handling and Record Keeping 64
10.1.9. Data Collection and Management Responsibilities 64
10.1.10. Study Records Retention 65
10.1.11. Public and Data Sharing Policy 65
10.1.12. Conflict of Interest Policy 65
10.2. Additional Considerations 66
REFERENCES: 67

LIST OF TABLES

Table 1: Schedule of Assessments 41

LIST OF FIGURES

Figure 1: Study Design Schematic 22



LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ASM	Antiseizure medication
ATRQ	Antidepressant Treatment Response Questionnaire
AUA	American Urological Association
BAI	Beck Anxiety Inventory
BMI	Body mass index
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
CIWA-B	Clinical Institute Withdrawal Assessment - Benzodiazepines
CNS	Central nervous system
CRA	Clinical research associate
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Double-blind period
DBS	Deep brain stimulation
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ECT	Electroconvulsive therapy
EDC	Electronic data capture
ET	Early termination
FIH	First-in-human
fMRI	Functional magnetic resonance imaging
FOS	Focal onset seizure
GCP	Good Clinical Practice
HAM-D17	Hamilton Depression Rating Scale, 17-Item

Term	Definition
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IRB	Institutional review board
IRT	Interactive response technology
K^+	Potassium
KCNQ	Potassium voltage-gated channel subfamily Q (alias K_V7)
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	Missing at random
MDD	Major depressive disorder
MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
PD	Pharmacodynamic
PGI-I	Patient Global Impression of Improvement
PK	Pharmacokinetics
PP	Per protocol
PRT	Probabilistic reward task
QC	Quality control
QD	Once daily
QIDS-SR	Quick Inventory of Depressive Symptomatology, Self-Report
QTcF	QT interval corrected for heart rate by Fridericia's formula
SAE	Serious adverse event
SAFER	State versus trait, assessability, face validity, ecological validity, rule of three Ps
SAP	Statistical analysis plan

Term	Definition
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-D	Structured Interview Guide for the HAM-D
SIGMA	Structured Interview Guide for the MADRS
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TMS	Transcranial magnetic stimulation
VNS	Vagus nerve stimulation
VS	Ventral striatum

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:	A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder	
Protocol Number:	XPF-008-204	
Version Number:	3.0	
Phase:	Phase 2	
Indication:	Major Depressive Disorder (MDD)	
Objectives and Endpoints:	**Objectives**	**Endpoints**
	Primary Efficacy	
	Assess the efficacy of 10 mg and 20 mg doses of XEN1101 compared to placebo on improvement of depressive symptoms in subjects diagnosed with MDD.	Montgomery-Åsberg Depression Rating Scale (MADRS) score change through Week 6.

	Primary Safety	
	Assess the safety and tolerability of 10 mg and 20 mg of XEN1101 compared to placebo in subjects diagnosed with MDD.	• Treatment-emergent adverse events (TEAEs). • Serious adverse events (SAEs). • Adverse events (AEs) requiring reduction or withdrawal of study drug. • Changes in laboratory measures, vital signs, weight, and electrocardiograms (ECGs). • Suicide risk as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS). • Clinically significant changes in urological symptoms, including screening, using the American Urological Association (AUA) symptom index. • [redacted] • Withdrawal symptoms assessed using the Clinical Institute Withdrawal Assessment – Benzodiazepines (CIWA-B) scale.
	Secondary Efficacy	
	To assess the efficacy of XEN1101 compared to placebo on improvement of anhedonia symptoms.	Snaith-Hamilton Pleasure Scale (SHAPS) score change through Week 6.
	To assess the efficacy of XEN1101 compared to placebo on improvement of anxiety symptoms.	Beck Anxiety Inventory (BAI) score change through Week 6.
	Exploratory/Additional	
	To evaluate the effect of XEN1101 compared to placebo on depressive symptoms.	• Change in the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) score through Week 6. • Responder rate at Week 6, defined as the percentage of subjects with ≥50% reduction in MADRS score. • Percentage of subjects in remission (MADRS ≤10) at Week 6.

		• Hamilton Depression Rating Scale, 17-Item (HAM-D17) change in score through Week 6. • MADRS score, SHAPS score, BAI score, QIDS-SR score, and HAM-D17 score at all timepoints and change from baseline to all timepoints.
	To assess the effect of XEN1101 compared to placebo on overall health status.	• Clinical Global Impression of Improvement (CGI-I) score at Week 6. • Clinical Global Impression of Severity (CGI-S) change in score at Week 6. • Patient Global Impression of Improvement (PGI-I) score at Week 6.
	To assess the effect of XEN1101 compared to placebo on sleep and activity.	Change in sleep parameters and activity measures using a biometric device.
	To evaluate the pharmacokinetic (PK) effect of XEN1101.	Evaluation of PK parameters of XEN1101 and/or metabolites.
Duration of Study:	The total study duration per subject is estimated to be approximately 14 weeks (3.5 months). 1. Screening: up to 4 weeks. 2. Treatment period: 6 weeks. 3. Follow-up: 4 weeks. Definition of end of trial: Last subject last visit.	
Study Design Overview:	Blinding: Double-blind, subject and investigator. Randomization and stratification characteristics: Randomization 1:1:1 (XEN1101 10 mg:XEN1101 20 mg:placebo). Description of dosing schema: Parallel assignment (approximately N=50 subjects each in the placebo and XEN1101 10 and 20 mg arms). See Figure 1.	
Study Population:	Male and female subjects aged 18 through 65 years (inclusive), diagnosed with MDD. Approximately 150 randomized and evaluable subjects (approximately 50 subjects per treatment group).	

Eligibility Criteria:	**Inclusion Criteria:** Subjects will be considered eligible to participate in the study if they meet all the following inclusion criteria: 1. Be properly informed of the nature and risks of the study and given informed consent in writing, prior to entering the study. 2. Male or female, aged 18 through 65 years (inclusive) with a body mass index (BMI) ≤35 kg/m^2. 3. Subject must meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria for current MDD and currently in a moderate to severe major depressive episode (MDE), confirmed using the Mini International Neuropsychiatric Interview (MINI). 4. Current MDE duration ≥2 months and <24 months at the time of screening. 5. Current illness severity that is at least moderate, defined as a score of ≥20 on the HAM-D17 at screening and on Day 1. 6. Score ≥20 on the SHAPS at screening and on Day1. 7. Must be willing to comply with the contraception requirements as defined in the study protocol. 8. Male subjects must agree not to donate sperm from the time of the first dose of study drug until 3 months after the last dose of study drug. Female subjects must agree not to donate ova from the time of the first dose of study drug until 3 months after the last dose of study drug. 9. Ability and willingness to wear a biometric device for tracking sleep and activity for the full term of the study. 10. Able to participate for the full term of the study. 11. Confirmation of eligibility using the state versus trait, assessability, face validity, ecological validity, rule of three Ps (SAFER) Criteria Interview performed by the remote SAFER centralized rater. **Exclusion Criteria:** Subjects who meet any of the following criteria will not qualify for entry into the study: 1. A primary psychiatric diagnosis other than MDD as defined by DSM-5 (comorbid anxiety disorders [including agoraphobia, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), and panic disorder] are allowed). 2. Use of antidepressants and/or other disallowed pharmacotherapy (including benzodiazepines, see Section 6.6), within the 2 weeks (4 weeks for fluoxetine) or within a period less than 5-times the drug's half-life, whichever is longer, prior to randomization through the end of the treatment period. 3. History of schizophrenia or other psychotic disorder, MDD with psychotic features, bipolar I or II disorder, or MDD with mixed features. 4. History of non-response to >1 antidepressant drug due to lack of efficacy in the current MDE. Non-response is defined as persistent depressive symptoms despite treatment with adequate doses of an antidepressant for an adequate amount of

	time (at least 6 weeks), as determined by the Antidepressant Treatment Response Questionnaire (ATRQ). (Addition of an augmentation drug to the antidepressant regimen will be counted as an "antidepressant" treatment.) 5. Failing >3 antidepressant drug trials, for any reason, in the current MDE. 6. History of non-response to electroconvulsive therapy (ECT) in the past 10 years. 7. History of deep brain stimulation (DBS) or vagus nerve stimulation (VNS). 8. Use of transcranial magnetic stimulation (TMS) in the current MDE. 9. A current diagnosis of depression with peripartum onset. 10. A current diagnosis of MDD with catatonia (catatonic features). 11. A current diagnosis of MDD with seasonal pattern. 12. Active suicidal plan/intent in the past 6 months (a score of 3 or more in the Baseline/Screening C-SSRS suicidal ideation section), presence of suicidal behavior in the last 5 years (a score of 5 or more in the Baseline/Screening C-SSRS suicidal behavior section), or more than 1 lifetime suicide attempt. 13. History of non-suicidal self-harm in the current episode or past 12 months, whichever is longer (answer "yes" to non-suicidal self-harm question in the Baseline/Screening C-SSRS). 14. History of borderline personality disorder or presence of clinically significant borderline personality traits, as determined by the investigator. 15. History or presence, at screening, of any significant medical or surgical condition, uncontrolled medical illness, or any other condition that would place the subject at increased risk as determined by the investigator. This includes, but is not limited to, conditions involving the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, endocrine, hepatic, or urogenital systems. 16. History of seizures in the last 10 years. 17. Detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at screening. 18. History of cancer within the past 2 years, with the exception of appropriately treated basal cell or squamous cell carcinoma. 19. Alanine transferase (ALT; SGPT) or aspartate transferase (AST; SGOT) levels >2-times the upper limit of normal (ULN) at screening. 20. History of hypothyroidism or hyperthyroidism unless currently treated and treatment has remained stable for the last 3 months. 21. Thyroid stimulating hormone (TSH) <0.75-times or >1.25-times the normal range. 22. Any clinically significant abnormality in pre-study laboratories or physical examination, including vital signs and ECG, that indicates a medical condition that would preclude study participation, as determined by the investigator. This includes but is not limited to: A history of long QT syndrome; a QT interval corrected for heart rate by Fridericia's formula (QTcF) >450 ms at screening; a family history of sudden death of unknown cause; or an HbA1C >8.5%. 23. History of skin or retinal pigment epithelium abnormalities caused by ezogabine. 24. [redacted]

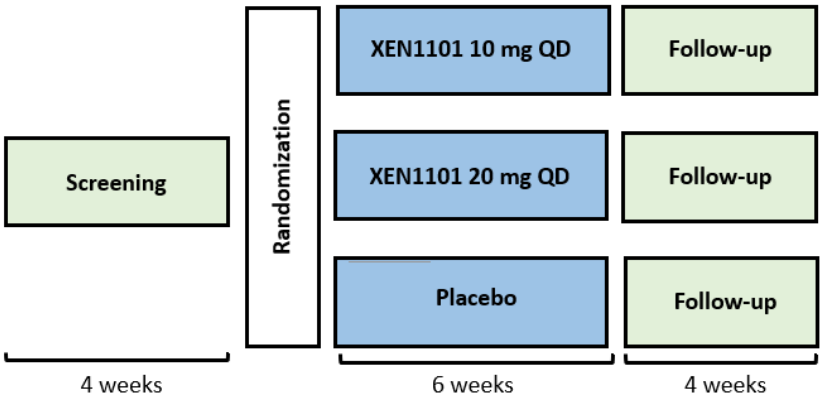
	25. Females who are pregnant, breastfeeding, or planning to become pregnant during the first administration of study drug until 3 months after the last dose of study drug. 26. Meets criteria for a substance use disorder within the past 12 months, with the exception of tobacco use, and/or has a positive urine toxicology screen for drugs of abuse. A positive urine test for cannabinoids at screening will not necessarily exclude the subject as long as the investigator deems the positive result does not meet DSM-5 criteria for a substance use disorder. In addition, a subsequent negative test will be required during the screening period before Visit 2. A positive urine test for benzodiazepines at screening in subjects prescribed benzodiazepines will not be considered exclusionary from the study. However, a subsequent negative test will be required during the screening period at the end of the tapering/wash-out period and before Visit 2. 27. Exposure to any other investigational drug or device within 5 half-lives or 30 days prior to screening, whichever is longer. 28. Have had multiple drug allergies or a severe drug reaction including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions. 29. Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the subject to unacceptable risk by participating in the study or prevents adherence to the protocol. 30. Employees of Xenon Pharmaceuticals Inc., the contract research organization (CRO), or study site personnel directly affiliated with this study and their immediate family members. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
Investigational Medicinal Product:	A capsule containing the active pharmaceutical ingredient XEN1101, to be administered orally.
Dose:	Study drug (10 mg, 20 mg, or matching placebo) taken once daily (QD), [redacted]

Prohibited Concomitant Medications:	The following concomitant medications and procedures are prohibited during the study: • Antidepressants, antipsychotics, antiseizure medications (ASMs), mood stabilizers, benzodiazepines, lithium, stimulants, and opioids within the 2 weeks (4 weeks for fluoxetine) or within a period less than 5-times the drug's half-life, whichever is longer, prior to randomization through the end of the treatment period. • ECT, DBS, TMS, and VNS. • Recreational or medicinal use of marijuana, cannabinoids, and/or derivatives, including cannabidiol (CBD). • Drugs of abuse or any prescribed or over-the-counter medication used in a manner that the investigator considers indicative of abuse, dependence, or habitual use. • Any other investigational drug or device within 5 half-lives of its pharmacological/therapeutic effect or 30 days prior to screening, whichever is longer.
Permitted Medications:	As needed (PRN) use of nonbenzodiazepine hypnotic agents (including zolpidem, zaleplon, eszopiclone, diphenhydramine, suvorexant, lemborexant, and ramelteon). Subjects receiving psychotherapy may continue treatment provided the therapy has been ongoing and stable for at least 3 months prior to screening and is expected to remain unchanged during the study treatment period. Subjects who need to start psychotherapy during the study will be discontinued.

Statistical Considerations:	The primary efficacy endpoint of change from baseline in MADRS score through Week 6 will be analyzed in all randomized and treated subjects (modified intent-to-treat [mITT]) population, based on a mixed-effect model for repeated measures (MMRM). The MMRM will use change from baseline as the outcome variable and will include the baseline MADRS score, sex, treatment group, visit, and treatment-by-visit interaction as fixed effects. The analysis will include all postbaseline assessments up to Week 6, regardless of treatment discontinuation status. All mITT subjects will, by definition, contribute postrandomization endpoint data to the primary analysis; data missing from other postbaseline visits will not be imputed and will be assumed to be missing at random (MAR). An unstructured covariance matrix shared across treatment groups will be used to model the within-subject variabilities. The model will be fitted using a restricted maximum likelihood method. The difference between treatment groups will be estimated based on least-squares means at the Week 6 visit within the framework of the MMRM model. Descriptive assessment of MAR assumption and sensitivity analyses to assess the impact of missing data will be described in the statistical analysis plan (SAP). The primary analysis will be performed after all randomized subjects have completed their Week 6 visit (or discontinued the study early). A MADRS change from baseline of -12 and -17 in placebo and both XEN1101 arms, respectively, and a common standard deviation of 9.5, are assumed and consistent with literature from other clinical trials in MDD. In a repeated measures (2-sided) test for the difference in 2 means, a sample size of 48 subjects per arm will provide 80% power to reject the null hypothesis of no difference between placebo and a XEN1101 dose arm using a 0.05 significance level, assuming compound symmetry and a correlation of 0.5 between observations within subject (PASS 2019, v19.06). Expanding this to all 3 intervention arms, and assuming an overall dropout rate of 10%, a total sample size of 150 subjects will provide at least 80% power to reject a specific hypothesis, and 96% power to reject at least 1, with the above assumptions for variance and effect size.

1.2. Schema

Figure 1: Study Design Schematic

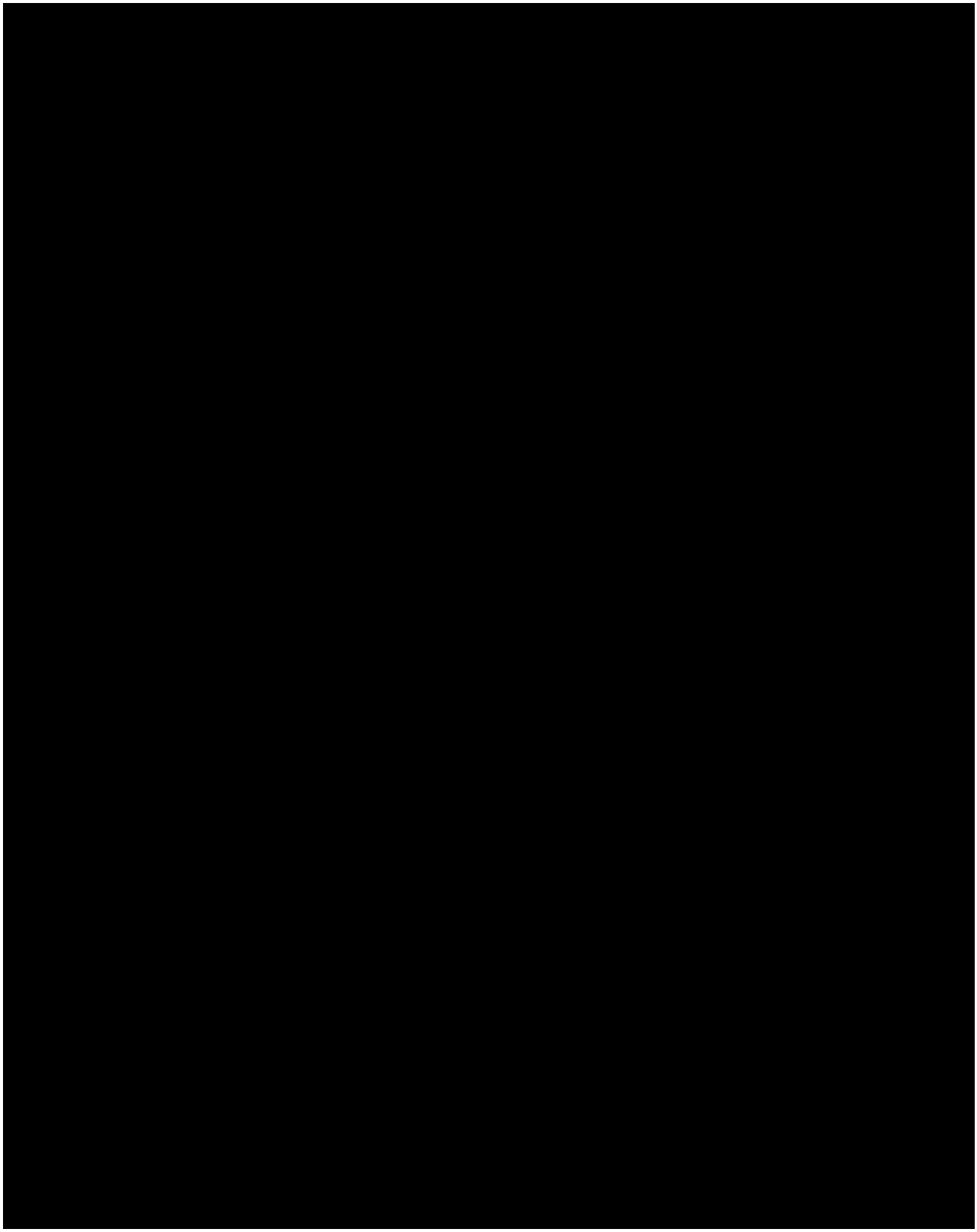


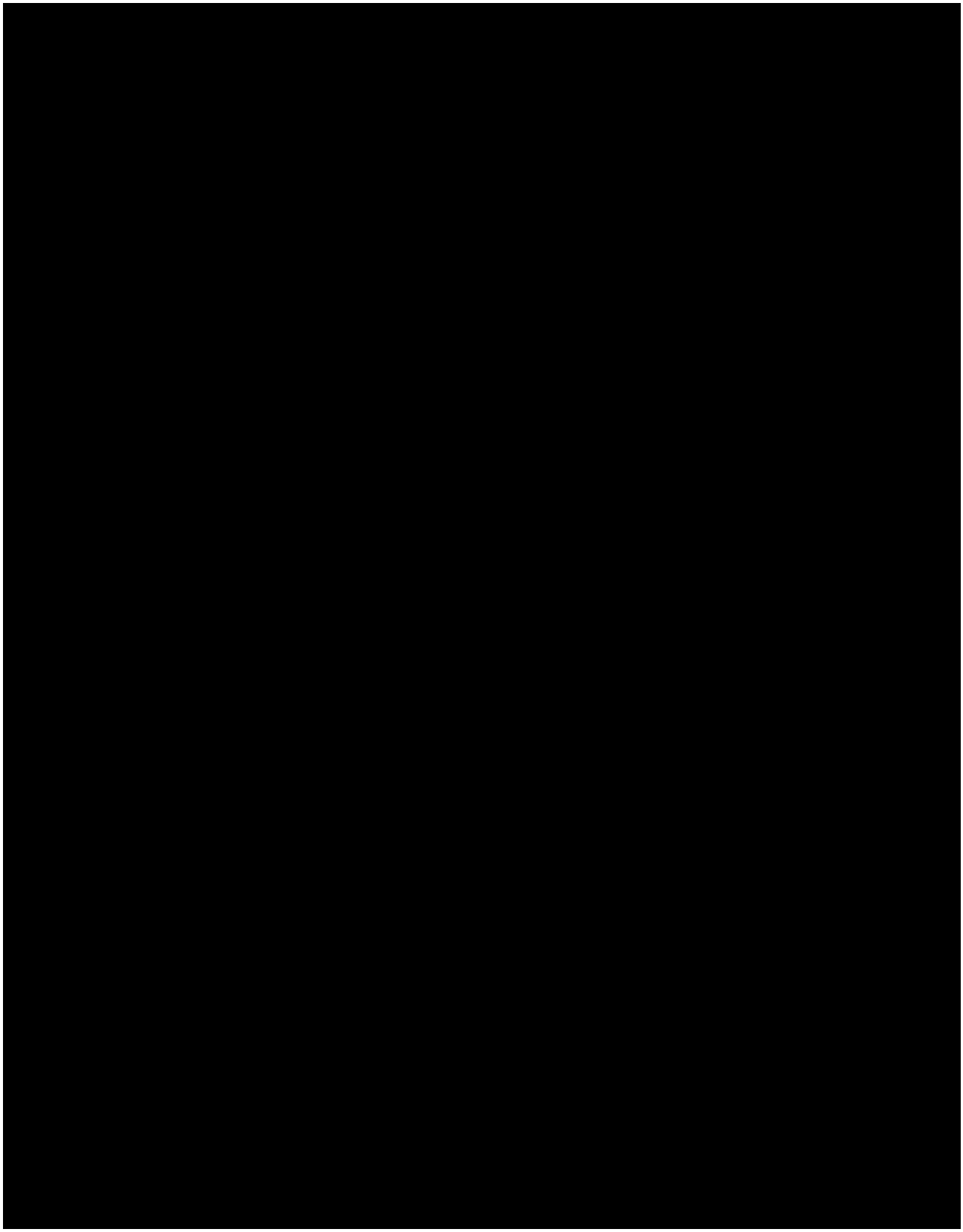
2. INTRODUCTION

2.1. Study Rationale

[redacted]

2.2. Background





2.3. Benefit-Risk Assessment

2.3.1. Potential for Harm Related to Study Drug

[redacted]

2.3.2. Suicidality

ASMs have been found to increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive-therapy) of 11 different ASMs showed that subjects randomized to 1 of the ASMs 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 subjects 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 ASM-treated subjects was 0.43% compared to 0.24% among 16,029 placebo-treated subjects, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 subjects treated. In these trials, there were 4 suicides in drug-treated subjects and 0 suicides in placebo-treated subjects; however, the number is too small to allow any conclusion about drug effect on suicide (Food and Drug Administration 2008).

Suicidal ideation and behavior will be monitored during the length of the study through clinical assessments at screening and exit visits as well as 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.

2.3.3. Activation of Mania/Hypomania:

Antidepressants can precipitate manic/hypomanic episodes in bipolar disorder patients during the depressed phase of their illness. [redacted]

2.3.4. Potential for Unforeseen Risks

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

2.3.5. Potential for Harm Unrelated to Study Drug

The following additional sources of potential discomfort or harm could occur:

- Venous puncture: Subjects 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 perform the procedure. Infection is avoided by adequate cleansing of the skin prior to intravascular line insertion.
- Questionnaires: Some subjects may experience psychological distress when asked to answer personal questions about their emotions. In this case, study investigators or designated study site staff will remind subjects that they can refuse to answer any upsetting questions. Clinicians will also be available to meet with any distraught individuals.
- Privacy risks: The potential for loss of private information always exists; however, there are procedures in place to minimize this risk (see Section 10.1.3).

2.3.6. Potential Benefits Related to Study Drug and Study Participation

Subjects may not receive any direct benefit from participating in this study. There is a small possibility that an unrelated medical condition will be detected during the procedures conducted in this study that could have health benefits for some individuals. Potential benefits of XEN1101 to the subjects diagnosed with MDD enrolled in this study may be a reduction in the severity of depression symptoms. However, some individuals may have no change in their symptoms or get worse due to the effects of the study drug or due to the natural course of their illness.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy	
Assess the efficacy of 10 mg and 20 mg doses of XEN1101 compared to placebo on improvement of depressive symptoms in subjects diagnosed with MDD.	Montgomery-Åsberg Depression Rating Scale (MADRS) change in score through Week 6.
Primary Safety	
Assess the safety and tolerability of 10 mg and 20 mg of XEN1101 compared to placebo in subjects diagnosed with MDD.	• TEAEs. • SAEs. • AEs requiring reduction or withdrawal of study drug. • Changes in laboratory measures, vital signs, weight, and electrocardiograms (ECGs). • Suicide risk as assessed by the C-SSRS. • Clinically significant changes in urological symptoms, including screening, using the American Urological Association (AUA) symptom index. • [redacted] • Withdrawal symptoms assessed using the Clinical Institute Withdrawal Assessment – Benzodiazepines (CIWA-B) scale.
Secondary Efficacy	
To assess the efficacy of XEN1101 compared to placebo on improvement of anhedonia symptoms.	SHAPS score change through Week 6.
To assess the efficacy of XEN1101 compared to placebo on improvement of anxiety symptoms.	Beck Anxiety Inventory (BAI) score change through Week 6.

Objectives	Endpoints
Exploratory/Additional	
To evaluate the effect of XEN1101 compared to placebo on depressive symptoms.	• Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) change in score though Week 6. • Responder rate at Week 6, defined as the percentage of subjects with ≥50% reduction in MADRS score. • Percentage of subjects in remission (MADRS ≤10) at Week 6. • Hamilton Depression Rating Scale, 17-Item (HAM-D17) change in score through Week 6. • MADRS score, SHAPS score, BAI score, QIDS-SR score, and HAM-D17 score at all timepoints and change from baseline to all timepoints.
To assess the effect of XEN1101 versus placebo on overall health status.	• CGI-I score at Week 6. • Clinical Global Impression of Severity (CGI-S) change in score at Week 6. • PGI-I score at Week 6.
To assess the effect of XEN1101 compared to placebo on sleep and activity.	Change in sleep parameters and activity measures using a biometric device.
To evaluate the PK effect of XEN1101.	Evaluation of PK parameters of XEN1101 and/or metabolites.

The estimand for the primary objective is the estimated 6-week difference in MADRS score between adults diagnosed with MDD who receive 10 mg or 20 mg XEN1101 versus placebo and provide at least 1 on-treatment MADRS result.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, Phase 2, double-blind, randomized, parallel-arm, placebo-controlled clinical trial to evaluate the efficacy, safety, and tolerability of XEN1101 in subjects with a primary diagnosis of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).

The initial intervention is a parallel assignment with approximately 50 subjects per treatment arm. A sufficient number of subjects will be screened to ensure approximately 150 randomized and evaluable subjects. Subjects will be randomized in a blinded manner to XEN1101 10 mg

QD, XEN1101 20 mg QD, or placebo in a 1:1:1 fashion. The blinding is double; subjects and investigators will be blind to treatment allocation.

The study is divided into 3 stages:

1. Screening – up to 4 weeks duration.
2. Treatment – 6 weeks duration.
3. Follow-up – 4 weeks duration.

The total study duration per subject is estimated to be up to approximately 14 weeks (approximately 3.5 months).

Subjects will be screened (Visit 1) within 28 days prior to entering the study on Day 1 (Visit 2/randomization visit). Each subject will receive verbal and written information followed by signing of the informed consent form (ICF) prior to any screening procedures taking place. Eligible subjects will be randomized and receive a supply of the study drug on Study Day 1. Each subject will receive 1 of the 3 experimental treatments and will take a daily dose of study drug or placebo for 6 weeks. Evaluations will be taken at screening (Week 0), Weeks 1, 2, 3, 4, and 6 (primary outcome, end of treatment [EOT]), and at Weeks 7 and 10 for post-treatment follow-up (see Table 1 and Figure 1).

4.2. Scientific Rationale for Study Design

The proposed study uses a randomized controlled design which is the gold standard for clinical trials. For a proof-of-concept study of this size, a parallel-group, dose-ranging, double-blind, randomized, placebo-controlled, multicenter study utilizing 6 weeks of treatment was chosen to efficiently detect signals for potential efficacy and safety in subjects diagnosed with MDD and to provide information for further exploration in subsequent studies, if warranted. Elements have been added to the conduct of the study to ensure the correct subjects are enrolled and to help reduce a potential placebo response. These include use of appropriate entry criteria, structured interviews, rater training, and surveillance and confirmation of subject eligibility by an external rater using the state versus trait, assessability, face validity, ecological validity, rule of three Ps (SAFER) Criteria Interview.





4.4. End of Study Definition

A subject is considered to have completed the study once the subject has completed all stages of the study including the last scheduled procedures (see Table 1).

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects will be considered eligible to participate in the study if they meet all of the following inclusion criteria:

1. Be properly informed of the nature and risks of the study and give informed consent in writing, prior to entering the study.
2. Male or female, aged 18 to 65 years (inclusive) with a body mass index (BMI) ≤35 kg/m^2.
3. Subjects must meet the DSM-5 criteria for current MDD and currently in a moderate to severe major depressive episode (MDE), confirmed using the Mini International Neuropsychiatric Interview (MINI).
4. Current MDE duration ≥2 months and <24 months at the time of screening.
5. Current illness severity that is at least moderate, defined as a score of ≥20 on the Hamilton Depression Rating Scale, 17-Item (HAM-D17) at screening and on Day 1.
6. Score of ≥20 in the SHAPS at screening and on Day 1.
7. Must be willing to comply with the contraception requirements as defined in protocol.
8. Male subjects must agree not to donate sperm from the time of the first dose of study drug until 3 months after the last dose of study drug. Female subjects must agree not to donate ova from the time of the first dose of study drug until 3 months after the last dose of study drug.

9. Ability and willingness to wear a biometric device for tracking sleep and activity for the full term of the study.
10. Able to participate for the full term of the study.
11. Confirmation of eligibility using the SAFER Criteria Interview performed by the remote SAFER centralized rater.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria will not qualify for entry into the study:

1. A primary psychiatric diagnosis other than MDD as defined by DSM-5 (comorbid anxiety disorders [including agoraphobia, generalized anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), and panic disorder] are allowed).
2. Use of antidepressants and/or other disallowed pharmacotherapy (including benzodiazepines, see Section 6.6), within the 2 weeks (4 weeks for fluoxetine) or within a period less than 5-times the drug's half-life, whichever is longer, prior to randomization through the end of the treatment period.
3. History of schizophrenia or other psychotic disorder, MDD with psychotic features, bipolar I or II disorder, or MDD with mixed features.
4. History of non-response to >1 antidepressant drug due to lack of efficacy in the current MDE. Non-response is defined as persistent depressive symptoms despite treatment with adequate doses of an antidepressant for an adequate amount of time (at least 6 weeks), as determined by the Antidepressant Treatment Response Questionnaire (ATRQ). (Addition of an augmentation drug to the antidepressant regimen will be counted as an "antidepressant" treatment.)
5. Failing >3 antidepressant drug trials, for any reason, in the current MDE.
6. History of non-response to electroconvulsive therapy (ECT) in the past 10 years.
7. History of deep brain stimulation (DBS) or vagus nerve stimulation (VNS).
8. Use of TMS in the current MDE.
9. A current diagnosis of depression with peripartum onset.
10. A current diagnosis of MDD with catatonia (catatonic features).
11. A current diagnosis of MDD with seasonal pattern.
12. Active suicidal plan/intent in the past 6 months (a score of 3 or more in the Baseline/Screening C-SSRS suicidal ideation section), presence of suicidal behavior in the last 5 years (a score of 5 or more in the Baseline/Screening C-SSRS suicidal behavior section), or more than 1 lifetime suicide attempt.
13. History of non-suicidal self-harm in the current episode or past 12 months, whichever is longer (answer "yes" to non-suicidal self-harm question in the Baseline/Screening C-SSRS).

14. History of borderline personality traits or presence of clinically significant borderline personality traits as determined by the investigator.
15. History or presence, at screening, of any significant medical or surgical condition, uncontrolled medical illness, or any other condition that would place the subject at increased risk as determined by the investigator. This includes, but is not limited to, conditions involving the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, endocrine, hepatic, or urogenital systems.
16. History of seizures in the last 10 years.
17. Detectable hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at screening.
18. History of cancer within the past 2 years, with the exception of appropriately treated basal cell or squamous cell carcinoma.
19. Alanine transferase (ALT; SGPT) or aspartate transferase (AST; SGOT) levels >2-times the upper limit of normal (ULN) at screening.
20. History of hypothyroidism or hyperthyroidism unless currently treated and treatment has remained stable for the last 3 months.
21. Thyroid stimulating hormone (TSH) <0.75-times or >1.25-times the normal range.
22. Any clinically significant abnormality in pre-study laboratories or physical examination, including vital signs and ECG, that indicates a medical condition that would preclude study participation, as determined by the investigator. This includes but is not limited to: A history of long QT syndrome; a QT interval corrected for heart rate by Fridericia's formula (QTcF) >450 ms at screening; a family history of sudden death of unknown cause; or an HbA1C >8.5%.
23. [redacted]
24. [redacted]
25. Females who are pregnant, breastfeeding, or planning to become pregnant during the first administration of study drug until 3 months after the last dose of study drug.
26. Meets criteria for a substance use disorder within the past 12 months, with the exception of tobacco use, and/or has a positive urine toxicology screen for drugs of abuse. A positive urine test for cannabinoids at screening will not necessarily exclude the subject as long as the investigator deems the positive result does not meet DSM-5 criteria for a substance use disorder. In addition, a subsequent negative test will be required during the screening period before Visit 2. A positive urine test for benzodiazepine at screening in subjects prescribed benzodiazepines will not be considered exclusionary from the study. However, a subsequent negative test will be required during the screening period at the end of the tapering/wash-out period and before Visit 2.

27. Exposure to any other investigational drug or device within 5 half-lives or 30 days prior to screening, whichever is longer.
28. Have had multiple drug allergies or a severe drug reaction, including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
29. Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the subject to unacceptable risk by participating in the study or prevents adherence to the protocol.
30. Employees of Xenon Pharmaceuticals Inc., the contract research organization (CRO), or study site personnel directly affiliated with this study and their immediate family members. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

5.3. Eligibility Confirmation

To ensure enrollment of appropriate subjects, remote raters will perform an independent eligibility assessment using the SAFER Criteria Interview. The assessments performed during the remote interview will include the MINI, ATRQ, SAFER Criteria Interview, and HAM-D17. The raters will review and approve eligibility for each subject entering the study. Only subjects who meet all eligibility criteria and are approved by the remote rater will be randomized.

5.4. 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 combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
  - Oral
  - Intravaginal
  - Transdermal
- Barrier method plus progestogen-only hormonal contraception associated with inhibition of ovulation as follows:

  - Oral
  - Injectable
  - Implantable
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner: Only if that partner is the sole sexual partner of the female trial participant who is of childbearing potential, and the vasectomized partner has documented evidence of surgical success, by confirmation of azoospermia, if possible.
- True sexual abstinence, when this is in-line with the preferred and usual lifestyle of the trial participant.

  Note: Periodic abstinence (ovulation calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicide only, and declaration of abstinence only for the duration of exposure to study drug, are not acceptable methods of contraception.

[redacted] 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.

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.

For male subjects who have had a vasectomy (with documented evidence of surgical success, by confirmation of azoospermia, if possible) and who agree to use a barrier method (male condom) for the stated time period, no additional contraceptive method is required by their female partner.

[redacted]

5.4.2. Sperm or Ova Donation

Male subjects should not donate sperm from the first dose of study drug, for the duration of the study, and for at least 3 months after the last dose of study drug. Female subjects should not

donate ova from the first dose of study drug, for the duration of the study, and for at least 3 months after the last dose of study drug.

5.4.3. Pregnancy

Subjects will be instructed to report to the investigator if they/their partner become pregnant during the study or within 3 months after the last dose of study drug. Refer to Section 8.5.3.8 for details on reporting a pregnancy.

5.5. Lifestyle Considerations

Subjects in the trial are encouraged to live a healthy lifestyle, with adequate sleep, and to avoid substance abuse, including excessive alcohol consumption. Alcohol consumption will be limited to 2 standard units of alcohol per day (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits). [redacted]

5.6. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are subsequently not eligible to enter the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information to be captured in the electronic case report form (eCRF) includes date of screening visit, demography, reason for screen failure and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened on a case-by-case basis (subject to sponsor review/approval).

6. STUDY INTERVENTION

6.1. Description of Study Drug

XEN1101 is a small molecule $K_V7.2/3$ potassium channel opener [redacted]

6.2. Dosing and Administration

Each subject who meets all the inclusion criteria and none of the exclusion criteria will be randomly assigned to 1 of the 3 arms of the study in a ratio of 1:1:1 (10 mg XEN1101:20 mg XEN1101:placebo). [redacted]

[redacted] Study drug compliance will be reviewed by site staff during scheduled and unscheduled visits.

Study drug capsules will be taken QD, and subjects should adhere to an approximately 24-hour interval between scheduled doses, as much as possible. Study drug will be supplied to the site through an interactive response technology (IRT) system. The site will provide subjects with one 14-count bottle of capsules of the study drug at randomization/study Visit 2 (Study Day 1) and a resupply of study drug biweekly at Visit 4 and Visit 6 (Study Day 14 and Study Day 28). Fourteen-count bottles may also be delivered directly to subjects via courier between study visits, as necessary, to ensure no interruption in dose administration. Subjects will be instructed to swallow the study drug capsules whole and never to chew, divide, open, sprinkle the contents, or crush the capsules.

[redacted]

[redacted] (see Section 7.1.3).

Detailed instructions for study drug administration and storage will be included in the pharmacy manual and the ICF.

6.3. Preparation, Handling, Storage, and Accountability

6.3.1. Acquisition and Accountability

The study drug will be stored in a locked storage unit with restricted access by the designated study personnel at each site. The site staff will perform an ongoing inventory of study drug supplies. The clinical research associate (CRA) monitoring the investigational site must keep an accurate inventory of study drug shipments received and the amount of study drug dispensed per subject. A full reconciliation of drug inventory will be performed, and the results of the inventory recorded in the drug accountability log. 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.

6.3.2. Formulation, Appearance, Packaging, and Labeling

[redacted] XEN1101 will be supplied in capsules at drug dosage strengths of 10 mg and 20 mg.

The matching placebo is formulated as identical-looking capsules filled with [redacted].

The drug product and placebo will be packaged in sealed [redacted] bottles.

The bottles will be labeled with an appropriate multi-language label, in compliance with applicable regulations for investigational drugs.

The following information will be included on the labels for the DBP:

- A statement indicating that the study drug is an investigational drug to be used only by a qualified investigator (eg, "for clinical trial use only").
- Bottle/kit number.
- Recommended storage conditions.
- Lot number.
- Name and address of the sponsor.
- Protocol number.

6.3.3. Product Storage and Stability

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). Refer to the pharmacy manual for further details.

Subjects 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.

6.4. Randomization and Blinding

Study drug will be administered under double-blind conditions; subjects and investigators will be blinded to treatment assignment. Sponsor and CRO staff will also remain blinded with the exception of pre-identified individuals from the sponsor or designee. If there is a medical need to reveal the assigned dose administered to a subject, the code-break procedures, as described by the IRT provider, will be followed. In the event of an emergency, it is the investigator's responsibility to evaluate the necessity of unblinding the subject's treatment assignment. If the investigator proceeds with the unblinding, the investigator should notify the medical monitor as soon as feasible that the unmasking event occurred, without revealing the result of the unblinding.

Training will be provided to site staff regarding ways to minimize the placebo-response effect.

6.5. Study Drug Compliance

Subsequent to randomization, subjects will be provided investigational medicinal product (IMP) or placebo in identical packaging. Subjects will be provided sufficient study drug to reach the next visit. Adherence to study drug dosing per protocol (PP) will be measured throughout the study using pill count, subject report, and plasma drug levels. Subjects will be asked to bring all 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 in a drug log. Venous blood samples will be collected for determination of plasma XEN1101 concentrations at the time points specified and will be summarized by visit. Drug concentrations will be used to determine protocol adherence, inclusion in the planned PP analysis, and to examine PK and PD relationships.

6.6. Concomitant Therapy

6.6.1. Prohibited Medications and Procedures

The following concomitant medications and procedures are prohibited during the study:

- Antidepressants, antipsychotics, ASMs, mood stabilizers, benzodiazepines, lithium, stimulants, and opioids, within the 2 weeks (4 weeks for fluoxetine) or within a period less than 5-times the drug's half-life, whichever is longer, prior to randomization through the end of the treatment period.
- ECT, DBS, TMS, and VNS.
- Recreational or medicinal use of marijuana, cannabinoids, and/or derivatives, including cannabidiol (CBD).
- Drugs of abuse or any prescribed or over-the-counter medication used in a manner that the investigator considers indicative of abuse, dependence, or habitual use.
- Any other investigational drug or device within 5 half-lives of its pharmacological/therapeutic effect or 30 days prior to screening, whichever is longer.

6.6.2. Permitted Medications and Interventions

Limited use of as needed (PRN) nonbenzodiazepine hypnotic agents (including zolpidem, zaleplon, eszopliclone, diphenhydramine, suvorexant, lemborexant, and ramelteon) is permitted. Subjects receiving psychotherapy may continue treatment provided the therapy has been ongoing and stable for at least 3 months prior to screening and is expected to remain unchanged during the study treatment period. Subjects who need to start psychotherapy during the study will be discontinued.

7. WITHDRAWAL CRITERIA

7.1.1. Discontinuation of Study Medication

Subjects should be instructed by the investigator to call immediately upon experiencing any SAE or any other events that are of significant concern to the subject. The investigator should use

caution with respect to continued dosing and monitor for progression of these events or other reactions. The investigator may choose to discontinue the study intervention in subjects with intolerable AEs despite reducing the dose of study drug.

Subjects MUST have the study drug withdrawn should any of the following occur during the study:

1. Any change in cardiac rhythm or atrioventricular conduction that, in the investigator's opinion, is a threat to the subject's safety.
2. Documented QTc prolongation (QTcF >500 ms) (verified by 3 consecutive measurements within 15 minutes).
3. Persistent systolic blood pressure <80 mmHg or >190 mmHg (verified by 3 consecutive measurements within 15 minutes).
4. Syncope considered related to study drug.
5. Severe CNS or psychiatric adverse effects persisting despite reducing the dose of study drug.
6. A female subject has a confirmation of pregnancy during the study from a positive serum pregnancy test.
7. Occurrence of active suicidal ideation (a score of 3 or more in the suicidal ideation section of the C-SSRS), suicidal behavior (a score of 5 or more in the suicidal behavior section of the C-SSRS), non-suicidal self-harm, or any suicidal ideation or behavior that the investigator determines should be treated outside of this clinical trial, and therefore, continued participation in this study is not indicated.
8. Occurrence of an SAE that is deemed definitely related to the study drug by the investigator.
9. Need to start psychotherapy during the study. Study drug should be stopped, and the subject withdrawn before starting new psychotherapy.

7.1.2. Subject Discontinuation/Withdrawal From the Study

Each subject is free to withdraw from the study drug and/or study at any time, without prejudice to their continued care. In addition to the study drug withdrawal criteria listed in Section 7.1.1, subjects must be withdrawn from the study if any of the following events occur:

1. Subject withdraws consent or requests discontinuation from the study drug and/or study for any reason.
2. Subject develops an illness that would interfere with continued participation.
3. Subject is noncompliant with the study procedures and assessments or administration of study drug to an extent that may impact the study results, or put the subject at unnecessary risk, in the opinion of the investigator.
4. The sponsor requests withdrawal of the subject.

Subjects may also be withdrawn if they take a prohibited concomitant medication or substance as defined in Section 6.6.1. These instances must be discussed with the medical monitor.

7.1.3. Procedures Following Early Treatment Discontinuation/Withdrawal

Subjects who stop study drug dosing early for any reason will be required to complete an early termination (ET) visit on the last day the subject administered study drug, or as soon as possible thereafter. If the ET occurs outside of the Visit F1 window (7 ± 3 days after last dose of study drug), the subject will be requested to complete a Visit F1. Subjects who terminate the study early will also be requested to complete a second follow-up visit 28 ± 7 days following the last dose study drug (Visit F2) (see Table 1).

The primary reason for and date of study drug discontinuation must be recorded on the subject's eCRF. If the reason for withdrawal is an AE or a potentially clinically significant abnormal laboratory test result, the AE or laboratory parameter should be monitored at the discretion of the investigator (eg, until the event resolves or stabilizes, the subject is referred to the care of an alternate health care professional, or a determination of a cause unrelated to the study drug or study procedure is made). The specific event(s) or test result(s) are to be recorded in the eCRF.

The investigator must notify the medical monitor whenever the subject's study medication is changed or permanently stopped for intolerability.

7.1.4. Lost to Follow-up

A subject will be considered lost to follow-up if the subject fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the site for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within 3 days and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls). A registered/certified letter should be sent to the subject. These contact attempts should be documented in the subject's medical record or study source file.

Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Procedures

It is recommended that assessments/procedures be performed in the order listed in Table 1 for each study visit. Where multiple procedures/assessments are scheduled at the same time point(s) relative to dosing, vital sign measurements and 12-lead ECG should be performed prior to blood specimen collection, where possible.

Table 1: Schedule of Assessments

Study Period	**Screening**	**Randomization**[a]	**Double-blind Treatment**					**Post-treatment Follow-up**[b]		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**F1**	**F2**	**ET**[c]
Study Day	**-28 to -1**	**1**	**7**	**14**	**21**	**28**	**42**	**49**	**70**	**-**
Study Week	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**7**	**10**	**-**
Informed consent	X									
Demographics	X									
MINI	X									
ATRQ	X									
SHAPS	X	X	X	X	X	X	X	X	X	X
BAI	X	X	X	X	X	X	X	X	X	X
QIDS-SR	X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Improvement							X			X
SIGMA/MADRS	X	X	X	X	X	X	X	X	X	X
SIGH-D/HAM-D17	X	X					X			X
C-SSRS[d]	X	X	X	X	X	X	X	X	X	X
Clinical Global Impression of Severity	X	X					X			X
Clinical Global Impression of Improvement							X			X
AUA Symptom Index	X	X	X			X	X		X	X
CIWA-B on-site[e]		X					X	X	X	X
CIWA-B diary provided/returned[f]							X	X	X	X
Medical and psychiatric history	X									

Table 1: Schedule of Assessments (Continued)

Study Period	Screening	Randomization[a]	Double-blind Treatment					Post-treatment Follow-up[b]		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**F1**	**F2**	**ET[c]**
Study Day	**-28 to -1**	**1**	**7**	**14**	**21**	**28**	**42**	**49**	**70**	**-**
Study Week	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**7**	**10**	**-**
Concomitant medications and concurrent therapies	X	X	X	X	X	X	X	X	X	X
Physical examinations[g]	X	X	X	X		X	X	X	X	X
Height, weight, and BMI[h]	X	X	X			X	X		X	X
[redacted]										
Vital signs[j]	X	X	X	X		X	X	X	X	X
Electrocardiogram (12-lead)[k]	X	X	X	X		X	X	X	X	X
Pregnancy test[l]	X	X		X		X	X		X	X
FSH[m]	X									
Urine toxicology	X	X					X		X	X
Clinical laboratory tests	X[n]	X	X	X		X	X		X	X
Eligibility assessment	X	X								
SAFER remote interview[o]	X									
Randomization		X								
PK blood samples[p]		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments (Continued)

Study Period	Screening	Randomization[a]	Double-blind Treatment					Post-treatment Follow-up[b]		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**F1**	**F2**	**ET[c]**
Study Day	**-28 to -1**	**1**	**7**	**14**	**21**	**28**	**42**	**49**	**70**	**-**
Study Week	**-4 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**7**	**10**	**-**
Biometric device supply/training/download[q]		X	X	X	X	X	X	X	Return	X
Dispense study drug to subject[r]		X		X		X	Return			Return
Study drug compliance check			X	X	X	X	X			X

AE: adverse event; ATRQ: Antidepressant Treatment Response Questionnaire; AUA: American Urological Association; BAI: Beck Anxiety Inventory; BMI: body mass index; CIWA-B: Clinical Institute Withdrawal Assessment – Benzodiazepines; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; ET: early termination; FSH: follicle-stimulating hormone; HAM-D17: Hamilton Depression Rating Scale, 17-Item; HBsAG: hepatitis B surface antigen; HCV: anti-hepatitis C virus; HIV: human immunodeficiency virus; MADRS: Montgomery-Åsberg Depression Rating Scale; MINI: Mini International Neuropsychiatric Interview; PK: pharmacokinetic; QIDS-SR: Quick Inventory of Depressive Symptomatology, Self-Report; SAFER: state versus trait, assessability, face validity, ecological validity, rule of three Ps; SHAPS: Snaith-Hamilton Pleasure Scale; SIGH-D: Structured Interview Guide for the HAM-D; SIGMA: Structured Interview Guide for the MADRS.

[a.] Assessments to be completed prior to administration of the first dose of study drug. Subjects who do not meet enrollment criteria should not undergo any of the Day 1 tests or assessments other than the required eligibility checks and the recording of AEs.

[b.] Subjects who complete double-blind treatment or stop taking the study drug early should complete all post-treatment follow-up assessments within 7 ± 3 days (Visit F1) and 28 ± 7 days (Visit F2) after the last administration of study drug.

[c.] Subjects who discontinue early from the study should have all ET evaluations performed on the last day of receiving study drug, or as soon as possible thereafter.

[d.] C-SSRS Baseline/Screening version to be used at the screening visit (Visit 1) and Since Last Visit version to be used thereafter.

[e.] Subjects will complete a CIWA-B (both the patient-rated portion and the clinician observations portion) on Visits 2, 7/ET, F1, and F2.

[f.] On Visit 7/ET, subjects will be provided a diary containing the patient-rated portion of the CIWA-B to be completed daily. Subjects should bring the completed diary to visits F1 and F2.

[g.] A full physical examination required at screening, randomization, Visit 7, ET visit, and Visit F2. A symptom-directed physical examination required at all other visits as indicated.

[h.] Height to be measured at initial screening only.

[redacted]

[j.] Vital signs include blood pressure and pulse measured in a semi-supine position after the subject has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes. Vital signs should be assessed prior to taking any blood samples.

[k.] Triplicate ECG readings, taken within 15 minutes, will be done at screening (Visit 1) and randomization (Visit 2). One ECG reading will be taken at each subsequent visit.
[l.] Serum pregnancy test in females of childbearing potential at screening (Visit 1); thereafter, urine pregnancy test, but if positive, a serum pregnancy test should be performed.
[m.] FSH test performed only in postmenopausal females who are less than 55 years of age.
[n.] HBsAG, HCV, and HIV assessed at screening.
[o.] SAFER remote interview for confirmation of eligibility to be completed within 1 week of the randomization visit.
[p.] PK sample analysis to include XEN1101, XEN1101 metabolite(s), and/or concomitant medications. Date and time of previous dose of study drug to be recorded relative to date and time of PK sample collection.
[q.] Device supply and training at Visit 2. Download of data at Visits 3 to F2 and ET. Return device at Visit F2.
[redacted]

8.2. Clinical Assessments

8.2.1. Demographics

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

8.2.2. Medical and Psychiatric History

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

8.2.3. Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and at each study visit, including ET. Dose, unit, route, frequency of dose administration, indication for administration, and dates of medication will be captured.

8.2.4. MINI (Version 7.0.2)

The MINI is a brief structured diagnostic interview for the major psychiatric disorders in the DSM-5. The standard MINI will be used, which assesses the 17 most common disorders in mental health.

8.2.5. ATRQ

The Massachusetts General Hospital (MGH) ATRQ is a clinician-rated questionnaire that examines the patient's antidepressant treatment history to define the adequacy of both dose and duration of each antidepressant trial, and the degree of symptomatic improvement obtained with each trial (Chandler et al. 2010, Freeman et al. 2017).

8.3. Efficacy Assessments

8.3.1. MADRS

The MADRS (Montgomery and Asberg 1979) is a 10-item instrument used for the evaluation of depressive symptoms in adults and for the assessment of any changes to those symptoms. 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. The Structured Interview Guide for the MADRS (SIGMA) will be used.

8.3.2. SHAPS

The SHAPS (Snaith et al. 1995) is a validated 14-item self-report questionnaire commonly used to assess anhedonia. Each item on the SHAPS is worded so that higher scores indicate greater anhedonia. A total score can be derived by summing the responses to each item. Items answered with “strongly agree” are assigned a score of 1, while

"strongly disagree" responses are 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.

8.3.3. BAI

The BAI (Beck et al. 1988) is a 21-question multiple-choice self-report inventory that is used for measuring the severity of anxiety in children and adults. The questions used in this measure ask about common symptoms of anxiety that the subject has had during the past week and takes 5 to 10 minutes to complete. Several studies have found the BAI to be an accurate measure of anxiety symptoms that minimizes the overlap between depression and anxiety scales. The BAI contains 21 questions, each answer being scored on a scale value of 0 (not at all) to 3 (severely), with higher scores indicating more severe anxiety symptoms.

8.3.4. HAM-D17

The HAM-D17 (Hamilton 1960) consists of 17 items that are used to rate the severity of depression symptoms. Each item is scored in a range of 0 to 2 or 0 to 4, with higher scores indicating a greater degree of depression. The score for each item is summed to compute a total score, which ranges from 0 to 52. The Structured Interview Guide for the HAM-D (SIGH-D) will be used.

8.3.5. QIDS-SR

The QIDS-SR (Rush et al. 2003) is a 16-item self-rated instrument designed to assess the severity of depressive symptoms. The 16 items cover the 9 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).

8.3.6. CGI-S

The CGI-S is widely administered clinician-rated global measure of subject overall illness severity. Subjects are rated on a 1-7 scale where 1 corresponds to "Normal, Not at All Ill", 2 is "Borderline Mentally Ill", 3 is "Mildly Ill", 4 is "Moderately Ill", 5 is "Markedly Ill", 6 is "Severely Ill", and 7 is "Among the Most Extremely Ill Patients".

8.3.7. CGI-I

The CGI-I is a widely administered clinician-rated global measure of the degree of improvement from the initial assessment in subject overall illness severity. Subjects are rated on a 1-7 scale where 1 corresponds to "Very Much Improved", 2 is "Much Improved", 3 is "Minimally Improved", 4 is "No Change", 5 is "Minimally Worse", 6 is "Much Worse", and 7 is "Very Much Worse".

8.3.8. PGI-I

The PGI-I is the patient-reported outcome (PRO) counterpart to the Clinical Global Impressions scale (CGI). It measures disease improvement. Subjects rate themselves on a 1-7 scale where 1 corresponds to "Very Much Improved", 2 is "Much Improved", 3 is

"Minimally Improved", 4 is "No Change", 5 is "Minimally Worse", 6 is "Much Worse", and 7 is "Very Much Worse".

8.3.9. Biometric Device for Monitoring Activity and Sleep

A wrist-worn biometric device is planned to be used to passively track activity and sleep measures. The parameters measured may include, but are not limited to, activity counts, steps taken, sleep latency, total sleep time, and other related metrics for an exploratory analysis. The device will also record time worn for compliance purposes.

8.4. Safety, PK, and Other Assessments

8.4.1. Physical Exams

A full physical exam consisting of general inspection, head and neck, thorax and respiratory system, cardiovascular, abdomen, skin, extremities, and neurological exam will be performed at screening, randomization, EOT (Visit 7 and ET visit), and F2 with a symptom-directed physical exam performed at selected visits as specified in Table 1.



8.4.3. Vital Signs, Height, Weight, and BMI

Vital signs include blood pressure and pulse, measured in a semi-supine position after the subject has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes and the results entered in the eCRF. Vital signs should be assessed prior to taking any blood samples.

Weight will be measured in kilograms or pounds at selected visits as specified in Table 1. Measurements should be taken with subjects wearing light clothing and without shoes, using a calibrated scale for all measurements.

Height will be measured in centimeters or inches at screening only.

8.4.4. ECG (12-Lead)

A 12-lead ECG will be performed at selected visits as specified in Table 1. Triplicate ECG readings, taken within 15 minutes, will be taken at screening and randomization. One ECG reading will be taken at each subsequent visit. ECG printouts will be filed in the subject's source documents for medical safety reviews.

Each ECG recorder will be set to the required technical specifications and will contain the information required to identify the records. Each ECG recording will be clearly identified (subject identification [ID], visit date, and the actual time of the ECG recording).

Twelve-lead ECG recordings will be taken after the subject has been resting in a semi-supine position for at least 10 minutes. The subject will avoid postural changes during the ECG recordings, and the site staff will ensure that the subject is awake during the ECG recording. Triplicate ECG readings within 15 minutes will be performed and recorded at the screening and randomization visits (V1 and V2). At subsequent visits, where applicable, only a single ECG reading will be performed and recorded.

All recorded ECGs will be reviewed by the investigator or medically qualified designee, and the review will be documented in the source. If a subject shows an abnormal ECG, a repeat ECG will be conducted.

8.4.5. Urological Symptoms as Measured by the AUA Symptom Index

This questionnaire includes 7 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 than 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 7 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.

8.4.6. Clinical Laboratory Tests

Blood and urine specimens will be collected last, after recording vital signs according to the schedule shown in Table 1. Subjects with lab samples that were not obtained or cannot be analyzed may be requested to return for an unscheduled visit. Clinically significant changes in laboratory tests will be recorded as AEs.

The central clinical laboratory will process all biological specimens for clinical laboratory analyses. Laboratory evaluations are list below.

Laboratory evaluations will include the following:

Hematology	**Biochemistry**	**Urinalysis**
Platelet count	Aspartate aminotransferase (AST)	Leukocytes
Hemoglobin	Alanine aminotransferase (ALT)	Nitrite
Hematocrit	Alkaline phosphatase	Urobilinogen
White blood cells (WBC)	Blood urea nitrogen (BUN)	Protein
Neutrophils	Gamma-glutamyl transferase (GGT)	pH
Eosinophils	Bicarbonate	Blood
Basophils	Creatinine	Specific gravity
Lymphocytes	Cholesterol	Ketones
Monocytes	Uric acid	Bilirubin
Red blood cells (RBC)	Total serum protein	Glucose
Reticulocyte count	Albumin	Appearance
Pregnancy Tests	Glucose	Color
Serum pregnancy test	Sodium	Urine microscopy (if applicable)
Urine pregnancy test	Potassium	
Coagulation	Calcium	
Prothrombin time (PT/INR)	Phosphorus	
Immunology (at screening only)	Chloride	
Hepatitis B surface antigen (HBsAg)	Creatine kinase	
Anti-hepatitis C virus (HCV)	Lactate dehydrogenase (LDH)	
Human immunodeficiency virus (HIV)	Bilirubin (total and direct)	
Endocrinology (at screening only)		
Thyroid stimulating hormone (TSH)		
Follicle-stimulating hormone (FSH)		
Hemoglobin A1C (HbA1C)		

8.4.7. Suicide Risk as Assessed by the C-SSRS

Subjects will undergo assessment by a trained health care professional using the C-SSRS questionnaires at each visit as described in Table 1. Further details regarding the assessment will be included in the study operations manual. The medical monitor should be notified if a subject reports suicidality. The Baseline/Screening version of the C-SSRS will be used at the screening visit, and the Since Last Visit version will be used at subsequent visits.

Details about the C-SSRS assessments (Posner et al. 2011), will be incorporated into the study eCRF.

8.4.8. Withdrawal Symptoms as Assessed by the CIWA-B

The CIWA-B is a rating tool for assessing and monitoring the severity of benzodiazepine withdrawal (Busto et al. 1989). It will be used to evaluate the presence of XEN1101 withdrawal symptoms. The CIWA-B comprises patient-reported symptoms and clinical observations. Subjects will undergo complete assessments (clinician observations and patient-reported) on Visits 2, 7/ET, F1, and F2. Subjects will also be provided a paper diary containing the patient-rated portion of the questionnaire to be completed daily during the follow-up period from their last dose of study drug until the end of the study.

8.4.9. PK Blood Samples

Blood samples for plasma concentration analysis will be collected during the study for a PK evaluation of XEN1101 and its major metabolite(s). The dates and times of the last dose of study drug intake, and the blood sample collection dates and times, will be recorded on the eCRF.

Plasma PK samples may also be used for other tests, such as profiling of drug-binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and/or to assess other actions of XEN1101 with plasma constituents. Assessment of the plasma levels of concomitant medications and potential changes with co-administration of XEN1101 may also be investigated.

8.5. AEs and SAEs

8.5.1. Definition of AEs

An AE is any unfavorable and unintended sign (including a new clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered related to the medicinal product.

An AE may be:

- A new symptom or medical condition.
- A new diagnosis.
- An intercurrent illness or an accident.

- A worsening of a medical condition/diseases existing before the start of the clinical trial.
- The recurrence of a disease.
- An increase in frequency or intensity of episodic diseases.
- A clinically significant change in a laboratory or other clinical test parameter that is considered to be an AE by the investigator or sponsor.

An AE does not necessarily include the following:

- An abnormal test that needs repeating, in the absence of accompanying symptoms, and/or any requirement for additional diagnostic testing or medical/surgical intervention. Any abnormal test result that is determined to be an error does not require reporting as an AE.
- Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial and has not worsened. In the latter case, the condition should be reported as medical history.
- Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

8.5.2. Definition of SAEs

An SAE is defined as any AE that fulfills any of the following criteria:

- Results in death.
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe).
- Requires hospitalization or prolongs existing hospitalization.

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not

worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is considered medically important.

  Note: Medical and scientific judgment should be exercised in deciding whether other AEs are to be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; and development of drug dependency or drug abuse.

8.5.3. Classification of an AE

8.5.3.1. Severity of Event

The investigator will assess the severity (intensity) of each AE as mild, moderate, or severe.

- Mild: Events that are easily tolerated, require minimal or no treatment, and do not interfere with the subject's usual daily activities.
- Moderate: Events that are sufficiently discomforting to interfere with the subject's usual daily activities.
- Severe: Events that are usually incapacitating with inability to work or perform normal daily activities, or events that are potentially life-threatening. Of note, the term "severe" does not necessarily equate to "serious".
- Life-threatening: Immediate risk of death; significant medical intervention/therapy required; extreme limitation in activity and significant assistance required; hospitalization or hospice care probable.
- Fatal: Death related to SAE.

8.5.3.2. Causal Relationship to Study Drug

The causality assessment of an AE to the study drug will be rated as follows by the investigator:

- Definitely related: A clinical event, including a laboratory test abnormality, occurring in a plausible time relationship to the study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

- Possibly related: A clinical event, including a laboratory test abnormality, with a reasonable time sequence to the study drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.
- Unlikely related: A clinical event, including a laboratory test abnormality, with little or no temporal relationship to study drug administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
- Not related: A clinical event, including a laboratory test abnormality, that has no temporal relationship to the study drug or has more likely alternative etiology.

The investigator should also comment on the AE page of the eCRF if an AE is not related to the study drug but is related to study participation (eg, study procedures).

8.5.3.3. Expectedness

The expectedness of an AE is determined by the sponsor. An AE, the nature, severity, or frequency of which is not consistent with the applicable reference safety information, is unexpected. The assessment of expectedness should be done from the perspective of events previously observed, not based on what might be anticipated from the pharmacological properties of a medicinal product.

For this protocol, the reference document for the assessment of expectedness is the XEN1101 IB and the XEN1101 IB Addendum.

8.5.3.4. Time Period and Frequency of Event Assessment and Follow-up

All (serious and non-serious) AEs detected by the investigator or spontaneously reported by the subject at each visit/examination must be reported in the source and eCRF.

The following information should be reported for each AE, whether or not it can be attributed to the study drug:

- Description of AE.
- Date of onset and date of resolution.
- Characteristics of the event (seriousness, intensity).
- Actions taken (treatment required or dose adjustments must be reported in the eCRF).
- Outcome.
- Relationship with the study drug (causality assessment) and/or study participation.

All AEs must be documented and followed until the event is either resolved, the condition stabilizes, a satisfactory alternative explanation is found, or the investigator considers it medically justifiable to terminate the follow-up. The reason(s) will be recorded in the source documents when the AE follow-up is terminated.

The investigator is responsible for following AEs, SAEs, and events that caused the subject to discontinue before completing the study, through an appropriate health care option. The subject should be followed until the event has resolved or is otherwise explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

8.5.3.5. AE Reporting

All AEs occurring from screening (after signing the ICF) until 28 days following the last administration of study drug must be recorded in the source document and eCRF in a timely fashion.

8.5.3.6. SAE Reporting

If an SAE occurs, the investigator will take appropriate action immediately to promote subject safety and will strive to identify the cause of the event.

All SAEs occurring from screening (after signing the ICF) until 28 days following the last administration of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence.

Initial Reports:

To report the SAE, complete the AE form with the SAE information electronically in the electronic data capture (EDC) system for the study. When the form is completed, [redacted] will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or call the [redacted] SAE reporting line, and fax/email the completed paper SAE form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered as soon as possible.

[redacted]

The following minimum criteria must be provided when reporting an SAE:

- Subject's study ID number.
- Name of study drug.
- Description of the event or outcome that can identify the case as serious.
- Name and contact information of the reporter.

Follow-up Reports:

Follow-up information should be actively sought and submitted as it becomes available. Relevant eCRFs, such as demography, medical history, and concomitant medications, as well as test results, consultant reports, a summary of the outcome of the SAE, and the investigator's opinion of the event's relationship to the study drug will be provided if and when available.

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, subject discharge summary or autopsy reports) to [redacted] Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The sponsor will also perform an evaluation of all SAEs.

The relevant health authorities and central ethics committees/institutional review boards (ECs/IRBs) will be notified of any suspected unexpected serious adverse reactions (SUSARs) by Xenon (or designee) within the required reporting timelines (within 7 calendar days for fatal and life-threatening SUSARs, or 15 calendar days for all other SUSARs). Where applicable, the investigational sites will submit any reported SUSARs to their local ECs/IRBs upon receipt of the essential documents from Xenon (or designee).

8.5.3.7. Reporting Events to Subjects

Any new information about the study drug's safety or important information that becomes available during the study that may affect the subject's decision to continue their participation will be communicated to the subject in a timely manner, including a revision to the ICF.

8.5.3.8. Reporting Pregnancy

Pregnancy is not considered an AE. Subjects will be instructed to inform the investigator of any pregnancy (subject/subject's partner) that occurs during the study or within 3 months after administration of the last dose of study drug. If a pregnancy occurs during study participation, but is not confirmed until after the subject has completed the study, the subject must notify the investigator of the pregnancy at the time of confirmation. Pregnancy should be confirmed with a serum pregnancy test. All pregnancy notifications to the investigator must be reported to [redacted] (see Section 8.5.3.6).

In the event a subject/subject's partner is found to be pregnant after the subject has been included in the study, consent will be sought from the subject/subject's partner to follow the pregnancy. If consent is given, the pregnancy will be followed by the investigational site until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, birth with congenital abnormality, etc). Pregnancy will be followed until the outcome is known even in cases where the male subject discontinues the study drug or withdraws from the study. Once the outcome is known, an updated report should be submitted to [redacted]. The status of the mother and/or

child will be reported to the sponsor. If the study has concluded by the time the outcome is known, the investigator should submit the updated report directly to the sponsor.

Female subjects reporting a pregnancy during the study will be discontinued from the study treatment, and every reasonable effort will be made by the investigational site to follow the pregnancy until the outcome is known. Male subjects may continue in the study if an accidental pregnancy of their female partner occurs despite adequate contraception.

8.5.3.9. Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgment should always be applied. In cases of a discrepancy in the study drug accountability, overdose will be established only when it is clear that the subject has taken additional dose(s), or the investigator has reason to suspect that the subject has taken additional dose(s).
- **Abuse:** Refers to intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect. The term abuse should not be used to describe accidental or inadvertent exposure to a prescription drug because abuse requires intentional administration on the part of the abuser.
- **Misuse:** Refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.
- **Medication error:** Refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a health care professional, subject, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of subjects missing doses of study drug are not considered reportable as medication errors.
- **Product complaint:** Refers to any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A Special Situations Report form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] within 24 hours of knowledge of the event. All AEs associated with these Special Situation Reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

9. STATISTICAL CONSIDERATIONS

A formal statistical analysis plan (SAP) will be developed and finalized before database lock and will provide more detailed definitions of the subject populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.1. Statistical Hypothesis

9.1.1. Primary Hypothesis

The primary objective of the study is to demonstrate that, compared to placebo, administration of XEN1101 will result in a significantly greater reduction in MADRS score through Week 6 postrandomization. The null hypothesis to be tested in relation to the primary estimand is that placebo is not significantly different from XEN1101 with respect to change in MADRS from baseline through Week 6 postrandomization. This null will be tested separately for both 10 mg and 20 mg doses.

9.1.2. Secondary Hypotheses

The secondary objective of the study is to demonstrate that, compared to placebo, administration of XEN1101 will result in a significantly greater improvement in 2 endpoints with the respective null hypotheses to be tested as follows:

- Placebo is not significantly different from XEN1101 with respect to change in SHAPS score from baseline through Week 6 postrandomization.
- Placebo is not significantly different from XEN1101 with respect to change in BAI score from baseline through Week 6 postrandomization.

These null hypotheses will be tested separately for both 10 mg and 20 mg doses.

9.2. Multiplicity Adjustment

The primary hypothesis will be tested for both the 10 mg and 20 mg XEN1101 arms. A simple Bonferroni adjustment will be used for these 2 hypotheses with the study-wide Type 1 Error probability for the primary analysis controlled at 0.1, and each p-value compared separately to 0.05. As a Phase 2 trial, there will be no adjustment for multiple testing among secondary endpoints.

9.3. Populations for Analysis

Modified Intent-to-Treat Population (mITT): All randomized subjects who receive at least 1 dose of study treatment and at least 1 postrandomization MADRS. Subjects will be analyzed as treated at Week 1, defined as the dose determined at Visit 3/Week 1, based on tolerance within the first week on-study. As described in Section 6.2, subjects randomized to the 20 mg group may be reduced to 10 mg, subjects randomized to 10 mg may be reduced to placebo, and subjects randomized to placebo will continue to receive placebo. Subjects who complete Visit 3/Week 1 with no dose modification will be

analyzed in their randomized group. Subjects who have their dose reduced prior to or at Visit 3/Week 1 clinic visit will be analyzed in the reduced dose group (10 mg or placebo). Subjects who reduce dose following the Visit 3/Week 1 visit will be categorized according to the dose received at the Visit 3 Week 1.

PP Population: All randomized subjects who return for at least 3 visits, including Visit 7, complete MADRS, SHAPS, and BAI scales for these visits, and receive at least 80% of expected doses of study treatment during the 6-week study period. Subjects who discontinue study treatment due to AEs, intolerance, lack of efficacy, or any other reason related to the safety or efficacy of the study treatment, will be included in this population if they received at least 80% of expected doses up to the time of discontinuation. Subjects will be analyzed as treated at Week 1, as defined for the mITT.

Safety Population: All subjects who receive at least 1 dose of study treatment.

PK Population: All subjects receiving at least 1 dose of study treatment and who provide PK samples.

9.4. Statistical Analysis

9.4.1. Primary Endpoint

The primary efficacy endpoint of change from baseline in MADRS score through Week 6 will be analyzed in all randomized and treated subjects (mITT) population according to the treatment received at Visit 3/Week 1, based on a mixed-effect model for repeated measures (MMRM). The MMRM will use change from baseline as the outcome variable and include the baseline MADRS score, sex, treatment group, visit, and treatment-by-visit interaction as fixed effects. All mITT subjects will, by definition, contribute postrandomization endpoint data to the primary analysis; data missing from other postbaseline visits will not be imputed and will be assumed to be missing at random (MAR).

An unstructured covariance matrix shared across treatment groups will be used to model the within-subject variabilities. The model will be fitted using a restricted maximum likelihood method. The difference between treatment groups will be estimated based on least-squares means at the target day for the Week 6 visit within the framework of the MMRM model. Descriptive assessment of MAR assumption and sensitivity analyses to assess the impact of missing data will be described in the SAP.

The primary analysis will be performed after all randomized subjects have completed their Week 6 visit (or discontinued the study early).

Least-square mean change from baseline and associated 95% CIs in all 3 arms will be estimated for Weeks 1, 2, 3, 4, 7, and 10.

The primary analysis will be repeated in the mITT population according to initially randomized groups and in the PP population.

9.4.2. Secondary Endpoints

Secondary endpoints will be analyzed with a similar modeling approach as described for the primary endpoint in both the mITT and PP populations.

9.4.3. Exploratory Endpoints

Details will be included in the SAP.

9.4.4. Safety Analysis

Overall safety evaluations will be descriptive and based on the safety population. Graphical and tabular displays will be presented by actual treatment received by subjects. [redacted]

9.4.4.1. AEs

All AE data will be summarized, sorted by SOC and Preferred Term (PT), assigned by the Medical Dictionary for Regulatory Activities (MedDRA), and presented by arm. The following summaries will be provided:

- Listings of all AEs.
- Listings of all SAEs.
- AEs leading to discontinuation of study drug.
- AEs leading to study withdrawal.
- Treatment-related AEs.

9.4.4.2. Clinical Laboratory Findings

The number of subjects with substantial changes from baseline will be summarized and presented by arm and visit. Criteria for substantial change will be provided in the SAP. Substantial changes deemed clinically significant by the investigator will be recorded as AEs. Summary statistics for each laboratory value and change from baseline for each visit will be presented by arm in tables and figures such as box plots and mean-plots over time.

9.4.4.3. ECGs

All ECG measures will be listed. The number of subjects found to have an abnormal ECG, confirmed on a repeat ECG, will be summarized, and details of abnormalities will be listed by arm.

9.4.4.4. C-SSRS

All C-SSRS data will be listed. All scores and changes from baseline will be summarized by visit and arm, including the frequency of suicidal ideation and suicidal behavior.

9.4.4.5. Vital Signs

The number of subjects with substantial changes from baseline will be summarized and presented by arm and visit. Criteria for substantial change will be provided in the SAP. Substantial changes deemed clinically significant by the investigator will be recorded as AEs. Summary statistics for each vital sign and change from baseline for each visit will be presented by arm in tables and figures such as box plots and mean-plots over time.

9.4.4.6. AUA Symptoms Index

The total score and each individual question will be summarized by arm. Total score will be compared across arms using an analysis of covariance (ANCOVA) with arm and baseline score as factors.

9.4.4.7. CIWA-B

The total score and each individual question will be summarized by arm. Total scores of complete assessments collected on discontinuation days 7 (Visit F1) and 28 (Visit F2) will be analyzed at each visit day, using an ANCOVA model with treatment group as fixed effect and end of DBP total score as a covariate. Total scores of patient diary collected every day in the discontinuation period will be analyzed using an MMRM with treatment group, discontinuation day, and treatment by day interaction as fixed effects, end of DBP total score as a covariate.

9.5. Sample Size Determination

While a higher dose of XEN1101 may be more effective, it may not be well-tolerated. As a result, a common treatment effect will be assumed in both 10 mg and 20 mg arms for the purposes of this power calculation.

A MADRS change from baseline of -12 and -17, in placebo and both XEN1101 arms, respectively, and a common standard deviation of 9.5, are assumed and consistent with literature from other clinical trials in MDD (Boulenger et al. 2014, CDER 2012, Mahableshwarkar et al. 2015). In a repeated measures (2-sided) test for the difference in 2 means, a sample size of 48 subjects per arm will provide 80% power to reject the null hypothesis of no difference between placebo and a XEN1101 dose arm using a 0.05 significance level, assuming compound symmetry and a correlation of 0.5 between observations within subjects (PASS 2019, v19.06).

Expanding this to all 3 intervention arms, and assuming an overall dropout rate of 10%, a total sample size of 150 subjects will provide approximately 80% power to reject a specific hypothesis, and 96% power to reject at least 1, with the above assumptions for variance and effect size.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Informed Consent Process

10.1.1.1. Consent/Assent Provided to Subjects

Consent forms describing, in detail, the study intervention, study procedures, and risks are given to the subject, and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol:

- ICF
- Pregnant partner ICF

10.1.1.2. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and continues throughout the individual's study participation. The ICF, and any changes made to the consent form during the course of the study, must be agreed to by Xenon and the EC/IRB prior to its use and must be in compliance with all ICH-GCP guidelines, local regulatory requirements, and legal requirements.

The patient will be asked to read and review the ICF. The investigator must ensure that each patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy.

The investigator will explain the research study to the patient and answer any questions that may arise. A verbal explanation will be provided, in terms suited to the patient's comprehension, of the purposes, procedures, and potential risks of the study and of the patient's rights as a research participant. The patient will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patient should have the opportunity to discuss the study with his/her family or surrogates and to think about his/her participation prior to providing consent. The patient will sign the informed consent document prior to any procedures being done specifically for the study. The patient must be informed that participation is voluntary and that the patient may withdraw from the study at any time, without prejudice. The original signed copy of the ICF must be maintained by the investigator and is participant to inspection by a representative of Xenon, their representatives, auditors, the EC/IRB, and/or health authorities. A copy of the ICF will be given to the patient for his/her records. The informed consent process will be documented in the source document (including the date), and the form signed by the patient before the patient undergoes any study-specific procedures. The rights and welfare of the patient will be protected by emphasizing that the quality of his/her medical care will not be adversely affected if the patient declines to participate in this study.

10.1.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, EC/IRB, and health authorities. If the study is prematurely terminated or suspended, the investigator will promptly inform study subjects and the local EC/IRB and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to the study visit schedule.

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

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

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, EC/IRB, and/or health authorities.

10.1.3. Confidentiality and Privacy

Data collected during this study may be used (i) to support the research, development, registration, or marketing of the medicinal product, and (ii) for research related to the development of other pharmaceutical products, diagnostics, or medical aids. Xenon will abide by all applicable privacy laws, including the Health Insurance Portability and Accountability Act and any other applicable state level privacy legislation in the US. As part of the study, the CRO may collect and process personal information on behalf of Xenon. In respect of such personal information, the CRO shall only act in accordance with the terms of this protocol and Xenon's reasonable written instructions. The CRO shall take appropriate technical and organizational measures against the unauthorized or unlawful processing of such personal information.

After subjects have consented to take part in the study, each subject will be assigned a unique study ID number. Subjects' data, including any medical records and personal information, collected during the study will be reviewed by Xenon and/or its representatives. These data may, in addition, be reviewed by independent auditors who validate the data on behalf of Xenon, health authorities, and the EC/IRB. Xenon and any third parties that review the data will only receive de-identified subject information; the code list that links the subject′s identity to their study ID number will be securely stored and kept confidential with the investigator.

Although subjects will be known by a unique study ID number, their year of birth may also be collected and used to verify the accuracy of the data; for example, that the results of study assessments are assigned to the correct subject. The results of this study, containing the unique study ID number, year of birth, relevant medical information, and personal information including ethnicity, may be recorded and transferred to and used in

other countries throughout the world including Canada. The purpose of any such transfer would be to support regulatory submissions made by Xenon in such countries.

10.1.4. Future Use of Stored Specimens and Data

With the subject's consent, and as approved by the EC/IRB, de-identified PK plasma samples will be stored at Xenon's designated bioanalytical laboratory. These samples could be used for tests other than planned PK analysis, such as profiling of drug-binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, and/or to assess other actions of XEN1101 with plasma constituents. The unique subject ID number will be used to ensure linking the biological specimens with the phenotypic data from each subject, maintaining the blind of the identity of the subject.

10.1.5. Safety Oversight

Investigators are responsible for monitoring the safety of subjects who have entered the study and for alerting the sponsor (or designee) to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for the appropriate medical care of subjects during the study. The sponsor, or medically qualified designee, will monitor safety data throughout the course of the study. Safety data will be reviewed periodically and include at a minimum SAEs, trends in AEs, and laboratory results.

Additionally, the sponsor will implement a Safety Review Committee (SRC), to meet on a quarterly basis to review ongoing safety data and trends from the study. The SRC may choose to convene an unscheduled meeting, as required, to review and discuss any urgent potential safety issues that have arisen during the course of the study. In addition to the sponsor representatives, the SRC will also consist of an independent physician, as described in the SRC charter.

10.1.6. Clinical Monitoring

All aspects of the study will be carefully monitored by the sponsor and its representatives for compliance with ICH-GCP guidelines, applicable local and national regulations and legal requirements, and current standard operating procedures (SOPs).

The monitoring of this study will be performed by the sponsor's and/or CRO's CRAs in accordance with the principles of GCP as laid out in the ICH "Good Clinical Practice: Consolidated Guideline".

The CRA, as a representative of the sponsor, has an obligation to ensure site staff follows the protocol. In doing so, the study monitor will visit the investigator and site periodically as well as maintain frequent telephone and email contacts. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Further details will be described in the monitoring plan.

10.1.7. Quality Assurance and Quality Control

A regulatory inspection of this study may be carried out by health authorities. In addition, the sponsor or EC/IRB may audit the study. Such inspections/audits can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and CRO agree to allow the auditor/inspector direct access to all relevant documents and to allocate their time and the time of their staff to the auditor/inspector to discuss any findings or relevant issues.

Quality control (QC) procedures at the CRO will be implemented to ensure data recorded into the eCRFs are accurate. QC checks will be carried out on an ongoing basis and according to the relevant SOPs. Records of QC checks will be documented and available for review.

10.1.8. Data Handling and Record Keeping

The study will utilize an EDC system with eCRFs. Data will be processed using validated computer systems conforming to applicable regulatory requirements.

Study data will be entered into the eCRFs and source documents by the site staff as the study is in progress; data entered in the eCRFs should be consistent with the data recorded in the source documents. The eCRF data will be reviewed and source data verified by the CRA during monitoring visits as outlined in the monitoring plan. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

Data handling will be detailed in the data management plan.

10.1.9. Data Collection and Management Responsibilities

Data will be entered using the EDC system (eCRFs) and electronic clinical outcome assessment (eCOA) system (tablet) while the study is active. The eCOA system consists of a tablet device for collection of select scales that are to be administered at the clinical site. Site staff will not be permitted to alter data entered by subjects in the tablet. Data will also be collected through a wearable biometric device. All passwords will be strictly confidential. These procedures must comply with the appropriate regulations.

Data collection is the responsibility of the investigational staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring that data collection and study documentation comply with Good Documentation Practices (GDPs) and that data is reported in a timely manner. GDPs should be followed to ensure all source documents are attributable, legible, contemporaneous, original, and accurate, plus complete, consistent, endurable (ie, retrievable and readable after archiving), and available (ALCOA+C), to ensure accurate interpretation of data.

Validation checks programmed within the database, as well as supplemental validation performed via review of the data listings, will be applied to the data to ensure accurate, consistent and reliable data. Data identified as erroneous, inconsistent, incomplete, or inaccurate, or data that are missing, will be referred to the site for resolution through data

queries where applicable. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

The eCRFs must be reviewed and signed by the investigator (or designee) who signed the protocol.

External study data collected outside of eCRFs such as clinical laboratory data and PK data will be sent to the sponsor's data management team for reconciliation and integration. Any discrepancies will be referred to the site for resolution through queries.

For medical information, the following will be used:

- Latest version of the MedDRA for medical history and AEs.
- World Health Organization Drug Dictionary (WHODD) (2018 or higher) for prior and concomitant medications.

Data management processes, including data management and validation, will be outlined in the data management plan.

10.1.10. Study Records Retention

Subject records (including Electronic Medical Records [EMR]), source documents, monitoring visit logs, eCRFs, inventory of study drug, study and regulatory documents, and other sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records should be retained in a secure file by the investigator according to the specifications in the ICH guidelines, relevant regulations, or as specified in the clinical trial agreement, whichever is longer. Prior to transfer or destruction of these study records, Xenon must be notified in writing and be given the opportunity to further store such records. If the study records no longer need to be retained, it is the sponsor's responsibility to inform the investigator.

10.1.11. Public and Data Sharing Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. The investigator is obligated to keep data pertaining to the study confidential. The investigator must consult with Xenon before any study data are submitted for publication. Xenon reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.1.12. Conflict of Interest Policy

Investigators are required to provide financial disclosure information to the sponsor to permit Xenon to fulfill its future reporting obligations to health authorities. In addition, the investigator must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after completion of the study.

10.2. Additional Considerations

Any amendments to the study protocol will be communicated to the investigators by Xenon (or designee). All substantive protocol amendments will undergo the same review and approval process as the original protocol. A substantive protocol amendment may be implemented only after it has been approved by the EC/IRB unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the EC/IRB within 5 business days.

REFERENCES:

Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.

Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. Int Clin Psychopharmacol. 2014;29(3):138-49.

Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. J Clin Psychopharmacol. 1989;9(6):412-6.

CDER. (Center for Drug Evaluation and Research). Application Number 204447Orig1s000. Medical Review(s). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000MedR.pdf2012.

Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. RESEARCH: Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci Ther. 2010;16(5):322-5.

Chaudhury D, Walsh JJ, Friedman AK, et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature. 2013;493(7433):532-6.

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58.

Costi S, Morris LS, Kirkwood KA, et al. Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results From a Randomized Controlled Trial. Am J Psychiatry. 2021;178(5):437-46.

Food and Drug Administration. Statistical Review and Evaluation. Antiepileptic Drugs and Suicidality. 2008.

Freeman MP, Pooley J, Flynn MJ, et al. Guarding the Gate. Journal of Clinical Psychopharmacology. 2017;37(2):176-81.

Friedman AK, Juarez B, Ku SM, et al. KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. Nat Commun. 2016;7:11671.

Friedman AK, Walsh JJ, Juarez B, et al. Enhancing depression mechanisms in midbrain dopamine neurons achieves homeostatic resilience. Science. 2014;344(6181):313-9.

Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.

Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. Psychopharmacology (Berl). 2015;232(12):2061-70.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-9.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Potiga [package insert]. Research Triangle Park, NC: GlaxoSmithKline. Research Triangle, NC: GlaxoSmithKline; 2016.

Premoli I, Rossini PG, Goldberg PY, et al. TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. Ann Clin Transl Neurol. 2019;6(11):2164-74.

Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54(5):573-83.

Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167(1):99-103.

Tan A, Costi S, Morris LS, et al. Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder. Mol Psychiatry. 2020;25(6):1323-33.