A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 as Adjunctive Therapy in Focal-onset Epilepsy, with an Open-label Extension

Protocol Number: XPF-008-201

European Clinical Trial (EudraCT) Identified Number: 2018-003221-29

Investigational New Drug (IND) Number: 130236

Sponsor: Xenon Pharmaceuticals Inc.
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Version Number: 4.2

22 January 2021

Table of Contents

STATEMENT OF COMPLIANCE

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

The protocol, informed consent form(s), recruitment materials, and all patient 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 patient is enrolled. Any amendment to the protocol will require review and approval by the EC/IRB before the changes are implemented to the study. 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 patients who provided consent, using a previously approved consent form.

SPONSOR APPROVAL

STUDY TITLE: A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 as Adjunctive Therapy in Focal-onset Epilepsy, with an Open-label Extension

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

PPD

Date

JAN.22.2021

PPD

Date

22 JAN 2021

INVESTIGATOR AGREEMENT

STUDY TITLE: A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 as Adjunctive Therapy in Focal-onset Epilepsy, with an Open-label Extension

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 patients.

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.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 as Adjunctive Therapy in Focal-onset Epilepsy, with an Open-label Extension
Protocol Number	XPF-008-201
Phase	Phase 2
Investigational Medicinal Product (IMP)	A capsule containing the active pharmaceutical ingredient XEN1101, to be administered orally.
Indication	Adult focal (partial-onset) epilepsy
Study Description	This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in adult patients diagnosed with focal epilepsy, followed by an optional open-label extension (OLE). Hypothesis: Patients treated with XEN1101 will demonstrate a greater decrease in total focal seizure frequency per 4 weeks from baseline compared to the double-blind period (DBP), versus patients treated with placebo in the DBP.
Objectives	Primary • To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency in adults with focal epilepsy taking 1 to 3 antiepileptic drugs (AEDs) in the DBP. • To assess the safety and tolerability of XEN1101 in adults with focal epilepsy taking 1 to 3 AEDs in the DBP. Secondary • To evaluate the 50% XEN1101 response rates in comparison to placebo in the DBP. • To evaluate trends in focal seizure frequency over time in the DBP. • To assess the effect of XEN1101 versus placebo on seizure severity and impact in adults with focal epilepsy taking 1 to 3 AEDs in the DBP. CCI [redacted] • CCI [redacted]

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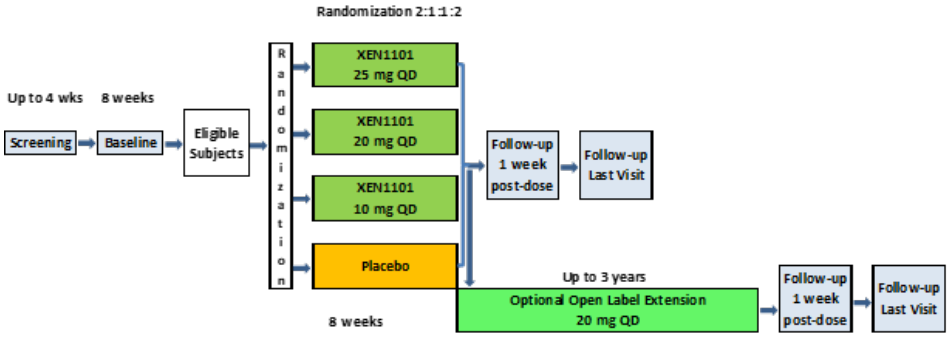
Study Population	Male and female patients 18 to 75 years of age (inclusive), diagnosed with focal epilepsy.
Duration of Study	Patients are planned to undergo: • Screening – up to 4 weeks duration. • Baseline – 8 weeks duration to assess the frequency of seizures. • DBP – 8 weeks duration. • For patients who qualify and consent for OLE: Open-label Treatment – up to 3 years duration. • Follow-up – 6 weeks duration. Total study duration per patient is estimated to be approximately 26 weeks (6 months) in the DBP. For those patients continuing in the OLE, total study duration would be up to 3.5 years. Note: The duration of the baseline period may be extended and randomization delayed up to 20 weeks (140 days) from the start of data capture, in cases where restrictions to site access caused by the COVID-19 pandemic prevent patients from attending site visits. This could add up to 3 months to planned study duration.
Study Design	Planned enrollment: A sufficient number of patients will be screened to ensure approximately 300 randomized and evaluable participants in the DBP. <u>Double-blind Period:</u> Allocation: Randomization 2:1:1:2 (XEN1101 25 mg: 20 mg: 10 mg: placebo). Intervention model: Parallel assignment (approximately N=100 patients in placebo and 25 mg arms, and n=50 patients in 10 and 20 mg arms).

	Blinding: Double (Participant, Investigator). Open-label Extension: All patients to receive XEN1101 (20 mg once daily [QD]).  The schedule of assessments is shown in Table 1a (DBP) and Table 1b (OLE).
Main Criteria for Inclusion	Patients will be considered eligible to participate in the study if they meet all of the inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2) listed below. 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, 18 to 75 years of age (inclusive) with a body mass index ≤40 kg/m^2. 3. Diagnosis (≥2 years) of focal epilepsy according to the International League Against Epilepsy [ILAE] Classification of Epilepsy (2017). 4. Prior neuroimaging within the last 10 years and documentation is available. 5. Treatment with a stable dose of 1 to 3 allowable current AEDs for at least one month prior to screening, during baseline, and throughout the DBP. 6. Must be willing to comply with the contraception requirements as defined in Section 5.4. 7. Males must agree not to donate sperm from the time of the first administration of IMP until 6 months after the last dose of IMP. Females must agree not to donate ova from the time of the first administration of IMP until 6 months after the last dose of IMP. 8. Able to keep accurate seizure diaries. 9. Able to participate for the full term of the study. Exclusion Criteria:

	1. Previously documented electroencephalogram (EEG) which shows any pattern not consistent with focal etiology of seizures. (A new EEG is not required, if not available.) 2. History of focal aware non-motor seizures only. 3. History of pseudoseizures or psychogenic seizures. 4. History of a primary generalized seizure. 5. Presence or previous history of Lennox-Gastaut syndrome. 6. Seizures secondary to illicit drug or alcohol use, ongoing infection, neoplasia, demyelinating disease, degenerative neurological disease, or central nervous system disease deemed progressive, metabolic illness, or progressive degenerative disease, progressive structural lesion or encephalopathy. 7. History of repetitive seizures within the 12-month period preceding study entry where the individual seizures cannot be counted. 8. Status epilepticus within the last 12 months prior to enrollment. 9. History of neurosurgery for seizures <1 year prior to enrollment, or radiosurgery <2 years prior to enrollment. 10. Schizophrenia and other psychotic disorders (eg, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified [NOS]), bipolar disorder, and/or obsessive-compulsive disorder, or other serious mental health disorders. Uncontrolled unipolar major depression where changes in pharmacotherapy are needed or anticipated during the study. 11. Active suicidal plan/intent in the past 6 months, or a history of suicide attempt in the last 2 years, or more than 1 lifetime suicide attempt. 12. History or presence of any significant medical or surgical condition or uncontrolled medical illness at screening including, but not limited to, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, endocrine, hepatic or urogenital systems, or other conditions that would place the patient at increased risk as determined by the investigator. 13. History of cancer within the past 2 years, with the exception of appropriately treated basal cell or squamous cell carcinoma. 14. Alanine transferase (ALT; SGPT) or aspartate transferase (AST; SGOT) levels >3 times the upper limit of normal (ULN) at screening or baseline. 15. Any clinically significant laboratory abnormalities or clinically significant abnormalities on pre-study physical examination, vital signs, or electrocardiogram (ECG) that in the judgment of the investigator indicates a medical problem that would preclude study participation including but not limited to:

	a. History of presence of long QT syndrome; QT corrected by Fridericia's formula (QTcF) >450 ms at baseline; family history of sudden death of unknown cause. b. History of skin or retinal pigment epithelium abnormalities caused by ezogabine. 16. Females who are pregnant, breastfeeding, or planning to become pregnant during the first administration of IMP until 6 months after the last dose of IMP. 17. History of illicit drug or alcohol abuse within 1 year prior to screening judged by the investigator to be excessive or compulsive, or currently using drugs of abuse or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse, dependence, or habitual use. 18. Exposure to any other investigational drug or device within 5 half-lives or 30 days prior to screening, whichever is longer. 19. Use of vigabatrin in the last 5 years without stable visual fields tested twice over the 12 months after the last dose of vigabatrin. (Patients stopping vigabatrin more than 5 years prior to screening, must have no vigabatrin-related visual field abnormalities confirmed by examination within the past 6 months - concomitant use of vigabatrin is not allowed). 20. If felbamate is used as a concomitant AED, patients must be on felbamate for at least 2 years, with a stable dose for 2 months (or no less than 49 days) prior to screening. They must not have a history of white blood cell (WBC) count below 2500/µL (2.50×10^9/L), platelets below 100,000/mm^3 (100×10^9/L), liver function tests above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If patients received felbamate in the past, it must have been discontinued 2 months (or no less than 49 days) prior to screening. 21. Have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions. 22. Current use of a ketogenic diet. 23. Any medical condition or personal circumstance that in the opinion of the investigator exposes the patient to unacceptable risk by participating in the study or prevents adherence to the protocol. 24. Employees of Xenon Pharmaceuticals Inc., the contract research organization, 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.
Additional Eligibility Criteria for DBP	In addition to meeting all of the inclusion criteria and none of the exclusion criteria during screening, and despite being on an appropriate treatment

	regimen with current medications, patients must also meet all of the following criteria to be eligible to participate in the DBP: 1. During the 8-week baseline period preceding the randomization visit (Visit 3), patients must have a documented seizure frequency of ≥4 focal seizures per 28 days on average. Note: In cases of delayed randomization caused by the COVID-19 pandemic preventing patients from attending site visits, data obtained during the 56 days of electronic diary (eDiary) entries prior to randomization will be used to define the "baseline period", for purposes of determining eligibility for randomization. In order to establish baseline seizure count, the types of countable focal seizures to be included in the count will be: • Focal aware seizures with motor signs, • Focal seizures with impaired awareness, and • Focal seizures that lead to generalized tonic-clonic seizures. 2. eDiary was completed a minimum of 80% of all days (ie, ≥45 days) during the 8-week baseline period as evidence of adequate compliance. 3. Patients should not be seizure-free for more than 21 consecutive days during the 8-week baseline period. 4. Patient does not show retinal macular disease, or retinal pigment epithelium abnormality on the dilated ophthalmic examination prior to randomization.
Criteria for Entering the OLE	In addition to meeting all of the entry criteria for the baseline and DBP, patients must also meet all of the following inclusion criteria and none of the exclusion criteria to be eligible to participate in the optional OLE. Inclusion Criteria: 1. Be properly informed of the nature and risks of the study and give informed consent in writing. 2. Must have met all eligibility requirements and completed the DBP (to Visit 8* with a minimum of 80% compliance with eDiary entries and IMP), did not terminate early, patient had no important protocol deviations, (eg, that may impact patient safety, or data integrity) that in the opinion of the sponsor should preclude participation in the OLE, and had no adverse events (AEs) that, in the opinion of the investigator, would preclude the patient's entry into the OLE.** 3. Patient is expected to experience benefit from their participation, in the opinion of the investigator. 4. Must be willing to comply with the contraception requirements as defined in the protocol. 5. Males must agree not to donate sperm until 6 months after the last dose of study drug. Females must agree not to donate ova until 6 months after the last dose of study drug.

	*A small number of patients may have completed treatment and continued with Visit F1a and/or Visit F2a post-treatment follow-up assessments before the initial availability/approval of the OLE. In these patients, assessments completed at Visit 8 or Visit F2a (as applicable) may be used to confirm eligibility for the OLE. Similarly, a small number of patients may be nearing completion of the DBP at the time of approval of the amendment which requires a dilated ophthalmic examination, these patients must complete the dilated ophthalmic examination prior to entry in the OLE and as such, may experience a delay of up to a few weeks from Visit 8 prior to entry in the OLE. The study day for all subsequent visits as outlined in Table 1b will be calculated from the date that Visit 8A is conducted. **Note: Patients who successfully completed 52 weeks of OLE treatment with XEN1101 (as per Protocol version 4.1) prior to approval of the amendment in Protocol version 4.2, and in whom it has been <6 months since their last treatment, will be permitted to resume OLE treatment with XEN1101 if they continue to meet criteria for participating in the OLE. This subgroup of patients will need to reconsent and complete Visit 14A assessments onsite in order to obtain study drug and paper diary. A urine pregnancy test must be performed for females of childbearing potential (if positive a serum pregnancy test will be performed). Exclusion Criteria: 1. Patients who met any of the withdrawal criteria in the DBP. 2. Any medical condition, personal circumstance, or ongoing AE that in the opinion of the investigator exposes the patient to unacceptable risk by participating in the OLE, or prevents adherence to the protocol. 3. Females who are pregnant, breastfeeding, or planning to become pregnant until 6 months after the last dose of study drug. 4. Patients planning to enter a clinical trial with a different investigational drug or plan to use any experimental device for treatment of epilepsy or any other medical condition.
Dose and Discontinuation	Dose Administration: Study drug is taken QD, in the evening and preferably with food. Dose Reduction for Intolerability during the DBP: If the study drug is not tolerated, and withdrawal from the study is the only alternative for the patient, the investigator may stop the medication for one week and then resume dosing at a dosing interval of one capsule every second day for the remainder of the DBP. If the IMP continues to be intolerable to the level of requiring withdrawal from the study, dosing should be stopped, but all efforts should be made to complete applicable study procedures. The investigator is requested to discuss with the medical monitor prior to making changes to the study drug regimen and must notify the medical monitor whenever the patient's study drug is temporarily stopped and the dosing interval changed, or permanently stopped for intolerability.

	Dose Intolerability during the OLE: If the 20 mg QD dose of XEN1101 is not tolerated during the OLE, and withdrawal from the study is the only alternative for the patient, the investigator may stop the drug for up to one week and then resume dosing at a dosing interval of one capsule every second day for the remainder of the OLE (Note: The period of stopping study drug is variable according to the clinical judgment of the investigator and could be from 1 to 7 days, unlike in the DBP when it is mandated to be 7 days). If XEN1101 continues to be intolerable to the level of requiring withdrawal from the study, dosing should be stopped and the patient withdrawn from the study. All efforts should be made to complete applicable study procedures. The investigator is requested to discuss with the medical monitor prior to making changes to the study drug regimen and must notify the medical monitor whenever the patient's study drug is temporarily stopped and the dosing interval changed, or permanently stopped for intolerability.
Prohibited Concomitant Medications	• Vigabatrin. • 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. • Other investigational drug or device within five half-lives or 30 days prior to screening, whichever is longer.
Permitted Medications	Patients are required to be on a stable dose of between 1 and 3 AEDs 1 month prior to Visit 1 (screening) and for the duration of the DBP. Patients are permitted to be on a stable dose of any AED (including benzodiazepines), with the exception of vigabatrin. Benzodiazepines may also be used intermittently as a rescue medication for the control of seizure clustering. Recreational or medicinal use of marijuana, cannabinoids and/or derivatives (eg, cannabidiol) is neither encouraged nor prohibited, but use should be recorded as a concomitant medication. Use of marijuana, cannabinoids and/or derivatives will not be counted as one of the 1 to 3 allowable current AEDs. For patients participating in the OLE, after completion of the DBP, the patient's existing background AED and/or neurostimulator therapy can be adjusted during the OLE to achieve the best efficacy/safety ratio, as needed, per investigator discretion.
Outcome Measures	Primary Endpoints: 1. Median percent change in monthly (28 days) focal seizure frequency from baseline to DBP for XEN1101 versus placebo. 2. Severity and frequency of associated AEs/serious adverse events (SAEs), clinically significant changes in clinical laboratory findings and/or 12-lead ECG, increase in suicide risk as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) including increase in suicidal thoughts or an attempt, clinically significant changes in vital signs including blood pressure, pulse, or

weight, and clinically significant changes in urological symptoms including retention as measured by the American Urological Association (AUA) Symptom Index in the DBP.

Secondary Endpoints:

3. Responders are defined as patients experiencing ≥50% reduction in monthly (28 days) focal seizure frequency from baseline to DBP.
4. Percent change from baseline in weekly focal seizure frequency for each week in the DBP.
5. Clinical Global Impression of Change (CGI) and Patient Global Impression of Change (PGI-C) scores during the DBP.

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13. CCI [redacted]
14. CCI [redacted]
15. CCI [redacted]

	16. CCI [redacted] 17. CCI [redacted] Time frame for the primary outcome measure and all of the secondary outcome measures is 8 weeks. CCI [redacted]

1.2 SCHEDULE OF ACTIVITIES

Table 1a. Schedule of Assessments (DBP)

Study Period	Screening	Baseline	Double-blind Treatment						Post-Tx Follow-up[K,L]		
Visit Number	1[A]	2	3[J]	4-TC[N]	5	6	7-TC[N]	8	F1a	F2a	ET
Study Day	-84 to -57	-56	0	7±3	14±3	28±5	42±4	56±3	63±3	98±7	
Study Week	-12 to -9	-8	0	1	2	4	6	8	9	14	
Informed consent	X										
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Eligibility assessment	X		X								
Medical and psychiatric history	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Physical and neurologic (including non-dilated ophthalmic) examinations	X	X[M]	X		X	X		X	X	X	X
Dilated ophthalmic examination[B]	X[B]	X[B]							X[B]		X[B]
Vital signs[C]	X	X	X		X	X		X	X	X	X
Height, weight, BMI[D]	X		X					X		X	X
Electrocardiogram (12-lead)	X	X[M]	X		X	X		X	X	X	X
AUA Symptom Index	X	X	X			X		X		X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[E]	X	X	X			X		X		X	X
FSH[F]		X									
Clinical laboratory tests	X	X	X		X	X		X	X	X	X
Clinical Global Impression of Change								X		X	X
Patient Global Impression of Change								X		X	X
QoL assessments (QOLIE-31)			X					X		X	X
Blood collection for genotype/biomarker assessment[G]			X					X			X
Training and/or compliance check of eDiary[H]		X	X	X	X	X	X	X	X	X	X
Randomization			X								
PK blood samples (XEN1101)[I]			X		X	X		X	X	X	X

Study Period	Screening	Baseline	Double-blind Treatment						Post-Tx Follow-up[K,L]		
Visit Number	1[A]	2	3[J]	4-TC[N]	5	6	7-TC[N]	8	F1a	F2a	ET
Study Day	-84 to -57	-56	0	7±3	14±3	28±5	42±4	56±3	63±3	98±7	
Study Week	-12 to -9	-8	0	1	2	4	6	8	9	14	
Dispense study drug to patient			X			X		return			return
Study drug compliance check					X	X		X			X

A: The dose of background AEDs must be unchanged for at least a month before screening and remain stable throughout baseline and double-blind treatment phase. (The screening period may be completed as soon the patient is found to qualify and does not need to take the full 28 days.)

B: In addition to a non-dilated ophthalmoscopic examination completed by the investigator or designee at each site visit as part of the neurologic examination, a dilated fundoscopic examination performed by an ophthalmic professional will be completed and reviewed prior to randomization (eg, during screening **or** baseline period) and within 1 month post-treatment in the DBP (for patients not continuing on to the OLE). For patients continuing on to the OLE that did not complete a dilated fundoscopic examination prior to randomization (ie, randomized prior to this requirement) a dilated fundoscopic examination performed by an ophthalmic professional will be completed as soon as possible and reviewed prior to initiation of treatment in the OLE (If the dilated ophthalmic examination requires more than 1 week from Visit 8 to be completed in these patients, a Visit F1A should be completed prior to entering the OLE.).

C: Vital signs include blood pressure and pulse, measured in semi-supine position after patient has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes and the average result entered in the eCRF. After the resting measurements, an orthostatic blood pressure test should be performed with blood pressure and heart rate measured within 2 to 5 minutes after standing up. Vital signs should be assessed prior to taking any blood samples.

D: Weight and BMI; height to be measured at initial screening only.

E: Serum pregnancy test in females of childbearing potential at baseline (Visit 2); thereafter urine pregnancy test, but if positive a serum pregnancy test will be performed.

F: FSH test in post-menopausal females.

G: Genotyping/biomarker sampling is not mandatory for inclusion in the study. Genotyping/ biomarker sample will not be collected at ET, if Visit 8 sample was already collected.

H: Includes eDiary set-up on Day -56 (Visit 2) and training on back-up paper diary; the eDiary device will be collected at the last follow-up visit (Visit F2a) or ET visit, as applicable.

I: Date and time of previous dose of study drug and concomitant AED(s) to be recorded relative to date and time of PK sample collection.

J: Assessments to be completed prior to administration of the first dose of study drug. Patients who do not meet enrollment criteria should not undergo any of the Day 0 tests or assessments other than the required eligibility checks and recording of AEs. Day 0 can start up to 66 days from start of baseline (eligibility for randomization is generally based on the initial 56 days of eDiary entries in the baseline period– Note: In cases where restrictions to site access caused by the COVID-19 pandemic prevent patients from attending site visits, the duration of the baseline may be extended and randomization delayed up to 20 weeks (140 days) from the start of data capture. In cases of delayed randomization, data obtained during the 56 days of eDiary entries prior to randomization will be used to define the "baseline period", for purposes of determining eligibility for randomization.

K: Patients who stop taking the study drug early should complete all post-treatment follow-up assessments within 7 ± 3 days (Visit F1a) and 42 ± 7 days (Visit F2a) after the last administration of study drug. For patients that complete the DBP but do not enter the OLE, the follow-up (F1a and F2a) visits will occur on the study days shown (63 ± 3 and 98 ± 7).

L: Patients 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.

M: Assessment does not need to be repeated if it was normal at screening (or unchanged) and the assessment was completed ≤3 days of the baseline visit.

N: Visits 4 and 7 will be conducted as telephone calls to the patient from investigator or designee.

AED = Antiepileptic drug; AUA = American Urological Association; BMI = Body mass index; CBC = Complete blood count; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = Double-blind period; eCRF = Electronic case report form; eDiary = Electronic diary; ET = Early Termination; FSH = Follicle-stimulating hormone; OLE = Open-label extension; PK = Pharmacokinetic; QoL = Quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory-31; TC = Telephone Call; Tx = Treatment.

Table 1b. Schedule of Assessments for Patients Continuing in the OLE

Study Period	Open-label Treatment														Post-Tx Follow-up[F,G]		
Visit Number	**8A***	**9**	**10**	**11**	**12**	**13A**	**14A-TC[I]**	**15A[I]**	**16-TC**	**17**	**18-TC**	**19**	**20-TC**	**21**	**F1b**	**F2b**	**ET**
Study Day	**56±3**	**77±3**	**161±7**	**245±7**	**329±7**	**420±7**	**511±7**	**602±7**	**693±7**	**784±7**	**875±7**	**966±7**	**1057±7**	**1148±7**	**1155±3**	**1190±10**	
Study Week	**8**	**11**	**23**	**35**	**47**	**60**	**73**	**86**	**99**	**112**	**125**	**138**	**151**	**164**	**165**	**170**	
Informed consent							X[I]										
C-SSRS	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility assessment	X																
Adverse events	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical and neurologic (including non-dilated ophthalmic) examinations	-	X	X	X	X	X		X		X		X		X	X	X	X
Dilated ophthalmic examination[A]						X		X[A]		X[A]		X[A]			X[A]		X
Vital signs[B]	-	X	X	X	X	X		X		X		X		X	X	X	X
Weight, body mass index	-	X	X	X	X	X		X		X		X		X		X	X
Electrocardiogram (12-lead)	-	X	X	X	X	X				X				X	X	X	X
AUA Symptom Index	-	X	X	X	X	X		X		X		X		X		X	X
Concomitant medications	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[C]	-	X	X	X	X	X	X[I]	X		X		X		X		X	X
Clinical laboratory tests	-	X	X	X	X	X		X		X		X		X	X	X	X
QoL assessments (QOLIE-31)	-		X	X	X	X		X		X		X		X		X	X
Clinical Global Impression of Severity (CGI-S)	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Patient Global Impression of Severity (PGI-S)	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Collect eDiary, Issue/Training of paper diary[D]	X																
Collect and compliance check of completed paper diary and issue new paper diary		X	X	X	X	X	X[I]	X		X		X		X	X	return	return
PK blood samples (XEN1101)[E]	-	X				X				X				X			X
Study drug compliance check	-	X	X	X	X	X		X		X		X		X			X

Study Period	Open-label Treatment														Post-Tx Follow-up[F,G]		
Visit Number	**8A***	**9**	**10**	**11**	**12**	**13A**	**14A-TC[I]**	**15A[I]**	**16-TC**	**17**	**18-TC**	**19**	**20-TC**	**21**	**F1b**	**F2b**	**ET**
Study Day	**56±3**	**77±3**	**161±7**	**245±7**	**329±7**	**420±7**	**511±7**	**602±7**	**693±7**	**784±7**	**875±7**	**966±7**	**1057±7**	**1148±7**	**1155±3**	**1190±10**	
Study Week	**8**	**11**	**23**	**35**	**47**	**60**	**73**	**86**	**99**	**112**	**125**	**138**	**151**	**164**	**165**	**170**	
Dispense study drug to patient	X	X	X	X	X	X	X[H]	X	X[H]	X	X[H]	X	X[H]				

*: Last day of double-blind treatment period. Patients entering the OLE will be dispensed 20 mg QD of XEN1101 and return their previous study drug.

A: In addition to a non-dilated ophthalmoscopic examination completed by the investigator or designee at each site visit, a dilated fundoscopic examination performed by an ophthalmic professional will be completed every 6 months (within 21 days of scheduled site visits) beginning at Visit 13A and including Visits 15A, 17, and 19 in all patients and within 1 month post-treatment in the OLE. For patients who did not complete a dilated fundoscopic examination performed by an ophthalmic professional prior to randomization in the DBP (ie, patients who were randomized in the DBP prior to the dilated fundoscopic examination requirement), a dilated fundoscopic examination performed by an ophthalmic professional will be completed as soon as possible and reviewed prior to initiation of XEN1101 treatment in the OLE.

B: Vital signs include blood pressure and pulse, measured in semi-supine position after patient has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes and the average result entered in the eCRF. After the resting measurements, an orthostatic blood pressure test should be performed with blood pressure and heart rate measured within 2 to 5 minutes after standing up. Vital signs should be assessed prior to taking any blood samples.

C: Urine pregnancy test in females of childbearing potential, but if positive a serum pregnancy test will be performed.

D: Includes training on paper diary on Day 56 (Visit 8A); the eDiary device will be collected at Visit 8 from those patients entering the OLE.

E: Date and time of previous dose of study drug and concomitant AED(s) to be recorded relative to date and time of PK sample collection.

F: Patients who stop taking the study drug early should complete all post-treatment follow-up assessments within 7 ± 3 days (Visit F1b) and 42 ± 10 days (Visit F2b) after the last administration of study drug.

G: Patients 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.

H: Provision of study drug to the study patient from the site.

I: Patients who successfully completed 52 weeks of OLE treatment with XEN1101 (as per Protocol version 4.1) prior to approval of the amendment in Protocol version 4.2, and in whom it has been <6 months since their last treatment, will be permitted to resume OLE treatment with XEN1101 if they continue to meet criteria for participating in the OLE. This subgroup of patients will need to reconsent and complete Visit 14A assessments onsite in order to obtain study drug and paper diary. A urine pregnancy test must be performed for females of childbearing potential (if positive a serum pregnancy test will be performed).

AED = Antiepileptic drug; AUA = American Urological Association; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = Double-blind period; eCRF = Electronic case report form; eDiary = electronic diary; ET = Early Termination; OLE = Open-label extension; PK = Pharmacokinetic; QoL = Quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory-31; Tx = Treatment.

2 INTRODUCTION

2.1 STUDY RATIONALE

XEN1101 is a novel, small molecule, selective KCNQ2/3 (K_V7.2/7.3) potassium channel positive allosteric modulator being developed for the treatment of partial-onset (focal) epilepsy. Enhancing the open state of KCNQ2/3 in neurons favors a hyperpolarized resting state, which reduces rapid action potential spiking. CCI [redacted]

XEN1101 was investigated at single doses of 5, 15, 20, 25, and 30 mg, as well as multiple doses of 15 or 25 mg once daily (QD) for up to 10 days in healthy volunteers. The influence of single doses was also investigated for effects on cortical and corticospinal excitability using transcranial magnetic stimulation (TMS) techniques. XEN1101 was well tolerated, adverse events (AEs) were generally transient, dose/exposure related, and the majority of AEs were mild. The most common related AEs were central nervous system (CNS) effects such as dizziness and sedation, consistent with this class of drugs (antiepileptics). The pharmacokinetics (PK) of XEN1101 were found to be suitable for QD dosing, with absorption of the drug enhanced by food. The terminal elimination half-life was approximately 1 week after repeat dosing in healthy volunteers. The results from the TMS studies in healthy volunteers suggest that the plasma levels expected at the dose regimens to be used in this study are anticipated to decrease cortical excitability and may suppress seizures in epilepsy patients. For detailed summaries of the results of these studies, please see the Investigator's Brochure.

The purpose of this Phase 2 clinical trial is to evaluate the safety, tolerability, and efficacy of XEN1101 as adjunctive therapy in adults with focal-onset epilepsy. For this study, plasma levels expected at the doses chosen were shown to be well tolerated in the first-in-human (FIH) study (XPF-008-101a) and pharmacologically active in the brain in the companion TMS crossover study (XPF-008-101b).

2.2 BACKGROUND

Focal (or partial) seizures account for 60% to 70% of seizures in adults with epilepsy. Currently available antiepileptic drugs (AEDs) act by a limited number of mechanisms of action, including potentiation of GABAergic neurotransmission, reduction of glutamate mediated excitatory neurotransmission, SV2A vesicle inhibition, or inhibition of voltage-gated sodium and/or calcium channels. XEN1101 is a novel, small molecule, selective KCNQ2/3 (K_V7.2/7.3) potassium channel positive allosteric modulator being developed for the treatment of partial-onset (focal) epilepsy. Enhancing the open state of KCNQ2/3 in neurons favors a hyperpolarized resting state, which reduces rapid action potential spiking. CCI [redacted]

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XEN1101 has been evaluated in 2 Phase 1 studies. The FIH study (XPF-008-101a) was a double-blind, placebo-controlled evaluation of the safety, tolerability, and PK of single and multiple ascending oral doses of XEN1101 and single dose preliminary open-label pharmacodynamics assessment with TMS in healthy subjects. XEN1101 was considered to be safe and well tolerated at single doses up to 30 mg and multiple doses up to 25 mg QD, as discussed below.

A double-blind, placebo-controlled crossover study (XPF-008-101b) was also conducted to evaluate the safety, tolerability, PK, and effects on TMS of oral administration of XEN1101 (20 mg) in healthy male subjects. Single 20 mg doses of XEN1101 resulted in C_{max} plasma concentrations in the range of CCI [redacted] XEN1101 showed plasma concentration dependent elevations in resting motor threshold and decreased amplitudes of TMS evoked potentials, indicative of reductions in corticospinal and cortical excitability, respectively. The most common AEs were sedation and dizziness, and the majority were transient and mild, which is similar to that seen in the FIH study. Additional results of these studies are included in the Investigator's Brochure.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

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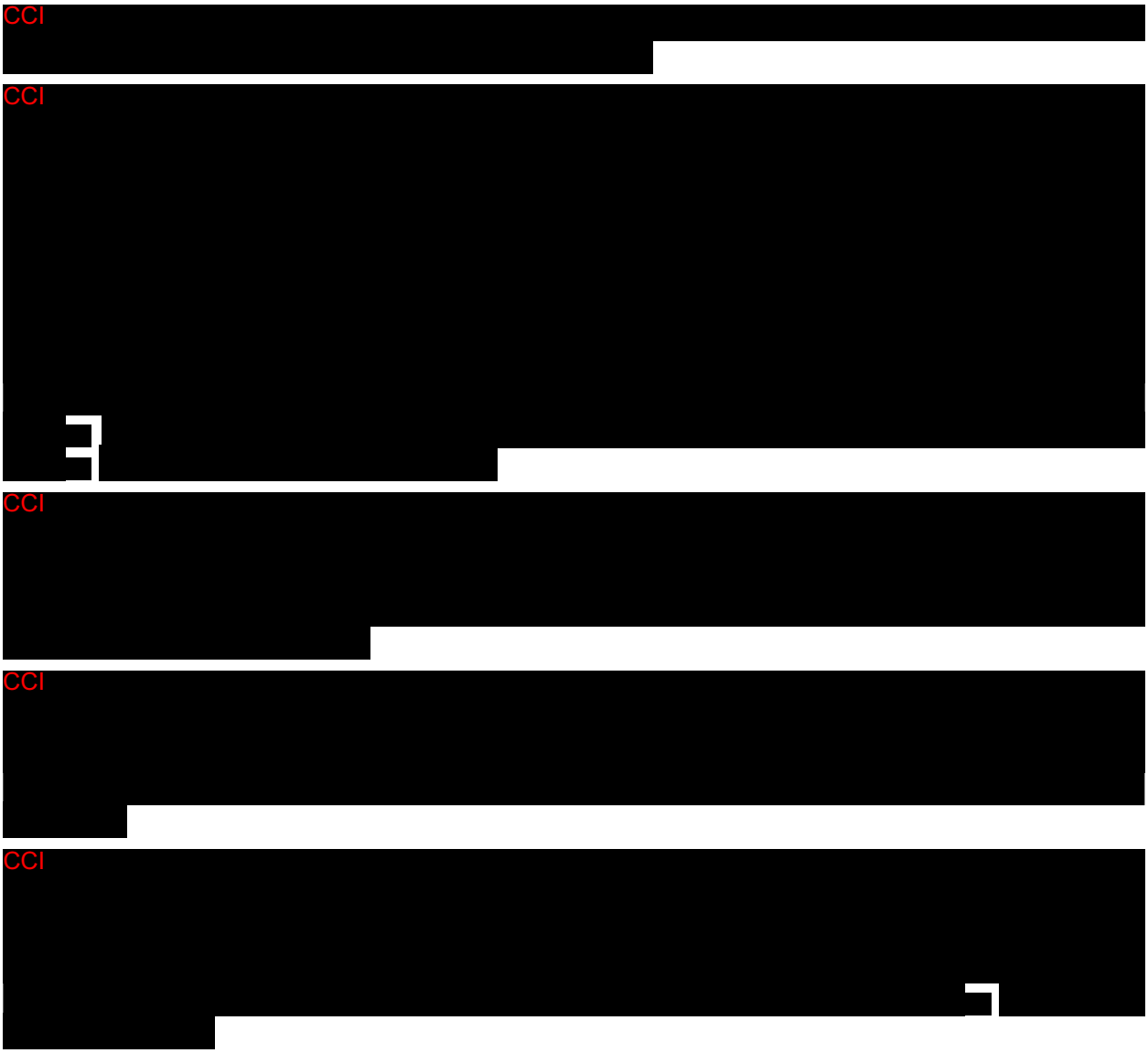
CCI [redacted]

CCI [redacted]



In the Phase 1 clinical studies, the majority of related AEs were mild and CNS-related and were consistent with this class of drugs. Sedation (including somnolence, drowsiness, etc) and dizziness (including lightheadedness and presyncope) were the most common AEs, while cognitive effects (eg, memory and speech impairment) and blurred vision were also reported. A higher incidence of moderate CNS AEs was reported with repeat dosing at 25 mg QD. Orthostatic hypotension (vasovagal reactions) and presyncope were seen in the FIH study, but not in the TMS crossover study conducted at a different site. Vasovagal reactions are occasionally seen in FIH studies in association with blood sampling and upon standing after prolonged supine positioning and as such, the relationship of these events to XEN1101 is unclear. The detailed safety profile of XEN1101 observed in the Phase 1 clinical studies is provided in the Investigator's Brochure.

2.3.2 KNOWN POTENTIAL BENEFITS

XEN1101 was given to healthy subjects to investigate safety and tolerability in the FIH study (XPF-008-101a) and in a TMS crossover study (XPF-008-101b). These subjects receiving the investigational medicinal product (IMP) experienced no medical benefit except for a general health examination. As such,

there are no proven benefits. Potential benefits of XEN1101 to the focal epilepsy patients enrolled in this trial may be a reduction in the incidence of seizures which may result in an improvement in their quality of life (QoL).

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

While this is the first time XEN1101 will be given to patients with epilepsy, it has been studied in healthy volunteers in the FIH study (XPF-008-101a) and the TMS crossover study (XPF-008-101b), as well as in a comprehensive nonclinical research program.

Nonclinical toxicology performed with XEN1101 indicates that monitorable and reversible CNS-related clinical signs may occur once anticipated therapeutic exposures have been attained or exceeded. Although urinary volume increase was seen in repeat-dose toxicology studies in rats, it did not occur in monkeys.

Based on the results in the Phase 1 studies completed to date, potential risks associated with repeat doses of XEN1101 up to 25 mg QD appear to be mainly CNS-related. Mild to moderate sedation, cognitive disorders, headaches, lightheadedness, dizziness, blurred vision, presyncope, muscle twitching, ataxia, orthostatic hypotension, myalgia, neuropsychiatric symptoms, and nausea or vomiting have been observed in healthy volunteers. These AEs may be more, or less common in epilepsy patients taking concomitant medications. There were no signs of urinary retention in the Phase 1 clinical studies to date. XEN1101 did not appear to increase QT intervals in healthy volunteers.

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3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency in adults with focal epilepsy taking 1 to 3 AEDs in the double-blind period (DBP).	• Median percent change (MPC) in monthly (28 days) focal seizure frequency from baseline to DBP for XEN1101 versus placebo.
To assess the safety and tolerability of XEN1101 in adults with focal epilepsy taking 1 to 3 AEDs in the DBP.	In the DBP: • Severity and frequency of associated AEs/serious adverse events (SAEs). • Clinically significant changes in clinical laboratory findings. • Clinically significant changes in 12-lead ECG. • Increase in suicide risk as assessed by the C-SSRS including increase in suicidal thoughts or an attempt. • Clinically significant changes in vital signs including blood pressure, pulse, or weight. • Clinically significant changes in urological symptoms including retention as measured by the American Urological Association (AUA) Symptom Index.
Secondary	
To evaluate the 50% XEN1101 response rates in comparison to placebo in the DBP.	• Responders are defined as patients experiencing ≥50% reduction in monthly (28 days) focal seizure frequency from baseline compared to DBP.
To evaluate trends in focal seizure frequency over time in the DBP.	• Percent change from baseline in weekly focal seizure frequency for each week of the DBP.
To assess the effect of XEN1101 versus placebo on seizure severity and impact in adults with focal epilepsy taking 1 to 3 AEDs in the DBP.	• Clinical Global Impression of Change (CGI) and Patient Global Impression of Change (PGI-C) scores during the DBP.
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OBJECTIVES	ENDPOINTS
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OBJECTIVES	ENDPOINTS
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CCI [redacted]	• CCI [redacted]
CCI [redacted]	• CCI [redacted]

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the clinical efficacy, safety, and tolerability of XEN1101 as adjunctive therapy in patients diagnosed with focal epilepsy, with an optional OLE.

The initial intervention is parallel assignment with approximately 50 to 100 patients per treatment arm. A sufficient number of patients will be screened to ensure approximately 300 randomized and evaluable patients in the DBP. Patients will be randomized in a blinded manner to one of 3 active treatment groups or placebo in a 2:1:1:2 fashion (XEN1101 25 mg: 20 mg: 10 mg: placebo). The masking is double; patients and investigators will be blind to treatment allocation. Randomization will be stratified by background use versus non-use of a CYP3A4 inducer medication (eg, any of carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, topiramate, or phenobarbital). Following successful completion of the DBP, eligible patients may enter OLE treatment phase and receive 20 mg QD XEN1101.

The study is divided into 5 stages:

1. Screening – up to 4 weeks duration.
2. Baseline – 8 weeks duration to assess frequency of seizures.
3. Treatment (DBP) – 8 weeks duration.

4. OLE treatment phase – up to 3 years duration.
5. Follow-up – 6 weeks duration to complete safety assessments.

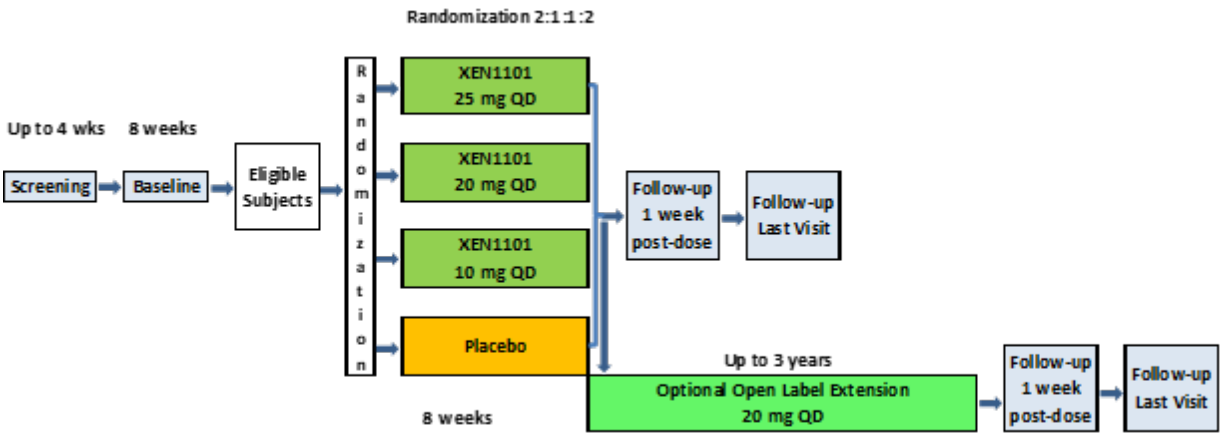
The total study duration per patient is estimated to be up to approximately 26 weeks (6 months), or up to 3.5 years for those entering the OLE.

Patients will be screened (Visit 1) within 28 days prior to entering the study on Day -56 (Visit 2; start of baseline period). Each patient will receive verbal and written information followed by signing of the informed consent form (ICF) prior to any screening procedures taking place. Patients will record the frequency and type of seizures during the planned 8-week baseline period. (Note: In cases where restrictions to site access caused by the COVID-19 pandemic prevent patients from attending site visits, the duration of the baseline period may be extended, and randomization delayed up to 20 weeks (140 days) from the start of data capture. This could add up to 3 months to the planned study duration.) Eligible patients will be randomized and receive a supply of the IMP on Study Day 0. During the DBP, on Study Days 14, 28, and 56, patients will return with their eDiary device and IMP bottle for assessments, compliance and safety. Patients will return their IMP bottle and receive a resupply of the IMP on Study Day 28 and will stop dosing on Study Day 56, at which time they will return the second IMP bottle. Patients will return for post-treatment follow-up visits on Study Days 63 (±3 days) and 98 (±7 days), unless they continue on with the OLE study at Study Day 56. All visits are outpatient visits except for Study Days 7 and 42 when the investigator or designee will call the patient for interim safety assessment between outpatient visits.

Eligible patients who successfully complete the DBP (including Visit 8) may enter an OLE treatment phase on Day 56 and switch to treatment with 20 mg QD XEN1101. During the OLE, on Study Day 77 and then at 3 month intervals for the first year, and then at 6 month intervals for the second and third year until completion of the OLE (Study Week 164), patients will return to the site with their OLE paper diary and IMP bottle for assessments, compliance, and safety checks. During Years 2 and 3, telephone call visits will be conducted at 3 months between each site visit. The last scheduled dose is Study Day 1148 and patients will return for post-treatment follow-up visits on Study Days 1155 (±3 days) and 1190 (±10 days).

The study flow chart is shown in Figure 4.1.

Figure 4.1: Study Flow Chart



The doses to be administered and the dose selection justification are described in Section 4.4.

4.2 LONG-TERM OPEN-LABEL EXTENSION

The patients who successfully complete the DBP on their assigned study drug through the treatment phase up to Study Day 56 (including all study visits) may be considered for the OLE. Patients continuing on to the OLE will stop double-blind dosing on Study Day 56 and then* may begin open-label dosing at the assigned 20 mg QD XEN1101 dose of the OLE.**

*A small number of patients may have completed treatment and continued with Table 1a: Visit F1a and/or Visit F2a post-treatment follow-up assessments before the initial availability/approval of the OLE. In these patients, assessments completed at Visit 8 or Visit F2a (as applicable) may be used to confirm eligibility for the OLE. Similarly, a small number of patients may be nearing completion of the DBP at the time of approval of the amendment which requires a dilated ophthalmic examination, these patients must complete the dilated ophthalmic examination prior to entry in the OLE and as such, may experience a delay from Visit 8 of up to a few weeks prior to entry in the OLE. (If the dilated ophthalmic examination requires more than 1 week from Visit 8 to be completed in these patients, then the Visit F1A should be completed prior to entering the OLE.) The study day for all subsequent visits as outlined in Table 1b will be calculated from the date that Visit 8A is conducted.

**Note: Patients who successfully completed 52 weeks of OLE treatment with XEN1101 (as per Protocol version 4.1) prior to approval of the amendment in Protocol version 4.2, and in whom it has been <6 months since their last treatment, will be permitted to resume OLE treatment with XEN1101 if they continue to meet criteria for participating in the OLE. This subgroup of patients will need to reconsent and complete Visit 14A assessments onsite in order to obtain study drug and paper diary. A urine pregnancy test must be performed for females of childbearing potential (if positive a serum pregnancy test will be performed).

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Placebo is considered an appropriate control as all patients are required to be on at least one AED prior to screening and for the duration of the trial. Therefore, all patients will be receiving medication for control of seizures. An 8-week baseline period is required to establish seizure frequency for eligibility determination. An 8-week treatment period was chosen to establish efficacy for seizure suppression while minimizing time assigned to placebo treatment. The study design includes parallel enrollment into 3 dose groups in addition to the placebo arm. This parallel-group, dose-ranging, study design will enable exploration of the expected therapeutic range, including evaluation of the minimal effective dose. If the drug is found to be well tolerated and effective, this study will inform dose selection for confirmatory trials. The OLE will evaluate long-term tolerability, safety, and maintenance of efficacy of a 20 mg QD dose of XEN1101.

4.4 JUSTIFICATION FOR DOSE

Oral administration is the intended dosing route for this drug in the treatment of patients with epilepsy. The doses for this trial were defined by the safety, tolerability, and PK data seen in the FIH study (XPF-008-101a) and the companion TMS crossover study (XPF-008-101b). Doses were selected based on data from the Phase 1 clinical and nonclinical studies. The high and mid doses are expected to provide steady-state C_{min} plasma levels at or above the EC_{50} CCI for suppression of seizures in rodent maximum electroshock (MES) epilepsy models. These plasma levels have also been shown to suppress

cortical excitability assessed by TMS-electroencephalogram (EEG) in healthy volunteers. The low dose of 10 mg is expected to provide C_{min} plasma levels CCI below the EC_{50} for suppression of seizures in rodent MES epilepsy models but still in the range for effects observed with TMS. Each patient will receive up to a maximum of 56 ± 3 doses of the IMP (XEN1101 or placebo) over 8 weeks during the DBP.

Patients entering the OLE will receive up to 3 years of additional daily doses of 20 mg XEN1101. Since there have been no completed epilepsy efficacy trials to definitively inform dose selection, this dose level was chosen for the OLE as it may provide the best risk/benefit profile of the 3 possible doses from the DBP portion of the study.

4.5 END OF STUDY DEFINITION

A patient not proceeding on to the OLE is considered to have completed the DBP portion of the study once he or she has completed all stages of the study including the last scheduled procedures (Visit F2a) shown in Section 1.2 Schedule of Activities Table 1a.

Patients who proceed to the OLE will be considered to have completed the OLE, once they have completed all of the study procedures up to and including the Visit F2b as shown in Section 1.2 Schedule of Activities Table 1b.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients will be considered eligible to participate in the study if they meet all of the inclusion criteria and none of the exclusion criteria (Section 5.2) listed below.

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, 18 to 75 years of age (inclusive) with a body mass index (BMI) ≤40 kg/m^2.
3. Diagnosis (≥2 years) of focal epilepsy according to the International League Against Epilepsy [ILAE] Classification of Epilepsy (2017).
4. Prior neuroimaging within the last 10 years and documentation is available.
5. Treatment with a stable dose of 1 to 3 allowable current AEDs for at least one month prior to screening, during baseline, and throughout the DBP.
6. Must be willing to comply with the contraception requirements as defined in Section 5.4.
7. Males must agree not to donate sperm from the time of the first administration of IMP until 6 months after the last dose of IMP. Females must agree not to donate ova from the time of the first administration of IMP until 6 months after the last dose of IMP.
8. Able to keep accurate seizure diaries.
9. Able to participate for the full term of the study.

5.2 EXCLUSION CRITERIA

Patients will be considered eligible to participate in the study if they meet all of the inclusion criteria (Section 5.1) and none of the exclusion criteria listed below.

1. Previously documented EEG which shows any pattern not consistent with focal etiology of seizures. (A new EEG is not required, if not available.)
2. History of focal aware non-motor seizures only.
3. History of pseudoseizures or psychogenic seizures.
4. History of a primary generalized seizure.
5. Presence or previous history of Lennox-Gastaut syndrome.
6. Seizures secondary to illicit drug or alcohol use, ongoing infection, neoplasia, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive, metabolic illness, or progressive degenerative disease, progressive structural lesion or encephalopathy.
7. History of repetitive seizures within the 12-month period preceding study entry where the individual seizures cannot be counted.
8. Status epilepticus within the last 12 months prior to enrollment.
9. History of neurosurgery for seizures <1 year prior to enrollment, or radiosurgery <2 years prior to enrollment.
10. Schizophrenia and other psychotic disorders (eg, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified [NOS]), bipolar disorder, and/or obsessive-compulsive disorder, or other serious mental health disorders. Uncontrolled unipolar major depression where changes in pharmacotherapy are needed or anticipated during the study.
11. Active suicidal plan/intent in the past 6 months, or a history of suicide attempt in the last 2 years, or more than 1 lifetime suicide attempt.
12. History or presence of any significant medical or surgical condition or uncontrolled medical illness at screening including, but not limited to, hematologic, cardiovascular, pulmonary, renal, gastrointestinal, endocrine, hepatic or urogenital systems, or other conditions that would place the patient at increased risk as determined by the investigator.
13. History of cancer within the past 2 years, with the exception of appropriately treated basal cell or squamous cell carcinoma.
14. Alanine transferase (ALT; SGPT) or aspartate transferase (AST; SGOT) levels >3 times the upper limit of normal (ULN) at screening or baseline.
15. Any clinically significant laboratory abnormalities or clinically significant abnormalities on pre-study physical examination, vital signs, or ECG that in the judgment of the investigator indicates a medical problem that would preclude study participation including but not limited to:
    a. History or presence of long QT syndrome; QTcF >450 ms at baseline; family history of sudden death of unknown cause.
    b. History of skin or retinal pigment epithelium abnormalities caused by ezogabine.
16. Females who are pregnant, breastfeeding, or planning to become pregnant during the first administration of IMP until 6 months after the last dose of IMP.

17. History of illicit drug or alcohol abuse within 1 year prior to screening judged by the investigator to be excessive or compulsive, or currently using drugs of abuse or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse, dependence, or habitual use.
18. Exposure to any other investigational drug or device within 5 half-lives or 30 days prior to screening, whichever is longer.
19. Use of vigabatrin in the last 5 years without stable visual fields tested twice over the 12 months after the last dose of vigabatrin. (Patients stopping vigabatrin more than 5 years prior to screening, must have no vigabatrin-related visual field abnormalities confirmed by examination within the past 6 months – concomitant use of vigabatrin is not allowed).
20. If felbamate is used as a concomitant AED, patients must be on felbamate for at least 2 years, with a stable dose for 2 months (or no less than 49 days) prior to screening. They must not have a history of white blood cell (WBC) count below 2500/µL (2.50×10^9/L), platelets below 100,000/mm^3 (100×10^9/L), liver function tests above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If patients received felbamate in the past, it must have been discontinued 2 months (or no less than 49 days) prior to screening.
21. Have had multiple drug allergies or a severe drug reaction to an AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
22. Current use of a ketogenic diet.
23. Any medical condition or personal circumstance that in the opinion of the investigator exposes the patient to unacceptable risk by participating in the study or prevents adherence to the protocol.
24. 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 ADDITIONAL ELIGIBILITY CRITERIA

In addition to meeting all of the inclusion criteria and none of the exclusion criteria during screening, and despite being on an appropriate treatment regimen with current medications, patients must also meet all of the following criteria to be eligible to participate in the DBP:

a) During the planned 8-week baseline period preceding the randomization visit (Visit 3), patients must have a documented seizure frequency of ≥4 focal seizures per 28 days on average.

   Note: In cases of delayed randomization caused by the COVID-19 pandemic preventing patients from attending site visits, data obtained during the 56 days of electronic diary (eDiary) entries prior to randomization will be used to define the “baseline period”, for purposes of determining eligibility for randomization.

   In order to establish baseline seizure count, the types of countable focal seizures to be included in the count will be:

   - Focal aware seizures with motor signs,
   - Focal seizures with impaired awareness, and
   - Focal seizures that lead to generalized tonic-clonic seizures.

b) eDiary was completed a minimum of 80% of all days (ie, ≥45 days) during the 8-week baseline period as evidence of adequate compliance.

c) Patients should not be seizure-free for more than 21 consecutive days during the 8-week baseline period.

d) Patient does not show retinal macular disease, or retinal pigment epithelium abnormality on the dilated ophthalmic examination prior to randomization.

ELIGIBILITY CONFIRMATION

To ensure enrollment of appropriate patients, The Epilepsy Study Consortium (TESC) may be consulted to assist in eligibility evaluation. TESC will review and approve seizure eligibility and classification for the first patient at each site at a minimum. Detailed instructions regarding TESC assistance are provided in the Study Operations Manual. TESC can be consulted at any point during the DBP enrollment phase to assist with eligibility determination.

CRITERIA FOR ENTERING THE OLE

In addition to meeting all of the entry criteria for the baseline and DBP, patients must also meet all of the following inclusion criteria and none of the exclusion criteria to be eligible to participate in the optional OLE:

Inclusion Criteria:

1. Be properly informed of the nature and risks of the study and give informed consent in writing.
2. Must have met all eligibility requirements and completed the DBP (to Visit 8* with a minimum of 80% compliance with eDiary entries and IMP), did not terminate early, patient had no important protocol deviations (eg, that may impact patient safety, or data integrity) that in the opinion of the sponsor should preclude participation in the OLE, and had no AEs that, in the opinion of the investigator, would preclude the patient's entry into the OLE.**
3. Patient is expected to experience benefit from their participation, in the opinion of the investigator.
4. Must be willing to comply with the contraception requirements as defined in the protocol.
5. Males must agree not to donate sperm until 6 months after the last dose of study drug. Females must agree not to donate ova until 6 months after the last dose of study drug.

*A small number of patients may have completed treatment and continued with Visit F1a and/or Visit F2a post-treatment follow-up assessments before the initial availability/approval of the OLE. In these patients, assessments completed at Visit 8 or Visit F2a (as applicable) may be used to confirm eligibility for the OLE. Similarly, a small number of patients may be nearing completion of the DBP at the time of approval of the amendment which requires a dilated ophthalmic examination, these patients must complete the dilated ophthalmic examination prior to entry in the OLE and as such, may experience a delay from Visit 8 of up to a few weeks prior to entry in the OLE. (If the dilated ophthalmic examination requires more than 1 week from Visit 8 to be completed in these patients, a Visit F1A should be completed prior to entering the OLE.) The study day for all subsequent visits as outlined in Table 1b will be calculated from the date that Visit 8A is conducted.

**Note: Patients who successfully completed 52 weeks of OLE treatment with XEN11201 (as per Protocol version 4.1) prior to approval of the amendment in Protocol version 4.2, and in whom it has been <6 months since their last treatment, will be permitted to resume OLE treatment with XEN1101. This subgroup of patients will need to reconsent and complete Visit 14A assessments onsite in order to

obtain study drug and paper diary. A urine pregnancy test must be performed for females of childbearing potential (if positive a serum pregnancy test will be performed).

Exclusion Criteria:

1. Patients who met any of the withdrawal criteria in the DBP.
2. Any medical condition, personal circumstance, or ongoing AE that in the opinion of the investigator exposes the patient to unacceptable risk by participating in the OLE, or prevents adherence to the protocol.
3. Females who are pregnant, breastfeeding, or planning to become pregnant until 6 months after the last dose of study drug.
4. Patients planning to enter a clinical trial with a different investigational drug or plan to use any experimental device for treatment of epilepsy or any other medical condition.

5.4 CONTRACEPTION REQUIREMENTS

Female patients must either be:

- Postmenopausal (as defined as amenorrhea for at least 12 months with no alternative medical cause and confirmed by a follicle-stimulating hormone (FSH) result of ≥40 IU/L) 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 one form of highly effective contraception as defined below, starting at least one menstrual cycle before first study drug administration and continuing until at least 6 months after the last dose of the study drug.

Highly effective contraceptive methods for females are as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
  - Oral.
  - Intravaginal.
  - Transdermal.
- 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 that 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, post-ovulation methods), withdrawal (coitus interruptus), spermicide only, and declaration of abstinence only for the duration of exposure to IMP are not acceptable methods of contraception.

Male patients, if heterosexually active and with a female partner of childbearing potential or a pregnant or breastfeeding partner, must agree to use barrier contraception (male condom) for the treatment period and for at least 6 months after the last dose of the study drug.

Male patients with female partners of childbearing potential must have that female partner use at least one form of highly effective contraception as defined above, starting at least one menstrual cycle before (the male patient's) first study drug administration and continuing until at least 6 months after their male partner's last dose of the study drug.

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

5.4.1 EXPOSURE TO PARTNERS DURING THE STUDY

There is a risk of drug exposure through the ejaculate (which also applies to vasectomized males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male patients. Therefore, a condom should be used by all male patients throughout the study and for 6 months after administration of the last IMP dose as specified in Section 5.4.

5.4.2 SPERM OR OVA DONATION

Males should not donate sperm from dosing and for the duration of the study and for at least 6 months after the last IMP dose. Females should not donate ova from dosing and for the duration of the study and for at least 6 months after the last IMP dose.

5.4.3 PREGNANCY

Patients will be instructed to report to the investigator if they/their partner become pregnant during the study or within 6 months after the administration of the last IMP dose. Refer to Section 8.4.4.5 for details on reporting a pregnancy.

5.5 LIFESTYLE CONSIDERATIONS

Patients in the trial are encouraged to live a healthy lifestyle, with adequate sleep and to avoid substance abuse, including excessive alcohol consumption. It is recommended to take the IMP consistently in the evening. As food enhances the absorption of XEN1101, it is recommended to take the IMP with food (eg, either before, during, or after the evening meal).

5.6 SCREEN AND BASELINE/RANDOMIZATION FAILURES

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

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

Patients who enter the baseline period, but are subsequently not eligible to randomize based on the Additional Eligibility Criteria (Section 5.3) will not be permitted to repeat baseline assessments. Patients who are ineligible for other reasons may be permitted to repeat baseline on a case-by-case basis (subject to sponsor review/approval).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

CCI [redacted]

The corresponding placebo drug product is formulated as identical-looking capsules filled with

CCI [redacted] of an inert material. CCI [redacted]

The study drug and placebo drug product will be packaged in sealed high-density polyethylene (HDPE) bottles, containing 33 capsules/bottle.

The labeling of the IMP will be in compliance with current Good Manufacturing Practice specifications, as described in The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products, and any other or local applicable regulations.

Sample label(s) will be submitted to the health authorities according to the submission requirements in the appropriate jurisdiction.

6.1.2 DOSING AND ADMINISTRATION

DOUBLE-BLIND PERIOD:

Each patient who meets all the inclusion criteria and none of the exclusion criteria at baseline will be randomly assigned to 1 of the 4 arms in the DBP of the study in a ratio of 2:1:1:2 (25 mg, 20 mg, or 10 mg of XEN1101, or placebo). Participants will be instructed to take a single daily oral dose of either XEN1101 or placebo (1 capsule/dose), with food at approximately the same time in the evening each day, for 56 days. As food enhances the absorption of XEN1101, it is recommended to take the IMP with food (eg, either before, with, or after the evening meal). IMP compliance should be recorded by patients using the electronic patient reported outcomes (ePRO) device/program provided (ie, eDiary) and reviewed by site staff during scheduled visits.

IMP capsules will be taken QD, and patients should adhere to an approximately 24-hour interval between scheduled doses as much as possible. IP will be supplied to the site through an interactive response technology (IRT) system, and the site will provide patients with one 33-count bottle of capsules of the IMP at randomization/study Visit 3 (Study Day 0) and resupply them on study Visit 6 (Study Day 28). Patients will be instructed to swallow the IMP capsules whole and never to chew, divide, open, sprinkle the contents, or crush the capsules.

Detailed instructions for IMP administration and storage will be included in the ICF.

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

The IMP or placebo will be dispensed monthly during the DBP as detailed in the table below.

Treatment	**IMP/Placebo Dispensed**
25 mg XEN1101	33 × 25 mg capsules
20 mg XEN1101	33 × 20 mg capsules
10 mg XEN1101	33 × 10 mg capsules
Placebo to match XEN1101	33 placebo capsules

If the IMP is found to be intolerable, and withdrawal from the study is the only alternative for the patient, unless the patient has met dose stopping criteria in Section 7.2 the investigator may temporarily stop the IMP for 1 week within the treatment period: after a one week washout period patients may then be instructed to continue with their assigned IMP, but to reduce the dosing frequency from QD, to once every second day (every other day). The investigator must notify the medical monitor whenever the patient's study drug is temporarily stopped and the dosing interval changed, or permanently stopped for intolerability.

If the every second day dosing regimen is not tolerated, to the level of requiring withdrawal from the study, the patient will be instructed to stop taking the IMP. Patients in whom IMP dosing has been permanently stopped for any reason will be required to complete a site visit one week (7 ± 3 days) following their last dose of IMP (Visit F1a) and to complete a follow-up visit 42 ± 7 days following their last dose (Visit F2a). Patients who withdraw early from the study and are unwilling or unable to complete these follow-up visits, will be requested to complete an early termination visit (Visit ET). Patients will be requested to continue completing their eDiary until the last study visit. Refer to Table 1a Schedule of Assessments.

OPEN-LABEL EXTENSION PHASE:

Each eligible patient entering the OLE will return the study drug dispensed during the DBP on the Day 56 visit and will receive a bottle of 20 mg capsules of XEN1101. Participants will be instructed to take a single daily 20 mg oral dose of XEN1101 with food at approximately the same time in the evening each day. Participants will be instructed to begin taking their open-label 20 mg dose at least one day after their last dose of double-blind study drug. Participants continuing in the OLE will be supplied with an additional 3 bottles of 20 mg capsules of XEN1101 at the Day 77 Visit and 3 bottles at each subsequent scheduled visit during the OLE treatment period. Subjects who have had their dose reduced to QOD dosing due to intolerability will be dispensed 2 bottles of XEN1101 at each subsequent visit following the dose reduction. (Note: XEN1101 may be sent from the site to patients by courier at the time of telephone call [TC] visits).

If the study drug is not tolerated, and withdrawal from the study is the only alternative for the patient, the investigator may stop the drug for up to 1 week and then resume dosing at a dosing interval of one capsule every second day for the remainder of the OLE. (Note: The period of stopping study drug is variable according to the clinical judgment of the investigator and could be from 1 to 7 days, unlike in the DBP when it is mandated to be 7 days.). If XEN1101 continues to be intolerable to the level of requiring withdrawal from the study, dosing should be stopped and the patient withdrawn from the study. All efforts should be made to complete applicable study procedures. The investigator is requested to discuss with the medical monitor prior to making changes to the study drug regimen and must notify the medical monitor whenever the patient's study drug is temporarily stopped and the dosing interval changed, or permanently stopped for intolerability.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The IMP (ie, XEN1101 and placebo) will be allocated during the DBP according to the randomization scheme generated by the IRT system. Shipments will be made to sites from a qualified depot under controlled ambient conditions. In the case of restricted access to sites (eg, due to the COVID-19 pandemic), sites may be required to use a certified courier to send IMP to patients who are ongoing in the trial.

The IMP will be stored in a locked storage unit with restricted access by the designated study personnel at each site who will perform an ongoing inventory of study drug supplies. The clinical research associate (CRA) monitoring the investigational site must keep an accurate inventory of IMP shipments received and the amount of IMP dispensed per patient. At the end of both the DBP and OLE, 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 IMP 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 IMP remains, this will be indicated in the drug accountability log.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

CCI [redacted]

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

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

The bottles will be labeled with an appropriate multi-language booklet, 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").
- Study drug number.
- Recommended storage conditions.
- Lot number.
- Expiry date.

- Name and address of the sponsor.
- Protocol number.

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

- 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”).
- A description of the study drug (eg, “XEN1101 capsules, 20 mg”).
- Recommended storage conditions.
- Lot number.
- Expiry date.
- Name and address of the sponsor.
- Protocol number.

6.2.3 PRODUCT STORAGE AND STABILITY

At the investigational site, the IMP must be stored at controlled ambient room temperature (15°C to 25°C, or 59°F to 77°F). While the IMP 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 Operations Manual for further details.

Patients 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. During brief transport from the site by/to the patient’s home controlled conditions are not required, beyond reasonable protection from excessive heat or freezing.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

During the DBP, IMP will be administered under double-blind conditions: Patients and investigators will be blinded to treatment assignment. Sponsor and CRO staff will also remain blinded with the exception of a pre-identified individual from the sponsor. If there is a medical need to reveal the assigned dose administered to a patient, 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 patient’s treatment assignment. If the investigator proceeds with the unblinding, he/she 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.

Randomization will be stratified by background use versus non-use of a CYP3A4 inducer medication (eg, any of carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, topiramate, or phenobarbital).

During the OLE, all participants will receive 20 mg XEN1101 capsules. The participants and investigators, as well as sponsor and CRO staff, will remained blinded to prior treatment assignments until all patients have completed the DBP and the database has been locked for that phase of the study.

6.4 STUDY INTERVENTION COMPLIANCE

The ePRO device or application (eDiary) selected for this study will provide a dose reminder and will be used by each patient to record IMP doses and any missed doses during the DBP.

Patients will be instructed to bring their eDiary and IMP bottle to applicable DBP study visits. Compliance during the DBP will be assessed by capsule count on scheduled study visits (Visits 6 and 8) and early termination (ET) by assigned site staff. Reconciliation will be conducted by the CRA via capsule count and eDiary review. Compliance during the treatment period will be based on daily eDiary entries and by capsule count at Visit 6/Week 4, Visit 8/Week 8, and ET. Patients must remain at least 80% compliant with their IMP and eDiary during the DBP (to be considered as having successfully completed the DBP), for purposes of OLE eligibility consideration.

During the OLE, patients will be issued a paper diary and instructed to bring their paper diary and study drug bottles to each study site visit. Compliance during the OLE will be assessed by capsule count on scheduled study site visits.

6.5 CONCOMITANT THERAPY

Patients are required to be on a stable dose of between 1 and 3 AEDs 1 month prior to Visit 1, during baseline and for the duration of the DBP of the trial. During the OLE only, the background AED and/or neurostimulator therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per investigator discretion. Dose regimen will be recorded in the eCRF. All current medication will be recorded at the screening visit and changes recorded throughout the trial.

All concomitant treatment, including nonpharmacologic treatments taken by the patient, in the 30 days prior to screening and then throughout the study, will be recorded on the eCRF along with start and stop dates, the indication for use, and the daily dose, at the visits shown in Table 1a and Table 1b Schedule of Assessments. Past AED use will also be recorded in the eCRF.

6.5.1 RESCUE MEDICINE

Benzodiazepines may be used intermittently for the control of seizure clustering as a rescue medication.

Details on use of rescue medication administration will be documented in the eCRF.

6.5.2 PROHIBITED MEDICATIONS AND SUBSTANCES

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

- Vigabatrin.
- 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.
- Other investigational drug or device within five half-lives or 30 days prior to screening, whichever is longer.

6.5.3 PERMITTED MEDICATIONS

Stable use of 1 to 3 AEDs is allowable from 1 month prior to screening through to the end of the DBP, with the exception of vigabatrin. Benzodiazepines may be used intermittently as described in Section 6.5.1.

Chronic use of a benzodiazepine for epilepsy and non-epilepsy conditions will be counted as 1 of the 3 AEDs, and the dose cannot be changed from 1 month prior to screening through to the end of the DBP. Benzodiazepines should be counted as an AED if used on a regular basis for epilepsy. As needed (PRN) benzodiazepine, if used for seizure exacerbations or other indications (such as anxiety), is allowed and not counted as an AED as long as this is documented. The use of benzodiazepine on a regular basis or on a PRN basis, averaging more than twice weekly (for any indication) during the baseline period of the DBP, should be counted as one of the AEDs for the study.

Recreational or medicinal use of marijuana, cannabinoids and/or derivatives (eg, cannabidiol) is neither encouraged nor prohibited, but use should be recorded as a concomitant medication. Use of marijuana, cannabinoids, and/or derivatives will not count as one of the 1 to 3 allowable current AEDs.

During the OLE only, the background AED and/or neurostimulator therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per investigator discretion.

Patients receiving treatment with a vagal nerve stimulator, deep brain stimulation, or responsive neurostimulator system may be included as long as the stimulator has been in place for at least 12 months prior to entry into the DBP, the battery is not due for replacement during DBP participation, and stimulation parameters have been kept constant for at least 3 months prior to screening. The stimulator device will not count as 1 of the 3 allowed concomitant AEDs.

7 STUDY DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 STUDY ARM STOPPING RULE

Patients who do not tolerate the study treatment will be managed on an individual basis through dose interruption and reduction in dosing frequency, as per protocol. Safety data will be reviewed quarterly by a Safety Review Committee (SRC) based on blinded data. There is no plan to stop a particular dose arm during the DBP, unless a major safety issue is raised by the SRC and confirmed by independent unblinded safety assessment. If enrollment of one arm is permanently terminated, randomization will be adjusted accordingly.

7.2 PARTICIPANT DISCONTINUATION OF STUDY INTERVENTION

Patients should be instructed by the investigator to call immediately upon experiencing any SAE, or any other events that are of significant concern to the patient. The investigator should use caution with respect to continued dosing and monitor for progression of these, or other reactions.

Patients MUST have the IMP withdrawn should any of the following occur:

1. Any changes in cardiac rhythm or atrioventricular conduction that, in the investigator's opinion, is a threat to patient 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, unless considered not related to study drug.
5. Severe CNS adverse effects persisting despite reducing the dose to a one capsule every second day regimen.
6. A female patient has a confirmation of pregnancy during the study from a positive serum pregnancy test.
7. Occurrence of significant suicidal ideation or suicidal behavior.
8. Occurrence of a SAE that is deemed definitely related to the IMP by the investigator.

During the DBP, patients in whom IMP dosing has been stopped for any reason will be required to complete a site visit one week (7 ± 3 days) following their last dose of IMP (Visit F1a) and to complete a

follow-up visit 42 ± 7 days following their last dose (Visit F2a). Patients will be requested to continue completing their eDiary until the last study visit (refer to Table 1a Schedule of Assessments).

During the OLE, patients in whom study drug dosing has been stopped for any reason will be required to complete a site visit one week (7 ± 3 days) following their last dose of IMP (Visit F1b) and to complete a follow-up visit 42 ± 10 days following their last dose (Visit F2b). Patients will be requested to continue completing their diary until the last study visit (refer to Table 1b Schedule of Assessments).

7.3 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Each patient is free to withdraw from the IMP and/or study at any time, without prejudice to their continued care. In addition to the IMP withdrawal criteria listed in Section 7.2, patients must be withdrawn from the study if any of the following events occur:

1. Patient withdraws consent or requests discontinuation from the IMP and/or study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMP to an extent that may impact the study results, or put the patient at unnecessary risk, in the opinion of the investigator.
4. Patient takes a prohibited concomitant medication or substance as defined in Section 6.5.2.
5. The sponsor requests withdrawal of the patient.

If withdrawal occurs after administration of any IMP, but before all evaluations are completed, efforts should be made to complete the evaluations and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation should be performed at the time of the patient's withdrawal, giving an explanation for the withdrawal. (Note: Patients who withdraw from the study and are unwilling or unable to complete follow-up visits [F1a and F2a] should have all ET evaluations performed on the last day of receiving the IMP, or as soon as possible thereafter.) The reason for and date of the withdrawal must be recorded on the patient'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 resolved or stabilized, the patient was referred to the care of a health care professional, or a determination of a cause unrelated to the IMP or study procedure was made). The specific event(s) or test result(s) are to be recorded in the eCRF. Final evaluations (ET visit procedures and assessments) for patients who withdraw from the study should be performed on the last day the patient was treated with the IMP or as soon as possible thereafter.

7.4 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he or she fails to return for his or her scheduled visit and is unable to be contacted by the study site staff.

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

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

Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up/withdrawal of consent.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 PROCEDURES

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

Screening

Visit 1 (starts at Study Day -84 to -57)

Up to 28 days may be used to complete the screening period, but patients can begin the baseline period as soon as the investigator (or designee) has performed all screening assessments and the investigator has confirmed that the patient meets the criteria to start the baseline assessments.

Screening assessments include:

- Informed consent.
- C-SSRS.
- AEs.
- Eligibility assessment.
- Medical and psychiatric history.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Height, weight, and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including AEDs.

- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CCI [redacted]

Baseline

Visit 2 (Study Day -56)

Baseline assessments may begin as soon as the investigator has confirmed that the patient meets the criteria to enter the baseline period. An assessment marked with an asterisk (*) does not need to be repeated if it was normal at screening (or unchanged) and the assessment was completed within ≤3 days of the baseline visit.

Baseline assessments include:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.*
- Vital signs.
- 12-lead ECG.*
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Site set-up of the eDiary and patient training.
- Serum pregnancy test for females of childbearing potential.
- FSH, if a postmenopausal female.
- Clinical laboratory tests.*
- CCI [redacted]

During the 8-week baseline period, the site study team should review the eDiary data regularly to check the patient's daily entries and follow-up as appropriate.

Double-blind Period

At the end of the planned 8-week baseline period and prior to randomization and administration of the first dose, the following assessments outlined below should be performed.

Note: Day 0 can start up to 66 days from start of baseline (eligibility for randomization is generally based on the initial 56 days of eDiary entries in the baseline period. – Note: In cases where restrictions to site access caused by the COVID-19 pandemic prevent patients from attending site visits, the duration of the baseline period may be extended, and randomization delayed up to 20 weeks (140 days) from the start of data capture. In cases of delayed randomization caused by the COVID-19 pandemic preventing patients from attending site visits, data obtained during the 56 days of eDiary entries prior to randomization will be used to define the "baseline period", for purposes of determining eligibility for randomization).

If the patient is deemed to be ineligible (baseline/randomization failure), only the assessments highlighted with an asterisk below need to be completed. If ineligibility is determined prior to completion of the baseline period through eDiary data monitoring, the investigator will decide if the patient should be informed by phone or required to attend Visit 3.

Visit 3 – Study Day 0

- Eligibility assessment confirmation.*
- C-SSRS.
- AEs.*
- Return of eDiary (only if patient is a deemed to be ineligible at this visit).*
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood collection for biomarker/genotype assessment (not mandatory for inclusion in the study).
- Blood sample for PK analysis (XEN1101).
- Randomization.
- IMP supply to patient.

Visit 4 (Telephone Call) – Study Day 7 (± 3 days)

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- Check of eDiary compliance.

Visit 5 – Study Day 14 (± 3 days)

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- 12-lead ECG.
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary and IMP compliance.
- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).

Visits 6 – Study Day 28 (± 5 days)

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary and IMP compliance (IMP container should be returned to the site).
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).
- IMP resupply to patient.

Visit 7 (Telephone Call) – Study Day 42 (± 4 days)

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- Check of eDiary compliance.

Visit 8/End of double-blind treatment – Study Day 56 (± 3 days) for patients NOT entering the OLE

At the end of the 8-week DBP and after administration of the last blinded dose, the following assessments should be performed:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- Clinical Global Impression (CGI) of change.
- Patient Global Impression of Change (PGI-C).
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary and IMP compliance.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood collection for biomarker assessment (not mandatory for inclusion in the study).
- Blood sample for PK analysis (XEN1101).
- Collect remaining IMP supply from patient.

Post-treatment Follow-up for Patients NOT Entering the OLE

For those patients not entering the OLE, follow-up evaluations are to be performed 7 ± 3 days (Visit F1a) and 42 ± 7 days (Visit F2a) following the last blinded dose.

Patients in whom IMP dosing has been stopped for any reason will be required to complete a site visit one week (7 ± 3 days) following their last dose of IMP (following Visit F1a procedures) and to complete a follow-up visit 42 ± 7 days following their last dose (following Visit F2a procedures). Patients will be requested to continue completing their eDiary until the last study visit. Refer to Table 1a Schedule of Assessments.

Patients who discontinue early from the study and are unwilling or unable to complete follow-up visits (F1a and F2a) should have all ET evaluations performed on the last day of receiving the IMP, or as soon as possible thereafter.

Visit F1a – Study Day 63 (7 ± 3 days post last dose) in patients NOT entering the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- 12-lead ECG.
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary compliance.
- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).
- CCI [redacted]

Visit F2a – Study Day 98 (42 ± 7 days post last dose) in patients NOT entering the OLE

Upon completion of Visit F2a (or the ET visit, when applicable), the patient's participation in the study will be finished. The following assessments should be completed at Visit F2a:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- CGI.
- PGI-C.
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary compliance.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).

- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).
- Return of eDiary device.

Unscheduled Visit(s)

Patients may return to the site between scheduled study visits as required for safety management, eDiary re-training/maintenance or for other reasons. The investigator will determine the tests and procedures to be performed at an unscheduled visit, which should be recorded in the source and eCRF.

Early Termination (when applicable)

If the patient discontinues or is withdrawn from the study, and is unwilling or unable to complete the follow up visits (F1a and F2a), efforts should be made to complete the ET evaluations and report the observations up to the time of withdrawal as thoroughly as possible. The following assessments should be performed on the last day the patient was treated with the IMP or as soon as possible thereafter:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- CGI.
- PGI-C.
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary and IMP compliance.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood collection for biomarker assessment (not mandatory for inclusion in the study).
- Blood sample for PK analysis (XEN1101).
- Collect remaining IMP supply from patient.
- Return of eDiary device.
- CCI [redacted]

PROCEDURES FOR PATIENTS ENTERING THE OLE

Upon successful completion of all study visits in the DBP up to and including Visit 8 (Study Day 56), patients may be considered for entry into the OLE. Eligible patients continuing in the OLE will stop their double-blinded dosing as per protocol, complete the Day 56/Visit 8 procedures (including the additional procedures outlined below and in Table 1b), and return the eDiary device. Participants will begin dosing with XEN1101 at a 20 mg QD dose (at least 1 day following their last blinded dose) for the duration of the OLE. Subsequent visits will be conducted as outlined in the Schedule of Assessments, Table 1b, and as described below.

Visit 8/Study Day 56 (± 3 days) End of DBP and Start of OLE

For patients entering the OLE, the following assessments should have been performed at the end of the 8-week DBP and after administration of the last blinded dose (and do not need to be duplicated):

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.†
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- Clinical Global Impression (CGI) of change.
- Patient Global Impression of Change (PGI-C).
- Concomitant medications, including any changes to AEDs.
- Site check of eDiary and IMP compliance.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood collection for biomarker assessment (not mandatory for inclusion in the study).
- Blood sample for PK analysis (XEN1101).
- Collect remaining IMP supply from patient.

CCI [redacted]

ADDITIONAL VISIT 8A PROCEDURES FOR PATIENTS ENTERING THE OLE

For patients entering the OLE, the following assessments should also be performed:

- Eligibility assessment for OLE.
- Return of eDiary.
- Training and supply of paper diary.
- Clinical Global Impression of Severity (CGI-S).
- Patient Global Impression of Severity (PGI-S).
- Dispense study drug for OLE (20 mg capsules XEN1101).

Visit 9/Study Day 77 (± 3 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and dispense study drug (20 mg capsules XEN1101).

Visit 10/Study Day 161 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.

- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and dispense study drug (20 mg capsules XEN1101).

Visit 11/Study Day 245 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and dispense study drug (20 mg capsules XEN1101).

Visit 12/Study Day 329 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.

- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and dispense study drug (20 mg capsules XEN1101).

Visit 13A/Study Day 420 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Blood sample for PK analysis (XEN1101).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and return of study drug (20 mg capsules XEN1101).
- CCI [redacted]

Note: Patients who successfully completed 52 weeks of OLE treatment (as per Protocol version 4.1) prior to approval of the amendment in Protocol version 4.2, and in whom it has been <6 months since their last treatment, will be permitted to resume OLE treatment with XEN1101 if they continue to meet study criteria for participating in the OLE. This subgroup of patients will need to reconsent and complete Visit 14A assessments onsite in order to obtain study drug and the paper diary. A urine pregnancy test must be performed for females of childbearing potential (if positive a serum pregnancy test will be performed).

TC Visit 14A/Study Day 511 (± 7 days) – Patients Participating in the OLE

- Reconsent (for patients reentering the OLE)
- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed) (for patients reentering the OLE).
- CGI-S.
- PGI-S.
- Provision of study drug (20 mg capsules XEN1101) to patient.

Visit 15A/Study Day 602 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and return of study drug (20 mg capsules XEN1101).

- CCI [redacted]

TC Visit 16/Study Day 693 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Provision of study drug (20 mg capsules XEN1101) to patient.

Visit 17/Study Day 784 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Blood sample for PK analysis (XEN1101).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and return of study drug (20 mg capsules XEN1101).
- CCI [redacted]

TC Visit 18/Study Day 875 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Provision of study drug (20 mg capsules XEN1101) to patient.

Visit 19/Study Day 966 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and return of study drug (20 mg capsules XEN1101).
- CCI [redacted]

TC Visit 20/Study Day 1057 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.

- Provision of study drug (20 mg capsules XEN1101) to patient.

Visit 21/Study Day 1148 (± 7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.*
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- CGI-S.
- PGI-S.
- QoL assessment (QOLIE-31).
- Blood sample for PK analysis (XEN1101).
- Collect and check completed diary and resupply of new paper diary.
- Compliance check and return of study drug (20 mg capsules XEN1101).

* A non-dilated ophthalmic examination at Visit 21.

Post-treatment Follow-up – Patients Participating in the OLE

Patients who entered the OLE should complete follow-up evaluations 7 ± 3 days (Visit F1b) and 42 ± 10 days (Visit F2b) following their last open-label (20 mg) dose of XEN1101.

Patients in whom XEN1101 dosing has been stopped for any reason will be required to complete a site visit one week (7 ± 3 days) following their last dose of XEN1101 (following Visit F1b procedures) and to complete a follow-up visit 42 ± 10 days following their last dose (following Visit F2b procedures). Patients will be requested to continue completing their diary until the last study visit. Refer to Table 1b Schedule of Assessments.

Patients who discontinue early from the study and are unwilling or unable to complete the follow up visits (F1b and F2b) should have all ET evaluations performed on the last day of receiving the XEN1101, or as soon as possible thereafter.

Visit F1b – Study Day 1155 (7 ± 3 days post last OLE dose)

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- 12-lead ECG.
- Concomitant medications, including any changes to AEDs.
- Collect and check used diary and resupply of new paper diary.
- Clinical laboratory tests.
- CCI [redacted]

Visit F2b – Study Day 1190 (42 ± 10 days post last OLE dose)

Upon completion of Visit F2b (or the ET visit, when applicable), the patient's participation in the study will be finished. The following assessments should be completed at Visit F2b:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- CGI-S.
- PGI-S.
- Concomitant medications, including any changes to AEDs.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Return of paper diary.

Unscheduled Visit(s)

Patients may return to the site between scheduled study visits during the OLE as required for safety management, diary re-training or for other reasons. The investigator will determine the tests and procedures to be performed at an unscheduled visit, which should be recorded in the source and eCRF.

Early Termination (when applicable)

If the patient discontinues or is withdrawn from the OLE phase of the study, and is unwilling or unable to complete the follow-up visits (F1b and F2b), efforts should be made to complete the ET evaluations and report the observations up to the time of withdrawal as thoroughly as possible. The following assessments should be performed on the last day the patient was treated with the study drug, or as soon as possible thereafter:

- C-SSRS.
- AEs.
- Physical and neurologic examinations, including ophthalmoscopy.
- Vital signs.
- Weight and BMI.
- 12-lead ECG.
- AUA Symptom Index.
- QoL assessment (QOLIE-31).
- CGI-S.
- PGI-S.
- Concomitant medications, including any changes to AEDs.
- Site check of diary and study drug compliance.
- Urine pregnancy test for females of childbearing potential (if positive a serum pregnancy test will be performed).
- Clinical laboratory tests.
- Blood sample for PK analysis (XEN1101).
- Collect remaining study drug supply from patient.
- Return of paper diary.
- CCI [redacted]

8.2 EFFICACY ASSESSMENTS

8.2.1 SEIZURE TYPES

Seizure information will be collected on an ongoing basis by patient use of the eDiary throughout the baseline, DBP, and follow-up for patients not participating in the OLE, which will be reviewed at selected visits as specified in Table 1a (Schedule of Assessments). For patients participating in the OLE, the eDiary will be replaced with a paper diary at Visit 8 (end of DBP).

The following seizure types according to the ILAE 2017 classification (Fisher et al., 2017) will be recorded:

- Focal aware seizures.
- Focal impaired awareness seizures.
- Focal motor onset seizures (including subtypes).
- Focal non-motor onset seizures (including subtypes).
- Focal to bilateral tonic-clonic seizures.
- Generalized onset motor seizures (including subtypes).
- Generalized onset non-motor seizures (including subtypes).
- Unknown onset motor seizures (tonic-clonic and epileptic spasms).
- Unknown onset non-motor seizures.

8.2.2 SEIZURE/IMP/RESCUE MEDICATION DIARY

Patients will be instructed to complete a daily seizure diary for the entire duration of the study including the planned 8-week baseline period through post-treatment follow-up. An eDiary will be used to record type and frequency of seizures, IMP compliance, and administration of rescue medications. For patients participating in the OLE, the eDiary will be replaced with a paper diary at Visit 8 (end of DBP).

Training on the use of the eDiary will be provided at the Investigators Meeting and/or at the site initiation visit. Site staff will be responsible for training the patient on the use of the eDiary and back-up paper diary at the baseline visit and as required throughout the study. Details regarding provision of devices, training and data collection are located in the Study Operations Manual. Training on the use of the OLE paper diary will be provided during routine monitoring visits or through web casts.

8.2.3 QUALITY OF LIFE SURVEYS

Patients will complete the Quality of Life in Epilepsy (QOLIE-31; Cramer et al., 1998) questionnaire at the selected visits as specified in Table 1a and Table 1b Schedule of Assessments.

8.2.4 GLOBAL IMPRESSION SCALES

The CGI scale (Forkmann et al., 2011; National Institute of Mental Health [NIMH]) will be administered by a trained physician at selected visits as specified in Table 1a Schedule of Assessments. The CGI-S scale will be administered at selected visits during the OLE, as specified in Table 1b Schedule of Assessments.

The PGI-C scale (NIMH) will be provided to the patient for completion at selected visits as specified in Table 1a Schedule of Assessments. The PGI-S will be provided to the patient for completion at selected visits during the OLE, as specified in Table 1b Schedule of Assessments.

8.3 SAFETY, PHARMACOKINETIC, AND OTHER ASSESSMENTS

8.3.1 PHYSICAL, NEUROLOGIC, AND OPHTHALMOSCOPY EXAMINATIONS

Full physical and neurologic examinations (including ophthalmoscopy examination) will be performed at selected visits as specified in Table 1a and Table 1b (Schedule of Assessments).

The neurological examination will include evaluation of the patient's mental state including a cognitive assessment; cranial nerves II-XII including visual acuity, visual fields, and fundoscopy; motor and reflexes; gait and coordination; and sensation.

8.3.2 VITAL SIGNS

Vital signs (blood pressure and pulse) will be measured in semi-supine position after the patient has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes and the average result entered in the eCRF. After the resting measurements, an orthostatic blood pressure test should be performed: blood pressure and heart rate measured within 2 to 5 minutes after standing up. Vital signs (including the orthostatic test) will be measured at each study visit prior to taking any blood samples as specified in Table 1a and Table 1b Schedule of Assessments.

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

Height will be measured in centimeters or inches at the initial screening visit.

8.3.3 ELECTROCARDIOGRAPHIC MEASUREMENTS

A 12-lead ECG will be performed at selected visits as specified in Table 1a and Table 1b Schedule of Assessments. ECG printouts will be filed in the patient's source documents for medical safety reviews.

Each ECG recorder will be set-up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (patient identification [ID], visit date, and the actual times of ECG recordings).

Twelve-lead ECG recordings will be taken after the patients have been resting in a semi-supine position for at least 10 minutes. The patients will avoid postural changes during the ECG recordings and site staff will ensure that patients are awake during the ECG recording.

All recorded ECGs will be reviewed by the investigator or medically qualified designee, and the review will be documented in the source. If a patient shows an abnormal ECG, a repeat ECG will be conducted. A cardiologist review of abnormal ECG tracings will be requested if deemed necessary by the investigator.

8.3.4 AMERICAN UROLOGICAL ASSOCIATION SYMPTOM INDEX

Patients will be administered the AUA Symptom Index (Barry et al., 1992) at selected visits as specified in Table 1a and Table 1b Schedule of Assessments.

8.3.5 CLINICAL LABORATORY TESTS

Blood and urine specimens will be collected last, after recording vital signs (including orthostatic test) according to the schedule shown in Table 1a and Table 1b Schedule of Assessments. Patients with lab samples that were not obtained or cannot be analyzed, may be requested to return for an unscheduled

visit. Laboratory determinations will be performed by Medpace Reference Laboratories, located in Cincinnati, Ohio, United States (US) and Leuven, Belgium.

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 proteins	Glucose
Reticulocyte count	Albumin	Appearance
	Glucose	Color
Pregnancy Tests	Sodium	Urine microscopy (if applicable)
Serum pregnancy test	Potassium	
Urine Pregnancy Test	Calcium	
Follicle-Stimulating Hormone (FSH)	Phosphorus	
	Chloride	
Coagulation	Creatine kinase	
Prothrombin time (PT/INR)	Lactate dehydrogenase (LDH)	
	Bilirubin (total and direct)	

8.3.6 PK BLOOD SAMPLES

Blood samples for plasma concentration analysis will be collected during the study for a population PK evaluation of XEN1101. The dates and times of the last dose of background AED(s) and study drug intake, and the blood sample collection dates and times will be recorded on the eCRF. A subset of up to 40 patients may be requested to provide additional PK samples after providing informed consent to more fully define the PK profile of XEN1101.

A separate population PK analysis plan will be generated to support the population PK analysis in focal epilepsy patients. The population PK will be characterized by nonlinear mixed-effects modeling. A separate report to the clinical study report will be written to cover the population PK analysis.

The relationship between XEN1101 plasma concentration and QTcF, predefined efficacy, and AEs will be investigated in a population PK/PD exposure-response analysis. A separate report to the clinical study report will be written to cover the PK/PD analysis.

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 background AEDs and potential changes with co-administration of XEN1101 may also be investigated.

8.3.7 COLUMBIA-SUICIDE SEVERITY RATING SCALE

Patients will undergo assessment by a trained healthcare professional using the C-SSRS "Baseline/Screening" and "Since Last Visit" questionnaires at each visit as described in Table 1a

and Table 1b Schedule of Assessments. Further details of the assessment will be included in the Study Operations Manual. The medical monitor should be notified if a patient reports suicidality.

Details about the C-SSRS assessments (Posner et al., 2011), which will be incorporated into the study eCRF, can be found at the following link: http://cssrs.columbia.edu/.

8.3.8 BLOOD COLLECTION FOR GENOTYPE/BIOMARKER ASSESSMENT

A blood sample will be collected from each patient who provided informed consent for genotype/biomarker assessments during this study.

Pharmacogenomics Testing

Pharmacogenomic assessment, if conducted, could include potential analysis of the association of both known and unknown DNA and RNA genetic variations with clinical observations (PK, safety, efficacy, or other effects) in the study.

Biomarkers

Biomarkers are defined as biological substances that monitor physiological effects, assess drug activity, and predict clinical outcome, safety and response to therapy.

The collected samples may be stored for up to 10 years after the last visit in the study at a bioanalytical laboratory selected by the sponsor and then destroyed. Samples will only be used for investigations related to disease and/or response to the IMP or related investigational products.

Refer to the Study Laboratory Manual for sample collection, handling, shipping, and storage instructions.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS

An AE is any unfavourable 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 considered related to it.

An AE may be:

- A new symptom or medical condition.
- A new diagnosis.
- An inter-current 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.

- Recurrence of the patient's normal seizures are not considered an AE; however, occurrence of status epilepticus or other seizures requiring hospitalization will be counted as an SAE.

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.

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is defined as any AE that fulfils 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 patient 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.
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is considered medically important (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 patient 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; development of drug dependency or drug abuse).

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

The investigator will also 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 patient's usual daily activities.
- Moderate: Events that are sufficiently discomforting to interfere with patient's usual daily activities.
- Severe: Events that are usually incapacitating with inability to work or perform normal daily activities, or 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.

8.4.3.2 CAUSAL RELATIONSHIP TO STUDY INTERVENTION

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

- Definitely related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the IMP 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 laboratory test abnormality, with a reasonable time sequence to the IMP 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 laboratory test abnormality, with little or no temporal relationship to IMP administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
- Not related: A clinical event, including laboratory test abnormality that has no temporal relationship to the IMP or has more likely alternative etiology.

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

8.4.3.3 EXPECTEDNESS

The expectedness of an adverse reaction is determined by the sponsor. An adverse reaction, the nature or severity or frequency of which is not consistent with the applicable reference safety information is unexpected. Reports that add significant information on the specificity, increase in the occurrence or severity of a known and already documented serious adverse reaction are unexpected events. This assessment should be done from the perspective of events previously observed, not on the basis of 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 Investigator's Brochure for XEN1101.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All (serious and non-serious) AEs detected by the investigator or spontaneously reported by the patient 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 IMP:

- 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 IMP (causality assessment) and/or study participation.

All AEs must be documented and followed up 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 patient to discontinue before completing the study, through an appropriate healthcare option. The patient 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.

8.4.4.1 ADVERSE EVENT REPORTING

All AEs occurring from screening (after signing of the ICF) until 42 days following the last administration of IMP must be recorded in the source document and eCRF in a timely fashion.

8.4.4.2 SERIOUS ADVERSE EVENT REPORTING

Detailed reporting procedures will be contained in the Study Operations Manual.

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

All SAEs will be reported by the Investigator to the pharmacovigilance provider within 24 hours of first discovery using the SAE Report Form. The SAE Report Form will be sent by email or by fax to:

Pharmacovigilance Provider: Pivotal

Email: drugsafety@pivotal.es

SAE Fax line (North American sites): 1-877-853-3275

SAE Fax line (European sites): +34-91-307-6047

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

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

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 IMP will be provided if and when available.

The sponsor will also perform an evaluation of all SAEs.

The relevant health authorities and Central 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).

8.4.4.3 REPORTING EVENTS TO PARTICIPANTS

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

8.4.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

8.4.4.5 REPORTING OF PREGNANCY

Pregnancy is not considered an AE, but patients will be instructed to report to the investigator if they/their partner become pregnant during the study or within 6 months after administration of the last IMP dose. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient/patient's partner is subsequently found to be pregnant after the patient is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the sponsor after delivery. Any patient 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 delivery.

All pregnancy notifications to the investigator must be reported to the pharmacovigilance provider (refer to the contact information in Section 8.4.4.2). Any pregnancy should be followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even in the case when a male patient whose partner is pregnant discontinues the IMP or withdraws from the study. When the outcome of the pregnancy becomes known, an updated report should be submitted to the pharmacovigilance provider. If the study has completed by the time the outcome is known, the investigator should submit the updated report directly to the sponsor.

Male patients may continue in the study if an accidental pregnancy of their female partner occurs despite adequate contraception.

9 STATISTICAL CONSIDERATIONS

A formal statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant 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. Formal analysis of the DBP will be executed upon completion of that component of the study. Analysis of the OLE will be executed separately and upon completion of that component of the study.

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Hypotheses

The primary objective of this study is to assess the effect of 3 doses of XEN1101 on percent change in monthly focal seizure frequency from baseline to the DBP. The primary null hypothesis (H_0) is that all 3 dose groups are not different from placebo in median percent change in monthly (28 days) focal seizure frequency (MPC), with null hypothesis indicated below:

$$H_{0123}: MPC_{plac} = MPC_{10mg} = MPC_{20mg} = MPC_{25mg}$$

The alternative hypothesis is that there is a monotonic (non-decreasing) dose response trend for the 3 dose arms and the placebo. If the primary null hypothesis is rejected with 1-sided significance level of 0.05, the study will be considered positive with at least one dose better than placebo. Further hypotheses will be tested according the following hierarchy with the same 1-sided significance level of 0.05:

- Comparison between 25 mg versus placebo (H_{03}: $MPC_{plac} = MPC_{25mg}$).
- Comparison between 20 mg versus placebo (H_{02}: $MPC_{plac} = MPC_{20mg}$).
- Comparison between 10 mg versus placebo (H_{01}: $MPC_{plac} = MPC_{10mg}$).

The method for testing these null hypotheses for primary efficacy endpoint is described in Section 9.4.2. This endpoint will be analyzed when all enrolled participants have completed the DBP, or been withdrawn from the study.

Key Secondary Efficacy Endpoint

The following null hypotheses apply to the key secondary endpoint:

- The proportion of responders (experiencing at least 50% reduction in focal seizure frequency [RR50]) in the DBP is the same in placebo and each dose group

The secondary endpoints will be analyzed when all enrolled participants have completed the DBP or been withdrawn from the study.

9.2 SAMPLE SIZE DETERMINATION

The sample size of 300 intent-to-treat (ITT) participants in the DBP will provide 88% power to reject the null hypothesis H_{0123} at a 1-sided 0.05-level, assuming MPC_{plac} = -20%, MPC_{10mg} = -25%, MPC_{20mg} = -30%, MPC_{25mg} = -35%. This assumed dose response and MPC is similar to Porter et al. (2007), with slightly higher placebo effect (Khan et al., 2018).

Study power was determined through 5000 simulated trials using R (v 3.5, R Core Team). Baseline and treatment seizure rates for each participant were randomly generated using a negative binomial distribution parameterized as a mixture of Poisson distributions with mean μ and variance $\mu + \mu^2/\theta$. Parameters μ and θ were selected to achieve a baseline seizure frequency of approximately 10 seizures per 4-weeks and on-treatment seizure frequency to achieve the target MPC. In repeated samples of N = 100, the Hodges-Lehmann estimate and associated 95% confidence intervals were comparable compared to those for similar MPC differences in Porter et al. (2007), confirming reasonable variance of the simulated participant-level MPC.

9.3 POPULATIONS FOR ANALYSES

The analysis datasets will include the following:

- **ITT**: All randomized participants who received at least one dose of IMP during the DBP, and provided at least one record of post-treatment seizure frequency during the DBP. Participants will be analyzed as-randomized.
- **Per Protocol**: Participants analyzed according to product and dose received during the DBP, who completed at least 80% of all diary records for a minimum of 4 weeks during the DBP, complied with at least 80% of expected IMP administrations during the DBP, did not withdraw consent, terminate for administrative issues, or were otherwise lost to follow-up during the DBP.

- **Safety**: All participants who receive at least one dose of IMP during the DBP, analyzed according to product and dose received.
- **OLE Efficacy**: All participants entering the OLE who receive at least 1 dose of IMP following the DBP and who provide at least 1 month of diary data in the OLE. Participants will be analyzed as-treated.
- **OLE Safety**: All participants entering the OLE who receive at least 1 dose of IMP following the DBP. Participants will be analyzed as-treated.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A basic frequentist approach will be taken with this analysis. Efficacy analyses will generally be 1-sided, 0.05-level tests. The primary efficacy endpoint may include multiple hypothesis tests, with study-wide type I error controlled through a closed-testing procedure. In this Phase 2 study, safety endpoints and secondary efficacy endpoints will not be adjusted for multiplicity across endpoints or arms. All analyses will be accompanied by graphical presentations of results including forest, line, and bar graphs.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The monthly (28 days) seizure rate will be calculated separately in the baseline and DBP as the total number of focal seizures reported × 28 / the total number of days seizure information is available in that period. The countable seizures for the primary endpoint will include focal aware seizures with motor signs, focal seizures with impaired awareness with or without motor signs, and focal seizures that lead to generalized tonic-clonic seizures.

Percent change from baseline will be calculated as (post-treatment monthly [28 days] focal seizure frequency – baseline monthly (28 days) focal seizure frequency) / baseline monthly (28 days) focal seizure frequency, so that a more negative number will represent greater benefit.

Primary analysis to test the null hypothesis as described in Section 9.1 is based on the ITT population. Since the endpoint of percent change from baseline in monthly seizure count tends to be not normally distributed, an analysis of covariance (ANCOVA) model for the ranks of monthly (28 days) focal seizure frequency percent change from baseline will be used as the dependent variable, with baseline monthly (28 days) focal seizure frequency rank, arm (placebo, 10 mg, 20 mg, 25 mg), region, and background use of CYP3A4 inducer medication included as factors.

Under the assumption of a monotonic dose response relationship (true effect for the higher dose is not worse than the lower dose), the null hypothesis (H_{0123}: $MPC_{plac} = MPC_{10mg} = MPC_{20mg} = MPC_{25mg}$) will be tested based on linear contrast for the least square means (with coefficient of -3, -1, 1, 3 for placebo and the 3 treatment levels of 10, 20, and 25 mg) within the framework of the ranked ANCOVA model. Since only a positive dose response trend is of interest to demonstrate treatment effect, a 1-sided test with significance level of 0.05 will be used.

If a significant result is achieved ($p<0.05$) under H_{0123}, the study will be considered positive and at least one dose level of XEN1101 should be better than placebo.

After H_{0123} is rejected, further testing (with the same significance level of 0.05) will be performed to formally test the pairwise difference H_{03}: $MPC_{plac} = MPC_{25mg}$, H_{02}: $MPC_{plac} = MPC_{20mg}$ and H_{01}: $MPC_{plac} =$

MPC_{10mg} in sequential order (H_{03} -> H_{02} -> H_{01}) to assess whether each dose level is significantly better than placebo in percent reduction of monthly focal seizure count, within the same ANCOVA model. To control the type I error, only when the early null hypothesis is rejected, then the later hypothesis can be formally tested.

On the other hand, if the primary null hypothesis H_{0123} is not rejected, then additional formal statistical testing will not be performed. However, the nominal p-value comparing each of the doses versus placebo will still be provided for exploratory purposes.

With this a-priori specified stepwise testing procedure, the overall type I error will be controlled at 0.05 (1-sided).

Note that this study was designed as a Phase 2 study; therefore, 1-sided alpha of 0.05 was proposed to determine the efficacy of XEN1101. Further study will be needed to confirm the efficacy of XEN1101. It is the sponsor's understanding that in order for this study to be considered as a pivotal study, the 1-sided p-value will need to be <0.025 in favor of XEN1101.

Additional sensitivity analyses for the primary endpoint will be specified in the SAP.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary analyses will be performed in the ITT population on data from the DBP as follows:

- **RR50 (Key Secondary Efficacy Endpoint)**: The proportion of participants experiencing a monthly (28 days) focal seizure frequency improvement from baseline of ≥50% will be compared using a logistic regression model with baseline monthly (28 days) focal seizure frequency, region, background use of CYP3A4 inducer medication and treatment included as factors. Pairwise comparisons will be performed to characterize the dose response. Odds ratios and their 95% confidence intervals will be calculated for each comparison.
- **Stability of Weekly Seizure Frequency**: Within study arm, the absolute and percent change in weekly focal seizure rate will be calculated for every week of the treatment period and a linear test for trend will be evaluated and estimated to determine whether there is an average increase or decrease over time. A quadratic and spline effect may also be estimated for each dose, if the linear model appears inadequate for the data.
- **Clinical and Patient Global Impression of Change**: Change scores in each dose group will be compared to placebo using an ANCOVA, including for rank of baseline seizure frequency, region, and background use of CYP3A4 inducer medication. Estimated medians, and Hodges-Lehman estimates statistics for differences, will be calculated.

Analysis detail on statistical testing for secondary endpoints will be provided in the SAP.

9.4.4 SAFETY ANALYSES

Overall safety evaluations will be descriptive and based on the Safety Population. Graphical and tabular displays will be presented by arm. Safety will be assessed similarly, but separately in the DBP and OLE based on the Safety Population and OLE Safety Populations, respectively.

9.4.4.1 EXPOSURE

Complete dosing experience for all participants in the DBP will be listed, summarized, and presented graphically by arm including the total number of doses given and cumulative dose over time. All dropouts and the associated cumulative dose and arm will also be presented. Exposure in the OLE will be presented similarly to the DBP but will be cumulative including exposure from the DBP.

9.4.4.2 ADVERSE EVENTS

All AE data will be summarized, sorted by system organ class and preferred term assigned by 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.

9.4.4.3 LABORATORY FINDINGS

The number of participants 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.

9.4.4.4 ELECTROCARDIOGRAMS

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

9.4.4.5 COLUMBIA-SUICIDE SEVERITY RATING SCALE

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 thoughts and suicide attempts.

9.4.4.6 VITAL SIGNS

The number of participants 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.

9.4.4.7 AMERICAN UROLOGICAL ASSOCIATION SYMPTOMS INDEX

The total score and each individual question will be summarized descriptively by arm and scheduled visit.

9.4.4.8 OTHER SAFETY MEASURES

Any other significant physical or neurological examination findings will be presented by arm.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

All baseline demographic, physical examination, medical history, epilepsy medication history, and clinical presentation variables will be presented in tabular form by study arm. Similar descriptives for participants in the OLE will be presented separately.

9.4.6 PLANNED INTERIM ANALYSES

The study database will be locked after the last patient completes the DBP visit in order to perform the primary analysis for the study. The treatment assignments will be unblinded for analysis purposes following the DBP database lock.

Safety data will be assessed periodically, through an SRC. This periodic review will include AEs, laboratory tests, vital signs, and ECG. If the blinded data suggests a potential safety or tolerability issue for XEN1101, an external group will perform an unblinded interim review of safety to provide further recommendations to the sponsor on a possible modification to the study that may include adjustment of randomization ratio, etc. The external independent reviewer may request additional trial data to better assess the benefit-risk of the patients in the study. The details on blinded and unblinded safety reviews, as well as the decision process, will be documented in the SRC charter and SAP.

9.4.7 SUBGROUP ANALYSES

The primary and secondary analyses will be repeated in the per protocol population to assess the impact of varying degrees of availability of seizure diary information and treatment adherence.

Effect of geographic region will be explored with efficacy and safety analyses.

Efficacy analyses may also be repeated separating those who have and have not had concomitant use of CYP3A4 inducer medication (ie, use of any of carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, topiramate, or phenobarbital).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All safety and efficacy data will be presented in patient-level listings.

9.4.9 EXPLORATORY ANALYSES

Details of exploratory analyses, including analyses of the OLE data, will be provided in the study SAP.

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 AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the patient 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 the individual's agreeing to participate in the study and continues throughout the individual's study participation. The ICF and any changes to the consent form made during the course of the study must be agreed to by Xenon and the Ethics Committee/Institutional Review Board (EC/IRB) prior to its use and must be in compliance with all International Council for Harmonisation Good Clinical Practice (ICH GCP), 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 their rights as research patients. Patients will have the opportunity to carefully review the written consent form and ask questions prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they 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 patients for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline 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 patients and the local EC/IRB and will provide the reason(s) for the termination or suspension. Study patients 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 patients.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination that the primary endpoint has been met.
- 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 to support the development, registration, or marketing of the medicinal product. Xenon will control all data collected during the study, and will abide by the Applicable Data Protection Laws, including the General Data Protection Regulation (GDPR) in the European Union, the Health Insurance Portability and Accountability Act in the US and the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada. For the purpose of the Applicable Data Protection Law, Xenon will be the data controller. To the extent that the CRO processes personal data on behalf of Xenon, in relation to such data 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 data.

De-identification will be assured by assignment of a unique number to each patient at screening, which will be used for all patient related data collected in the study database. After obtaining patient informed consent, the investigator or the investigator's designee will access the electronic data capture (EDC) system at screening to obtain the patient's unique ID number, consisting of a 5-digit site identifier and 4-digit sequentially assigned subject number. Following confirmation of study entry criteria, the Investigator or the investigator's designee will utilize the EDC system to randomize the patient into the study. During this contact, the investigator or designee will provide the unique patient ID number assigned at screening. Patients will be assigned to receive their treatment according to the randomization schedule.

After patients have consented to take part in the study, their medical records and the data collected during the study will be reviewed by Xenon and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Xenon, health authorities, and the EC/IRB. The sponsor will only receive de-identified patient information; the code list that links the patient's personal information to the study will be securely stored and kept confidential with the investigator and the investigator's designee.

Although patients will be known by a unique 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 patient. The results of this study, containing the unique number, year of birth and relevant medical information including ethnicity, may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection. 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 patient'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 patient ID number will be used to ensure linking the biological specimens with the phenotypic data from each patient, maintaining the blind of the identity of the patient.

Blood samples from patients who provide additional consent for genotype and biomarker assessments will be stored and analyzed at Xenon's designated bioanalytical laboratory as described in Section 8.3.8 above.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

A Steering Committee will be formed to provide oversight of the conduct of the clinical trial. This may include oversight of the practical aspects of the study as well as ensuring that the study is conducted in a way that is both safe for the patients and provides appropriate safety and efficacy data to the sponsor and investigators (refer to the Steering Committee Charter).

10.1.6 SAFETY OVERSIGHT

Investigators are responsible for monitoring the safety of patients 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 patient. The investigator is responsible for the appropriate medical care of patients 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 (refer to the Medical Monitoring Plan). Reports will be provided to the Steering Committee per an agreed upon schedule, but no less than twice per year.

Additionally, the sponsor will implement a SRC, to meet on a quarterly basis to review ongoing safety data/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.

In the event that blinded data suggests a potential tolerability issue for XEN1101, safety data will be unblinded to a designated external clinician who is independent from the company and the study team to provide further recommendation to sponsor on potential modification to the study. This may include adjustment to the current randomization ratio. The details on blinded and unblinded safety review, as well as the decision process will be documented in the SRC charter.

10.1.7 CLINICAL MONITORING

All aspects of the study will be carefully monitored by the sponsor and its representatives for compliance with ICH GCP, 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.

10.1.8 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.

10.1.9 DATA HANDLING AND RECORD KEEPING

The study will utilize an EDC system with eCRFs and an ePRO system with an eDiary. 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.

In addition to the EDC system, an ePRO system will be used by the study personnel and patients to record seizure and rescue medication data. The data collected through the ePRO system (eDiary devices) is considered as source data. Data will be transferred from the ePRO system to the clinical database on an ongoing basis. During the OLE, the eDiary will be replaced with a paper-based diary. Data collected on the paper-based diary is considered as source data and will be entered into the eCRF by the site. Patients will answer daily questions in the paper diary about seizure occurrence, but the eCRF will only capture data for days on which a seizure occurred.

Data handling will be detailed in the Data Management Plan.

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data will be entered using the EDC system (eCRFs) and ePRO system (eDiary) while the study is active. The ePRO system consists of a patient eDiary device for collection of daily seizure activity and daily use of rescue medications to treat seizures. Investigational site personnel and patients will be granted a secure username and password in order to enter, review or correct study data, as applicable. Site staff will not be permitted to alter data entered by patients in the eDiary. A patient's personal seizure diary or study approved back-up paper diary may be used to supplement missing eDiary data only for missing days related to a documented temporary technical issue with the patient's eDiary and may not be used to correct poor patient compliance. The eDiary is the primary source and if the temporary issue is solved and data from the eDiary is available, data from the back-up paper diary will not be used. All passwords will be strictly confidential. These procedures must comply with appropriate regulations. During the OLE, the eDiary will be replaced with a paper diary.

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 the data collection and study documentation comply with the ALCOA+C principles, and the timeliness of the data reported. Good Documentation Practices (GDP) should be followed to ensure all source documents are attributable, legible, contemporaneous, original and accurate (ALCOA), plus complete, consistent, endurable (ie, retrievable and readable after archiving), and available (+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 in order 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 thesauri will be used:

- Latest version of the MedDRA for medical history and AEs; and
- 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.

10.1.9.2 STUDY RECORDS RETENTION

Patient records (including Electronic Medical Records [EMR]), source documents, monitoring visit logs, eCRFs, inventory of IMP, 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.

If the investigator relocates, retires, or for any reason withdraws from the study, the sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Xenon.

Canadian federal law requires all records created during the conduct of a clinical trial be retained for 25 years under Division 5 of the Health Canada Food and Drug Regulations. The US Food and Drug Administration (FDA) requires all such records to be retained for 2 years following the date a marketing application is approved for the drug in the indication for which it is being investigated, or 2 years after the investigation is discontinued and FDA notified. Requirements in the European Union require these records to be retained for 15 years after completion or discontinuation of the trial or for at least 2 years after the last approval of a marketing application in the region.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol and ICH GCP requirements. The noncompliance may be either on the part of the patient, the investigator, or the investigational site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the investigator and sponsor designated CRA to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and recorded in the study protocol deviation log. Protocol deviations must be sent to the site's reviewing EC/IRB as per their policies. The investigator is responsible for adhering to the reviewing EC/IRB requirements. All deviations relating to COVID-19 will be well documented in accordance with ICH GCP E6 4.5.3.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Following completion of the double-blind portion 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 patient safety. In this case, the situation must be documented and reported to the EC/IRB within 5 business days.

10.3 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AED	Antiepileptic drug
ALCOA+C	Attributable, legible, contemporaneous, original and accurate, plus complete, consistent, endurable (ie, retrievable and readable after archiving) and available
ALT	Alanine transferase
ANCOVA	Analysis of covariance
AST	Aspartate transferase
AUA	American Urological Association
$AUC_{0\text{-}24hr}$	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
BMI	Body mass index
CGI	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
C_{max}	Observed maximum plasma concentration
C_{min}	Observed minimum plasma concentration
CNS	Central nervous system
CRA	Clinical research associate
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Double-blind period
EC	Ethics Committee

Abbreviation	Definition
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EEG	Electrocephalogram
ePRO	Electronic patient reported outcomes
ET	Early termination
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HDPE	high-density polyethylene
H_0	Null hypothesis
HPMC	(hydroxypropyl)methylcellulose
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
ILAE	International League Against Epilepsy
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
K_V	Voltage-gated potassium channel
MedDRA	Medical Dictionary for Regulatory Activities
MES	Maximum electroshock
MPC	Median percent change
NIMH	National Institute of Mental Health
NOAEL	No-observed-adverse-effect level
NOS	Not otherwise specified
OLE	Open-label extension
PGI-C	Patient Global Impression of Change scale
PGI-S	Patient Global Impression of Severity scale
PK	Pharmacokinetic
PRN	As needed
QC	Quality control
QD	Once daily
QoL	Quality of life
QOLIE-31	Quality of Life in Epilepsy Inventory-31
QTcF	Fridericia QT interval correction formula
RR50	50% reduction in seizure frequency
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
SRC	Safety Review Committee

Abbreviation	Definition
SUSAR	Suspected unexpected serious adverse reaction
TESC	The Epilepsy Study Consortium
TC	Telephone Call
TMS	Transcranial magnetic stimulation
ULN	Upper limit of normal
US	United States
WBC	White blood cell

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