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

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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.

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.

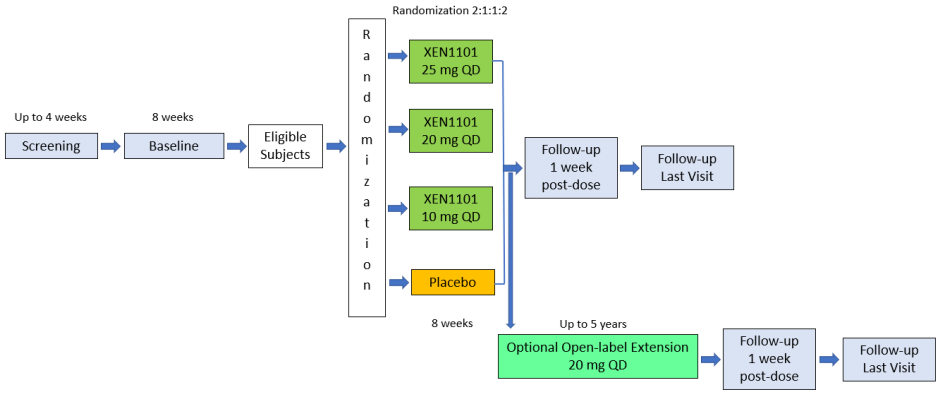
I agree to conduct this study in full accordance with applicable local regulations, Ethics Committee/Institutional Review Board regulations, and International Council for Harmonisation Guidelines for Good Clinical Practice.

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. Exploratory • To assess the efficacy of XEN1101 on focal seizures in adults including the OLE.

	• To assess the safety and tolerability of XEN1101 in adults with focal epilepsy including the OLE. • To evaluate pharmacokinetics (PK) and exposure-response relationship of XEN1101. • To assess the impact of XEN1101 on quality of life in the DBP and OLE. • To evaluate the number of seizure-free days compared to baseline in the DBP and the OLE. • To evaluate the impact of XEN1101 on specific seizure types or change in frequency or need for rescue medication in the DBP and the OLE. • To evaluate the time to reach the baseline monthly focal seizure count for XEN1101 compared to placebo through the end of the DBP. • To assess time to withdrawal due to lack of efficacy in placebo compared to XEN1101 through the end of the DBP and OLE. • To explore epilepsy-associated genes and mode-of-action related pathways, safety and efficacy responses. • To explore the relationship between body fluid biomarkers with XEN1101 concentrations and clinical responses.
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 5 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 5.5 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). <u>Open-label Extension:</u> All patients to receive XEN1101 (20 mg once daily [QD]).  The schedule of assessments is shown in Table 1a (DBP), Table 1b (OLE Years 1 to 3), and Table 1c (OLE Years 3 to 5).
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. <u>Inclusion Criteria</u>: 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 and Table 1c 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 on-site 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. However, if satisfactory seizure control is not achieved, return to QD dosing at 20 mg is permitted. (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-C) and Patient Global Impression of Change (PGI-C) scores during the DBP. Exploratory Endpoints: 6. Median percent change in monthly (28 days) focal seizure frequency from baseline compared to each 4-week period in the OLE. 7. Severity and frequency of associated AEs/SAEs, clinically significant changes in clinical laboratory findings and/or 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, and clinically significant changes in urological symptoms including retention as measured by the AUA Symptom Index in the OLE. 8. Evaluation of the steady-state PK of XEN1101 (and potentially other AEDs) using a population PK approach (refer to Section 8.3.6), including correlation between XEN1101 plasma concentrations and changes in QTc interval, and XEN1101 plasma exposure-response relationship with safety and efficacy endpoints. 9. Change from baseline in quality of life (ie, QOLIE-31) in the DBP and OLE. 10. Evaluate disease severity with Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Severity (PGI-S) in the OLE. 11. Change in seizure-free days per month (28 days) from baseline to DBP and OLE. 12. Change in seizure frequency per month (28 days) for each seizure subtype from baseline to DBP and OLE. 13. Proportion of patients experiencing ≥75%/100% of reduction in monthly (28 days) seizure frequency from baseline for the DBP and OLE; incidence of new seizure types in patients without history of these seizure types (eg, status epilepticus, myoclonic, absence) during the treatment period and incidence of use of rescue medications in the DBP and OLE.

	14. Number of days post-randomization to reach the same number of seizures as the baseline monthly focal seizure rate through the end of the DBP. 15. Percent of participants and number of days post-randomization to withdrawal for lack of efficacy through the DBP and the OLE. 16. Exploratory evaluation of the correlation of variants in genes known to cause epilepsies; analysis of variants in the genome to identify novel genes and variants that may cause epilepsies and correlate to response to XEN1101; and exploratory correlation of variants in specific drug metabolism genes on safety and efficacy. 17. Mean change from baseline in body fluid biomarkers versus treatment, seizure frequency, and response status; and correlation of exploratory body fluid biomarkers with XEN1101 concentration. Time frame for the primary outcome measure and all of the secondary outcome measures is 8 weeks. For exploratory endpoints, the time frame for some measures may be evaluated up to 14 weeks, where data are available, or up to 5.5 years for assessment in the OLE.

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 nondilated 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
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 1 month before screening and remain stable throughout baseline and the DBP. (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 nondilated 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 the 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 postmenopausal 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: Years 1 to 3

Study Period	Open-label Treatment													
Visit Number	**8A***	**9**	**10**	**11**	**12**	**13A**	**14A[G] TC**	**15A**	**16 TC**	**17**	**18 TC**	**19**	**20 TC**	**21**
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**
Study Week	**8**	**11**	**23**	**35**	**47**	**60**	**73**	**86**	**99**	**112**	**125**	**138**	**151**	**164**
Informed consent							X[G]							
C-SSRS		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
Physical and neurologic (including nondilated ophthalmic) examinations		X	X	X	X	X		X		X		X		X
Dilated ophthalmic examination[A]						X		X		X		X		X
Vital signs[B]		X	X	X	X	X		X		X		X		X
Weight, body mass index		X	X	X	X	X		X		X		X		X
Electrocardiogram (12-lead)		X	X	X	X	X				X				X
AUA Symptom Index		X	X	X	X	X		X		X		X		X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[C]		X	X	X	X	X	X[G]	X		X		X		X
Clinical laboratory tests		X	X	X	X	X		X		X		X		X
QOL assessments (QOLIE-31)			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
Patient Global Impression of Severity (PGI-S)	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[F]	X	X[F]	X	X[F]	X	X[F]	X
PK blood samples (XEN1101)[E]		X				X				X				X
Study drug compliance check		X	X	X	X	X	X[F]	X	X[F]	X	X[F]	X	X[F]	X
Dispense study drug to patient	X	X	X	X	X	X	X[F]	X	X[F]	X	X[F]	X	X[F]	X

*: Last day of the DBP. Patients entering the OLE will be dispensed 20 mg QD of XEN1101 and return their previous study drug.

A: In addition to a nondilated 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, 19, and 21 in all patients. 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: For visits conducted via TC, study drug and new paper diaries will be provided to the subject via courier. Subjects must also return bottles, any unused study drug, and completed paper diaries via the courier.

G: 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 on-site 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; OLE = Open-label extension; PK = Pharmacokinetic; QD: Once daily; QOL = Quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory-31; TC: Telephone call.

Table 1c. Schedule of Assessments for Patients Continuing in the OLE: Years 3 to 5

Study Period	Open-label Treatment								Post-Tx Follow-up[F]		
Visit Number	**22 TC**	**23**	**24 TC**	**25**	**26 TC**	**27**	**28 TC**	**29**	**F1b**	**F2b**	**ET[G]**
Study Day	**1239 ±7**	**1330 ±7**	**1421 ±7**	**1512 ±7**	**1603 ±7**	**1694 ±7**	**1785 ±7**	**1876 ±7**	**1883 ±3**	**1918 ±10**	
Study Week	**177**	**190**	**203**	**216**	**229**	**242**	**255**	**268**	**269**	**274**	
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Physical and neurologic (including nondilated ophthalmic) examinations		X		X		X		X	X	X	X
Dilated ophthalmic examination[A]		X		X		X		X[B]		X[B]	X[B]
Vital signs[C]		X		X		X		X	X	X	X
Weight, body mass index		X		X		X		X		X	X
Electrocardiogram (12-lead)				X				X	X	X	X
AUA Symptom Index		X		X		X		X		X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[D]		X		X		X		X		X	X
Clinical laboratory tests		X		X		X		X	X	X	X
QOL assessments (QOLIE-31)		X		X		X		X		X	X
Clinical Global Impression of Severity (CGI-S)	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
Collect and compliance check of completed paper diary and issue new paper diary	X[H]	X	X[H]	X	X[H]	X	X[H]	X	X	return	return
PK blood samples (XEN1101)[E]				X				X			X
Study drug compliance check	X[H]	X	X[H]	X	X[H]	X	X[H]	X			X
Dispense study drug to patient	X[H]	X	X[H]	X	X[H]	X	X[H]				

A: In addition to a nondilated 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) including Visits 23, 25, 27, and 29 (and/or ET if applicable) in all patients.

B: If abnormalities are detected at Visit 29 or at the ET visit, a follow-up dilated fundoscopic examination will be completed 4 to 8 weeks after the subject's last dose of XEN1101.

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

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: For visits conducted via TC, study drug and new paper diaries will be provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

AED = Antiepileptic drug; AUA = American Urological Association; C-SSRS = Columbia-Suicide Severity Rating Scale; DBP = Double-blind period; eCRF = Electronic case report form; ET = Early Termination; OLE = Open-label extension; PK = Pharmacokinetic; QOL = Quality of life; QOLIE-31 = Quality of Life in Epilepsy Inventory-31; TC: Telephone call; 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. This mechanism has been clinically proven to be effective for treatment of partial-onset seizures in adults with epilepsy with the KCNQ2/3 opener, retigabine.

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. This mechanism has been clinically proven to be effective for treatment of partial-onset seizures in adults with epilepsy with the KCNQ2/3 opener, retigabine/ezogabine. XEN1101 was synthesized to improve upon the potency, selectivity and PK of retigabine, with the goal of a reduced clinical risk profile in the treatment of focal seizures.

The pharmacology, PK, and toxicology of XEN1101 (N-[4-(6-Fluoro-3,4-dihydro-1H-isoquinoline-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl butyramide) have been investigated in a comprehensive nonclinical development program which comprised primary and secondary pharmacodynamics, PK, genotoxicity, safety pharmacology, and repeat-dose toxicity studies (up to 6 and 9 months in rats and monkeys, respectively).

The voltage-gated K_V7 family comprises 5 subunit channels, K_V7.1 to K_V7.5. XEN1101 is inactive on K_V7.1, which is involved in repolarization of the cardiac action potential; however, it is a potent opener of

subtypes $K_V7.2$ to $K_V7.5$, which influences neuronal excitability. In in vitro assays, it is approximately 2-fold more potent on $K_V7.2/7.3$ (EC_{50} values ~20 nM) relative to $K_V7.4$ and $K_V7.5$ subtype channels. In testing conducted to date, it is a selective molecule for K_V7 against other ion channels and receptors. XEN1101 was protective against both electrically- and chemically-induced seizures as tested in rodent in vivo assays.

XEN1101 exhibited no genotoxicity in Ames, chromosomal aberration, and rat micronucleus assays.

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 30 to 80 ng/mL, generally occurring within 2 to 8 hours after dose. 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 POTENTIAL FOR HARM RELATED TO STUDY DRUG

In the Phase 1 clinical studies, the majority of related TEAEs were mild, related to the CNS, and consistent with this class of drugs. Sedation (including somnolence and drowsiness), headache, and dizziness (including light-headedness and presyncope) were the most common TEAEs, while cognitive effects (eg, memory and speech impairment) and blurred vision were also reported at XEN1101 doses of 15 to 25 mg QD. A higher incidence of moderate CNS TEAEs was reported with repeat dosing at 25 mg QD. The most common TEAEs of XEN1101 in the TMS crossover study were dizziness, somnolence, fatigue, headache, and disturbance in attention (Premoli et al. 2019).

In the double-blind treatment period of this Phase 2 focal-onset epilepsy study (XPF-008-201), 67.4% (31 of 46), 68.6% (35 of 51), and 85.1% (97 of 114) of subjects in the 10 mg, 20 mg, and 25 mg QD groups, respectively, and 62.3% (71 of 114) of placebo group subjects experienced at least 1 TEAE. The most common TEAEs across all XEN1101 dose groups were dizziness (52 of 211 subjects, 24.6%), somnolence (33 of 211 subjects, 15.6%), fatigue (23 of 211 subjects, 10.9%), and headache (21 of 211 subjects, 10.0%). The incidence of SAEs was similar in all arms of the study, with 4.3% (2 of 46), 3.9% (2 of 51), and 2.6% (3 of 114) of subjects in the 10 mg, 20 mg, and 25 mg QD groups, respectively, and 2.6% (3 of 114) of placebo group subjects experiencing at least 1 treatment-emergent SAE. All subjects in the study were taking at least 1 other AED, and most subjects (51%) were taking 3 concomitant AEDs. Two TEAEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and both subjects remained on drug with no further changes or intervention. Mild increases in body weight (1.9 ±2.9 kg) were observed in the double-blind treatment period of this Phase 2 study at 25 mg QD over 8 weeks.

Skin and retinal discoloration/pigmentation changes were observed during long-term surveillance of subjects treated with ezogabine (retigabine). Although the pigmentation risk related to ezogabine's

chemical structure is not expected to occur with XEN1101 treatment, physical and ophthalmologic exams will be performed to closely monitor for these potential changes.

The detailed safety profile of XEN1101 observed in the Phase 1 and 2 clinical studies is provided in the XEN1101 IB. See Section 8.3 for additional study safety evaluations implemented to mitigate these risks.

2.3.2 SUICIDALITY

AEDs have been found to increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that subjects randomized to 1 of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% confidence interval: 1.2, 2.7) of suicidal thinking or behavior compared to subjects randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated subjects was 0.43% compared to 0.24% among 16,029 placebo-treated subjects, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 subjects treated. In these trials, there were 4 suicides in drug-treated subjects and 0 suicides in placebo-treated subjects; however, the numbers were too small to allow any conclusion about drug effect on suicide (Food and Drug Administration 2008).

Suicidal ideation and behavior will be monitored during the study using the C-SSRS at each study visit.

2.3.3 POTENTIAL FOR UNFORESEEN RISKS

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

2.3.4 POTENTIAL BENEFITS RELATED TO THE STUDY DRUG

Subjects may not receive any direct benefit from participating in this study. Potential benefits of XEN1101 may include a reduction in seizure frequency; however, some individuals may have no change in their symptoms or get worse due to the effects of the study drug or due to the natural course of their illness.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
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.

OBJECTIVES	ENDPOINTS
	• 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-C) and Patient Global Impression of Change (PGI-C) scores during the DBP.
Exploratory	
To assess the efficacy of XEN1101 on focal seizures in adults including the open-label extension (OLE).	• MPC in monthly (28 days) focal seizure frequency from baseline compared to each 4-week period in the OLE.
To assess the safety and tolerability of XEN1101 in adults with focal epilepsy including the OLE.	In the OLE: • Severity and frequency of associated AEs/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 AUA Symptom Index.
To evaluate the PK and exposure-response relationship of XEN1101.	• Evaluation of the steady-state PK of XEN1101 (and potentially other AEDs) using a population PK approach (refer to Section 8.3.6).

OBJECTIVES	ENDPOINTS
	• Correlation between XEN1101 plasma concentrations and changes in QT corrected by Fridericia's formula (QTcF) interval. • XEN1101 plasma exposure-response relationship with safety and efficacy endpoints.
To assess the impact of XEN1101 on QoL in the DBP and OLE.	• Change from baseline in QOLIE-31 in the DBP and OLE. • Evaluate disease severity with Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Severity (PGI-S) in the OLE.
To evaluate the number of seizure-free days compared to baseline in the DBP and OLE.	• Change in seizure-free days per month (28 days) from baseline to DBP and OLE.
To evaluate the impact of XEN1101 on specific seizure types or change in frequency or need for rescue medication in the DBP and OLE.	• Change in seizure frequency per month (28 days) for each seizure subtype from baseline to DBP and OLE. • Proportion of responders experiencing ≥75%/100% of reduction in monthly (28 days) seizure frequency from baseline for the DBP and monthly response rate in OLE. • Incidence of new seizure types in patients without history of these seizure types (eg, status epilepticus, myoclonic, absence) in the DBP and OLE. • Incidence of use of rescue medications in the DBP and OLE.
To evaluate the time to reach the baseline monthly focal seizure count for XEN1101 compared to placebo through the end of the DBP.	• Number of days post-randomization to reach the same number of seizures as the baseline monthly focal seizure rate through the end of the DBP.
To assess time to withdrawal due to lack of efficacy in placebo compared to XEN1101 through the end of the DBP and OLE.	• Percent of participants and number of days post-randomization to withdrawal for lack of efficacy through DBP and OLE.
To explore epilepsy-associated genes and mode-of-action related pathways, safety, and efficacy responses.	• Exploratory correlation of variants in genes known to cause epilepsies (eg, variant enrichment in responders versus non-responders). • Exploratory analysis of variants in the genome to identify novel genes and variants that may cause epilepsies and correlate to response to XEN1101 (eg, variant enrichment in novel genes in responders versus non-responders).

OBJECTIVES	ENDPOINTS
	• Exploratory correlation of variants in specific drug metabolism genes on safety: number of AEs, types of AEs, events dependent on XEN1101 dose-by-gene interactions. • Exploratory correlation of variants in specific drug metabolism genes on efficacy: reduction on seizure frequency, type of seizures, and dose of XEN1101 required, efficacy dependent on XEN1101 dose-by-gene interactions.
To explore the relationship between body fluid biomarkers with XEN1101 concentrations and clinical responses.	• Mean change from baseline in fluid biomarkers versus treatment, seizure frequency, and response status (eg, responders versus non-responders). • Correlation of exploratory fluid biomarkers with XEN1101 concentration.

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 CYP 3A4 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 5 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 5.5 years for those entering the OLE.

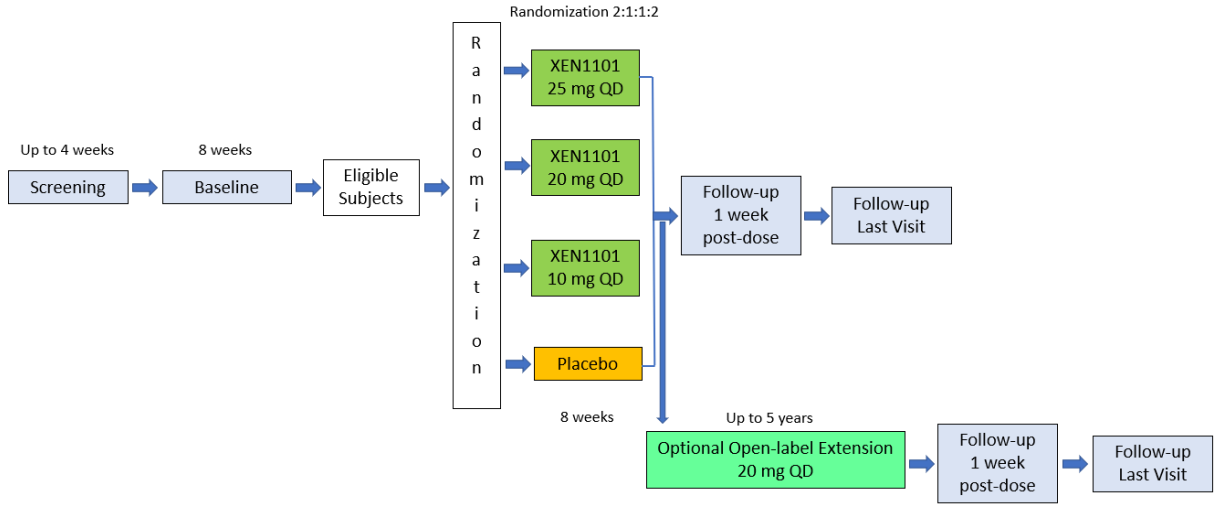
Patients will be screened (Visit 1) within 28 days prior to entering the study on Day -56 (Visit 2; start of baseline period). Each patient will receive verbal and written information followed by signing of the

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 checks. 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, third, fourth, and fifth years until completion of the OLE (Study Week 268), patients will return to the site with their OLE paper diary and IMP bottle for assessments, compliance, and safety checks. During Years 2 through 5, telephone call visits will be conducted at 3 months between each site visit. The last scheduled dose is Study Day 1876 and patients will return for post-treatment follow-up visits on Study Days 1883 (±3 days) and 1918 (±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 and Table 1c 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 on-site 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} (55 ng/mL) 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 (~30 ng/mL) 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 5 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 and Table 1c.

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 and Table 1c 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. This subgroup of patients will need to reconsent and complete Visit 14A assessments on-site 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:

- Barrier method plus combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Barrier method plus progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner; only if that partner is the sole sexual partner of the female trial participant who is of childbearing potential, and 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.

The efficacy of hormonal contraceptives may be compromised by the coadministration of the study drug, therefore if combined or progesterone-only hormonal contraceptives are used, the subject must agree to use an additional barrier method of contraception: condoms (male or female) with or without a spermicidal agent, diaphragm, or cervical cap with spermicide.

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

XEN1101 is formulated as an immediate release capsule filled with the active pharmaceutical ingredient XEN1101 suitable for oral administration. XEN1101 will be supplied in opaque white (hydroxypropyl)methylcellulose (HPMC) capsules containing 25 mg, 20 mg, or 10 mg XEN1101 for the DBP. The corresponding placebo drug product is formulated as identical-looking capsules filled with 10 mg of an inert material (microcrystalline cellulose). XEN1101 will be supplied in opaque white HPMC capsules containing 20 mg XEN1101 for the OLE.

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.

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 every second day 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 . However, if satisfactory seizure control is not achieved, return to QD dosing at 20 mg is permitted. (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

XEN1101 is formulated as an immediate release capsule filled with the active pharmaceutical ingredient XEN1101 suitable for oral administration. XEN1101 will be supplied in capsules at drug dosage strengths of 25 mg, 20 mg, and 10 mg.

The matching placebo is formulated as identical-looking capsules filled with microcrystalline cellulose.

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 CYP 3A4 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, Table 1b, and Table 1c. 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 may be changed 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).

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 1c).

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.
- In addition to the nondilated ophthalmic examination at Visit 1, a dilated ophthalmic examination will also be conducted and reviewed prior to Visit 3/randomization (ie, during screening or baseline) by an ophthalmic professional, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy.

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.*
- In addition to the nondilated ophthalmic examination at Visit 2, a dilated ophthalmic examination will also be conducted during the baseline period (if not completed during the screening period) and reviewed prior to Visit 3/randomization by an ophthalmic professional, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy.

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 (±3days)

- 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 of Change (CGI-C).
- 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 1 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.

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).
- A dilated ophthalmic examination will also be conducted prior to Visit F2a (within 1 month of the last dose of the IMP) by an ophthalmic professional, which includes: 1) best corrected visual

acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy.

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-C.
- 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-C.
- 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.
- A dilated ophthalmic examination will also be conducted within 1 month following the last dose of the IMP by an ophthalmic professional, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy.

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 Table 1c, 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).
- CGI-C.
- 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.

†For patients without a dilated fundoscopic examination completed prior to Visit 3 randomization (ie, patients randomized in the DBP prior to the dilated fundoscopic examination requirement), a dilated ophthalmic examination which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy will also be completed (as soon as possible during DBP) by an ophthalmic professional and reviewed prior to 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.)

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, return of bottles, 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, return of bottles, 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, return of bottles, 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, return of bottles, 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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination should be completed by an ophthalmic professional, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy within 21 days of Visit 13.

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 on-site 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 re-entering 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 re-entering the OLE).
- CGI-S.
- PGI-S.

- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 15.

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.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 17.

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.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 19.

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.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

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, return of bottles, and dispense of study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 21.

TC Visit 22/Study Day 1239 (±7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

Visit 23/Study Day 1330 (±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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 23.

TC Visit 24/Study Day 1421 (±7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

Visit 25/Study Day 1512 (±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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 25.

TC Visit 26/Study Day 1603 (±7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

Visit 27/Study Day 1694 (±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, return of bottles, and dispense study drug (20 mg capsules XEN1101).
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic

examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 27.

TC Visit 28/Study Day 1785 (±7 days) – Patients Participating in the OLE

- C-SSRS.
- AEs.
- Concomitant medications, including any changes to AEDs.
- CGI-S.
- PGI-S.
- Study drug (20 mg capsules XEN1101) and new paper diaries provided to the patient via courier. Patients must also return bottles, any unused study drug, and completed paper diaries via the courier.

Visit 29/Study Day 1876 (±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 bottles and any unused study drug.
- A dilated ophthalmic examination, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy should be completed by an ophthalmic professional within 21 days of Visit 29.

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 1c.

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.

If abnormalities are detected during the dilated examination at Visit 29 or at the ET visit, a dilated ophthalmic examination will also be conducted by an ophthalmic professional 4 to 8 weeks after the subject's last dose of XEN1101, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy.

Visit F1b – Study Day 1883 (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.

Visit F2b – Study Day 1918 (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.

- A dilated ophthalmic examination will also be conducted within 21 days following the last dose of the IMP by an ophthalmic professional, which includes: 1) best corrected visual acuity, 2) anterior slit lamp examination, and 3) dilated fundoscopy via slit lamp as well as enhanced ophthalmic examination of the posterior segment using indirect ophthalmoscopy. If abnormalities are detected during the dilated examination at the ET visit, a follow-up dilated ophthalmic examination will be completed 4 to 8 weeks after the subject's last dose of XEN1101, as detailed in the "Post-treatment Follow-up – Patients Participating in the OLE" section above.

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 periods for patients not participating in the OLE, which will be reviewed at selected visits as specified in Table 1a. For patients participating in the OLE, the eDiary will be replaced with a paper diary at Visit 8A (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, Table 1b, and Table 1c.

8.2.4 GLOBAL IMPRESSION SCALES

The CGI-C 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. The CGI-S scale will be administered at selected visits during the OLE, as specified in Table 1b and Table 1c.

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

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, Table 1b, and Table 1c.

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 system 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, Table 1b, and Table 1c.

Weight will be measured in kilograms or pounds at selected visits as specified in Table 1a, Table 1b, and Table 1c. 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, Table 1b, and Table 1c. 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, Table 1b, and Table 1c.

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, Table 1b, and Table 1c. 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, Table 1b, and Table 1c. 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 CYP 3A4 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 CYP 3A4 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 CYP 3A4 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 CYP 3A4 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-C	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
CYP 3A4	Cytochrome P450 3A4
DBP	Double-blind period
EC	Ethics committee
EC_{50}	Half-maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EEG	Electroencephalogram
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

Abbreviation	Definition
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
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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Signature Manifest

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XPF-008-201 (X-TOLE) Protocol V6.0

Statistical Analysis Plan (for the Double-blind Period)

Protocol XPF-008-201

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

Sponsor:	Xenon Pharmaceuticals Inc. 200-3650 Gilmore Way Burnaby, BC V5G 4W8 Canada		
Study Number:	XPF-008-201		
IND Number:	130236	**Eudra CT Number:**	2018-003221-29
Compound:	XEN1101		
Date:	31 August 2021	**Version:**	2.0

CONFIDENTIALITY STATEMENT

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1.0 LIST OF ABBREVIATIONS

Term	Definition
ADaM	Analysis data model
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomic and therapeutic category
AUA	American Urological Association
BMI	Body mass index
CGI-C	Clinical Global Impression of Change
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	Cytochrome P450 3A4
DBP	Double-blind period
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
ePRO	Electronic patient-reported outcomes
ET	Early termination
IMP	Investigational medicinal product
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MPC	Median percent change
OLE	Open-label extension
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PK	Pharmacokinetic(s)
PT	Preferred term
QD	Once daily
QOLIE-31	31–item Quality of Life in Epilepsy Inventory
QTcF	Fridericia corrected QT interval
RR50	Response rate ≥50%
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

2.0 INTRODUCTION AND SCOPE

This study is being conducted under the sponsorship of Xenon Pharmaceuticals Inc. The clinical monitoring, data management, and medical writing are being performed under contract with NCGS, in collaboration with Xenon Pharmaceuticals Inc. Statistical analyses are being performed under contract with Pivotal.

The statistical analysis plan (SAP) was written based on Protocol Version 4.2 (22 January 2021). This SAP provides a detailed description of the strategy and statistical techniques to be used to perform the analyses of data for the double-blind period (DBP) of the study. Analysis of data from the open-label extension (OLE) will be covered in a separate SAP.

This document does not address the specific analysis of exploratory and pharmacokinetic (PK) data collected in this study. These analyses will be discussed in a separate analysis plan to support the population PK report and a PK/pharmacodynamic (PD) report.

This SAP supersedes any statistical considerations that were identified in the study protocols approved prior to the date of this SAP. Substantial changes from the Protocol Version 4.2 are summarized in this plan.

This SAP is the final version for the DBP portion of the study. Any additional analyses or major changes performed after this version will be identified in the appropriate section of the clinical study report (CSR).

SAS code presented in this document is example code and may differ slightly from final analysis code.

2.1 Brief 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 γ-aminobutyric acid (GABA)ergic neurotransmission, reduction of glutamate mediated excitatory neurotransmission, synaptic vesicle glycoprotein 2A inhibition, or inhibition of voltage-gated sodium and/or calcium channels.

XEN1101 is a novel, small molecule, selective KCNQ2/3 (Kv7.2/7.3) potassium channel positive allosteric modulator being developed for the treatment of patients with partial-onset (focal) epilepsy. Enhancing the open state of KCNQ2/3 in neurons favors a hyperpolarized resting state, which reduces rapid action potential spiking. This mechanism has been clinically proven to be effective for treatment of partial-onset seizures in adults with epilepsy with the KCNQ2/3 opener, retigabine/ezogabine. XEN1101 was synthesized to improve upon the potency, selectivity, and PK of retigabine, with the goal of a reduced clinical risk profile in the treatment of focal seizures.

XEN1101 has been evaluated in two Phase 1 studies (XPF-008-101a and XPF-008-101b), 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 techniques. Based on available data, XEN1101 was well tolerated; adverse events (AEs) were generally transient, dose/exposure-related, and mild in severity.

2.2 Study Design and Randomization

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 subjects diagnosed with focal epilepsy, with an optional OLE for eligible subjects.

Approximately 400 adult subjects will be screened from approximately 100 sites in at least 4 countries, with a target of approximately 300 randomized subjects. The key eligibility criteria for the DBP includes adult subjects, aged between 18 to 75 years, with a diagnosis (≥2 years) of focal epilepsy according to the International League Against Epilepsy (ILAE) Classification of Epilepsy, currently being treated with a stable dose of 1 to 3 allowable AEDs for at least 1 month prior to screening, and willing to stay on the AEDs during the DBP.

In addition, subjects are required to have at least 80% compliance with electronic diary (eDiary) completion during the baseline period, with a documented seizure frequency of ≥4 focal seizures per 28 days on average during the 8-week baseline period, and not be seizure-free for 21 consecutive days during the 8-week baseline period. The types of countable focal seizures included for baseline focal seizures and for eligibility criteria will be:

- Focal aware seizures with motor signs (type 1).
- Focal seizures with impaired awareness (type 2 and 3).
- Focal seizures that lead to generalized tonic-clonic seizures (type 4).

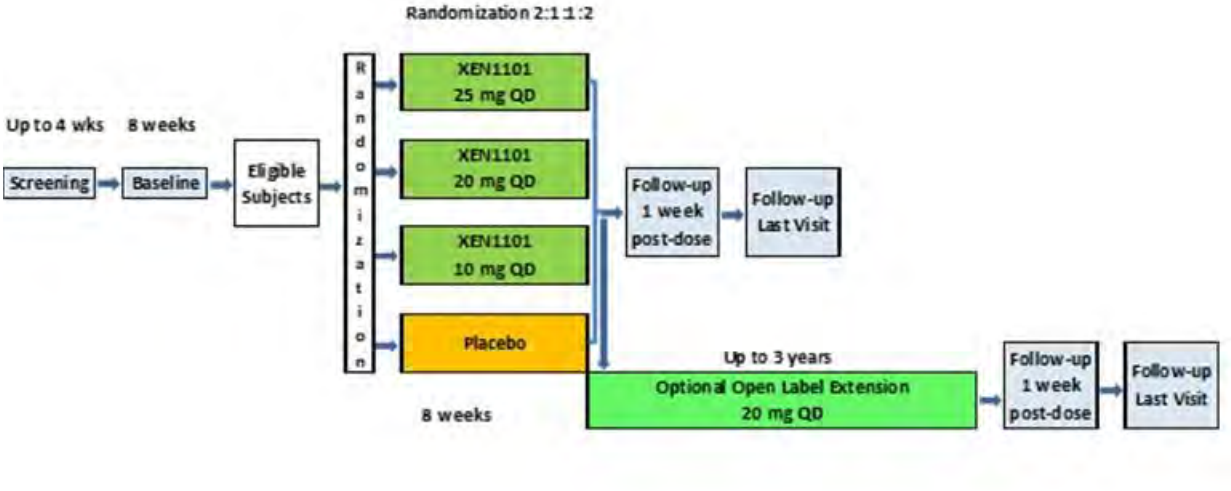
Those subjects who complete the baseline period and meet the additional eligibility criteria during the baseline period will be randomized to 1 of 3 active treatment groups or placebo and undergo an 8-week double-blind treatment period. Following successful completion of the DBP, those subjects who meet the OLE-specific eligibility criteria may enter the OLE treatment phase and receive XEN1101 20 mg QD for up to an additional 3 years.

Subjects will be randomized centrally in a blinded manner to 1 of 3 active treatment groups or placebo in a 2:1:1:2 fashion (XEN1101 25 mg: 20 mg: 10 mg: Placebo). Randomization will be stratified by background use versus non-use of a cytochrome P450 3A4 (CYP3A4) inducer medication (eg, carbamazepine, eslicarbazepine, oxcarbazepine, phenytoin, topiramate or phenobarbital). Randomization will be implemented centrally in the Medidata Rave Randomization and Trial Supply Management (RTSM) system, using a dynamic allocation randomization algorithm (non-deterministic).

The study is divided into the following 5 periods, which are also shown in Figure 1:

- Screening – up to 4 weeks duration.
- Baseline – 8 weeks duration to assess frequency of seizures.
- Treatment (DBP) – 8 weeks duration.
- OLE treatment phase – up to 3 years duration.
- Follow-up – 6 weeks duration to complete safety assessments (for subjects who do not enter OLE directly).

Figure 1 Study Flow Chart



Subjects will be screened (Visit 1) within 28 days prior to entering the baseline period (Visit 2; start of baseline period). Each subject will receive verbal and written information followed by signing of the informed consent form prior to any screening procedures taking place. Subjects will record the frequency and type of seizures during the planned 8-week baseline period. Eligible subjects will be randomized and receive a supply of the investigational medicinal product (IMP) on the date of randomization. The baseline period may extend beyond 8 weeks from the start of baseline (see Protocol Section 4.1, Overall Design).

During the DBP, on Study Days 7, 14, 28, 42, and 56, subjects will be assessed for compliance and safety. Subjects will stop dosing on Day 56, at which time they will return the second IMP bottle. Subjects 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. However, in recognition of the accumulated safety data and to decrease subject travel and site requirements, site Visits 4 and 7 were replaced by telephone visits in Protocol Amendment 4.1.

Eligible subjects who successfully complete the DBP (including Visit 8) may enter an OLE treatment phase on Day 56 and switch to treatment with XEN1101 20 mg QD. During the OLE, on Study Days 77, 161, 245, 329, and 420, 511, 602, 693, 784, 875, 966, 1057, and 1148, subjects will return with their diary and IMP bottle for assessments, compliance, and safety checks. The last scheduled dose is on Day 1148 and subjects will return for post-treatment follow-up visits on Study Days 1155 (±3 days) and 1190 (±7 days).

The primary analysis for the DBP will be performed when all subjects have completed the DBP. Subjects and investigators will remain blinded to the randomized treatment until after database lock and the primary analysis is completed.

The schedule of assessments for the DBP are described in Appendix A.

2.3 Objectives

The primary objective of the study is to assess the efficacy of XEN1101 compared to placebo on focal seizure frequency, as well as to assess the safety and tolerability of XEN1101 in adults with focal epilepsy taking 1 to 3 AEDs.

The following table summarizes the primary, secondary, and exploratory objectives of the study and corresponding endpoints. Note that although the study objectives and endpoint covered both DBP and OLE period, only those endpoints relevant to the DBP will be addressed within the scope of the SAP.

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 DBP.	• Median percent change in monthly (28 days) focal seizure frequency from baseline to DBP.
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 adverse events/serious adverse events (AEs/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 AUA Symptoms Index.
Secondary	
To evaluate the 50% XEN1101 response rates in comparison to placebo in the DBP.	• Responders are defined as subjects 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 vs placebo on seizure severity and impact in adults with focal epilepsy taking 1 to 3 AEDs in the DBP.	• CGI-C and PGI-C scores during the DBP.
Exploratory	
To assess the efficacy of XEN1101 on focal seizures in adults including the OLE for up to 1 year.	• Median percent change in monthly (28 days) focal seizure frequency from baseline compared to each 4-week period in the OLE.

Objectives	Endpoints
To assess the safety and tolerability of XEN1101 in adults with focal epilepsy including the OLE for up to 1 year.	In the OLE: • Severity and frequency of associated AEs/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 AUA Symptoms Index.
To evaluate the PK and exposure response relationship of XEN1101.	• Evaluation of the steady-state PK of XEN1101 (and potentially other AEDs) using a population PK approach (refer to Section 8.3.6 of the protocol). • Correlation between XEN1101 plasma concentrations and changes in QTcF interval. • XEN1101 plasma exposure-response relationship with safety and efficacy endpoints.
To assess the impact of XEN1101 on quality of life in the DBP and OLE.	• Change from baseline in QOLIE-31 in the DBP and OLE. • Evaluate disease severity with CGI-C and PGI-C in the DBP and CGI-S and PGI-S in the OLE.
To evaluate the number of seizure-free days compared to baseline in the DBP and OLE.	• Change in seizure-free days per month (28 days) from baseline to DBP and OLE.
To evaluate the impact of XEN1101 on specific seizure types or change in frequency or need for rescue medication in the DBP and OLE.	• Change in seizure frequency per month (28 days) for each seizure subtype from baseline to DBP and OLE. • Proportion of subjects experiencing ≥75% and 100% of reduction in monthly (28 days) seizure frequency from baseline for the DBP and monthly response rate in OLE. • Incidence of new seizure types in subjects without history of these seizure types in the DBP and OLE. • Incidence of use of rescue medications in the DBP and OLE.
To evaluate the time to reach the baseline monthly focal seizure count for XEN1101 compared to placebo through the end of the DBP and OLE.	• Number of days post-randomization to reach the same number of seizures as the baseline monthly focal seizure frequency through the end of the DBP and OLE.
To assess time to withdrawal due to lack of efficacy in placebo compared to XEN1101 through the end of the DBP and OLE.	• Percent of participants and number of days post-randomization to withdrawal for lack of efficacy through DBP and OLE.

Objectives	Endpoints
To explore epilepsy-associated genes and mode-of-action related pathways, safety and efficacy responses.	• Exploratory correlation of variants in genes known to cause epilepsies (eg, variant enrichment in responders versus nonresponders). • Exploratory analysis of variants in the genome to identify novel genes and variants that may cause epilepsies and correlate to response to XEN1101 (eg, variant enrichment in novel genes in responders versus nonresponders). • Exploratory correlation of variants in specific drug metabolism genes on safety: number of AEs, types of AEs events dependent on XEN1101 dose-by-gene interactions. • Exploratory correlation of variants in specific drug metabolism genes on efficacy: reduction on seizure frequency, type of seizures, and dose of XEN1101 required, efficacy dependent on XEN1101 dose-by-gene interactions.
To explore the relationship between body fluid biomarkers with XEN1101 concentrations and clinical responses.	• Mean change from baseline in fluid biomarkers versus treatment, seizure frequency, and response status (eg, responders versus nonresponders). • Correlation of exploratory fluid biomarkers with XEN1101 concentration.

AE: adverse event; AED: antiepileptic drug; AUA: American Urological Association; CGI-C: Clinical Global Impression of Change; CGI-S: Clinical Global Impression of Severity; C-SSRS: Columbia-Suicide Severity Rating Scale; DBP: double-blind period; ECG: electrocardiogram; OLE: open-label period; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK: pharmacokinetic; QOLIE-31: 31-item Quality of Life in Epilepsy Inventory; SAE: serious adverse event.

2.4 Determination of Sample Size

Sample size is based on the primary efficacy endpoint of monthly percent change from baseline in focal seizure count.

Assuming that the true median percent change (MPC) for each dose arm is similar to that of retigabine (Porter et al. 2007), and that the placebo effect is slightly higher than that in the retigabine study (Khan et al. 2018), the estimated MPC from baseline for each arm is as follows: $(MPC)_{plac}$ = -20%, MPC_{10mg} = -25%, MPC_{20mg} = -30%, MPC_{25mg} = -35% for the 4 treatment arms. A target sample size of 300 subjects with 2:1:1:2 randomization will provide approximately 88% power to reject the null hypothesis of no difference between treatment arms versus an alternative hypothesis of linear dose response trend, based on a 1-sided test significance level of 5%.

Note that the sample size and assumptions will also result in 81% power to reject the same null hypothesis based on 1-sided test with significance level of 2.5% (or 2-sided test of 5%).

Study power was determined through 10,000 simulated trials using R (v 3.6, R Core Team). Baseline and treatment seizure frequency 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 median seizure frequency of 10 seizures per 4-weeks and on-treatment seizure frequency to achieve the target

MPC. Additional eligibility of ≥4/month for baseline seizure frequency was applied to the simulated baseline data. In repeated samples of N = 100, the Hodges-Lehmann estimate and associated 95% confidence intervals (CIs) were reasonably comparable to those for similar MPC differences reported by Porter et al. (2007), confirming reasonable variance of the simulated participant-level MPC. The simulated 300 subjects' data (2:1:1:2 randomization ratio) was then applied to a ranked analysis of covariance (ANCOVA) model with linear contrast (with contrast coefficients of -3, -1, 1, 3) to generate the study power (see Table 1).

Table 1 Simulated Outcome Based on Negative Binomial Distributions

	10,000 Simulated Trials			Large Sample Performance ($N=10^7$)		
	Target MPC	**Estimated MPC**	**Average Hodges-Lehman Boundaries**	**Median Baseline Seizure Frequency**	**Estimated MPC[2]**	**Estimated SD[2]**
Placebo	-20%	-20.3%	NA	10/mo	-20%	0.53
10 mg	-25%	-25.1%	[-17%, 7%]	10/mo	-25%	0.50
20 mg	-30%	-29.9%	[-21%, 2%]	10/mo	-30%	0.48
25 mg	-35%	-35.1%	[-25%, -3%]	10/mo	-35%	0.45

MPC: median percent change; NA: not applicable; SD: standard deviation.

Since the estimated MPC in the power calculation was based on the modified intent-to-treat (mITT) population from the retigabine study, assuming that treatment effect in the mITT population in the current study is comparable to the treatment effect in the mITT population in the retigabine study, no additional assumption is made to the dropout rate for this study. We expect that the dropout rate in this study will not be higher than that in the retigabine study.

2.5 Modifications to the Statistical Section of the Protocol

The previous version (1.0) of the SAP was based on Protocol Version 4.1 (27 March 2020). While the protocol has since been updated to Version 4.2 (22 January 2021), the updated protocol was changed only for the OLE portion of the study, with follow-up extension from 1 year to up to 3 years. There were no major differences between Version 4.1 and 4.2 of the protocol with regards to the double-blind study period, which is the focus of this SAP. The current SAP incorporated the update regarding the extended study visits and follow-up for the OLE part of the study design in the introduction section to be consistent with the most current version of the protocol. Major modifications to the statistical section of the protocol are described below. Since there is no planned interim analysis for this study, all changes have been made in a blinded manner.

- While the study protocol defines the step-down testing procedure based on the primary efficacy endpoint only, the current SAP defines study-wide step-down procedure to control type I error, which takes into consideration both the primary endpoint and key secondary endpoint. Specifically, after the null hypothesis for the overall test of the primary efficacy endpoint is rejected, the subsequent hierarchical testing procedure will compare the XEN1101 25 mg QD arm with the placebo for the primary endpoint (MPC in monthly seizure frequency), followed by the key secondary endpoint (50% seizure reduction from baseline). If both tests are shown to be significant, then next lower dose

level will be compared with placebo in the similar manner. See Section 3.4.8 for details.

- Sensitivity analyses were added for the primary efficacy endpoint to address robustness of the study outcome in Section 3.4.9.
- For the analysis of the key secondary efficacy endpoint of 50% reduction from baseline, the covariate of baseline seizure frequency in original scale has been replaced with the log-transformed baseline seizure frequency to make the logistic regression model more robust, since the baseline seizure frequency in original form could be highly skewed in distribution.
- For the analysis of the secondary endpoint of clinical and patient global impression of change (CGI-C or PGI-C), the covariate of rank of baseline seizure frequency used in the ANCOVA model has been replaced with the log-transformed baseline seizure frequency to make the model more interpretable.
- The definition of per protocol population was modified with narrowed exclusion criteria. Consideration will be made to exclude those subjects with major protocol deviations that will potentially impact the primary study objective based on blinded review of all protocol deviations.

2.6 Statistical Modifications Made in the Statistical Analysis Plan

The current version of the SAP includes further details and clarifications to the secondary, sensitivity analyses and safety analyses to assist programming implementation. Major changes from the previous version are described below:

- Sensitivity analysis for addressing potential deviation for the primary model assumption is revised to limit to the parametric model based on log transformed seizure frequency, which is a common statistical approach used in other epilepsy trials. See Section 3.4.9.2 for details.
- Calculation of weekly seizure frequency was modified to incorporate a weighted average approach when the number of evaluable days is less than 4 for a particular week (Section 3.1.3.2).
- Sensitivity analysis for handling the censoring caused by the 10-seizure daily entry limit of the eDiary is added in Section 3.4.9.3.
- Per protocol population definition was modified to exclude less patients from the per protocol population. Missing seizure data during baseline period was largely due to COVID-related extension of baseline period and is, therefore, no longer an exclusion criterion for per protocol population.
- Summary of the number and percent of days with rescue medication use will be obtained from the eDiary data based on evaluable days during the double-blind period since the eDiary data is expected to be more complete than the rescue medication case report form (CRF). Due to incompleteness of CRF data on rescue medication, details on rescue medication used will not be summarized in the table format but will be available in data listings only.

- Added additional information regarding handling of seizure type misclassification based on a blinded medical review of seizure descriptions and assigned seizure types. See 3.1.3.1 for details regarding seizure type remap and corresponding documentation for these changes.
- Due to inherent variability and susceptibility to artifacts (eg, noise) in Electrocardiogram (ECG) and vital signs with time and in order to provide a more representative and stable reference, the average of the available values recorded at V1 (screening), V2 (start of baseline period) and V3 (randomization visit) will be used to calculate the "Baseline" value for use in "Change from Baseline" calculations for ECG and vital signs and not just the pre-drug value as previously planned.

3.0 STATISTICAL AND ANALYTICAL PROCEDURES

- The primary analysis for the DBP will be performed after all subjects have completed the double-blind study period. A formal database lock will be completed prior to unblinding of the study treatment arms for the primary analysis. A CSR will be prepared after the DBP analysis has been conducted.
- To finalize the determination of analysis population, especially the per protocol population for the DBP analyses, a final blinded data review meeting will be carried out prior to the DBP database unblinding, with the objective to review all protocol deviations to determine which subjects should be excluded from each analysis population.
- Final analyses will be performed after all subjects who entered the OLE have completed the 3-year open-label follow-up period. A final CSR will be prepared and include the OLE analysis.

3.1 Analysis Endpoints

This SAP only covers the relevant endpoints or assessments for the DBP analyses. Endpoints for the OLE will be covered in a separate SAP.

3.1.1 Demographic and Baseline Characteristics

The baseline value is defined as the last non-missing value prior to randomization or equal to the randomization date, unless otherwise specified. Based on the protocol, the assessments performed on the randomization date should be prior to first study drug dosing.

3.1.1.1 Demographic Characteristics

Demographic variables include gender (male, female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White or Caucasian, Other), ethnicity (Hispanic or Latino, other/unknown), country and region (North America, Europe), height, weight, body mass index (BMI), and age at study entry (informed consent).

3.1.1.2 Randomization Strata

Background use of CYP3A4 inducer medication will be used as a stratification factor for randomization. For analysis purposes, in cases when a subject is misclassified at the randomization stage, the actual status (yes/no) as recorded on the electronic case report form (eCRF) will be used.

3.1.1.3 Medical and Psychiatric History

Medical history will include relevant past surgeries, and prior or existing medical or psychiatric conditions, including onset date, end date, and status (eg, ongoing, resolved). The onset of epilepsy disease will be based on the first non-missing onset date when a medical condition related to seizure or epilepsy was reported. This will be captured by selecting the medical history high level group term (HLGT) of 'seizures (incl subtypes)'. Age of disease onset will be derived from this information, comparing with the birth date or year.

3.1.1.4 Physical, Neurological, and Ophthalmic Examinations

Full physical and neurologic examinations (including ophthalmoscopy) will be performed prior to study treatment.

Neurological examination will consist of evaluation of the subject'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. Clinically significant abnormalities from any examination will be noted and recorded in the corresponding medical history page (if prior to informed consent) or AE form (if after informed consent).

Dilated ophthalmic examination will be completed and reviewed prior to randomization and within 1 month post-treatment in the DBP for those not entering the OLE (prior to Protocol Amendment 4.0 [30 January 2020] only nondilated ophthalmic examination was required).

3.1.1.5 Focal Seizure Disease Characteristics

The following information related to epilepsy disease history and characteristics will be collected at the screening or baseline visit:

1. Epilepsy history based on electroencephalography and imaging.
2. Epilepsy etiology.
3. Description of seizure types (types 1-5).

   The additional information related to each seizure type includes age of onset, average duration, and average number of seizures per month, loss of awareness, and date of most recent occurrence of seizure.
4. Pre-study AED use (name, highest dose, start and stop date), as well as reason for stopping medication, and whether the subject achieved seizure freedom for 6 months with the medication. A separate CRF of anti-epileptic history was used to collect these pre-study medications. Clinical and medical review will be performed to identify those medications to be counted for the number of pre-study AEDs.
5. Those AEDs started prior to the baseline visit and ongoing at the time of the baseline visit will be recorded in the concomitant medications form and considered baseline AEDs. Clinical and medical review may be needed to identify the baseline AEDs from the concomitant medication dataset based on drug class, indication, dose frequency and route of administration. Specifically, use of marijuana, cannabinoids and/or derivatives will not be counted a baseline AED for this study. Subjects with concomitant AEDs (excluding rescue medications) that started after the baseline visit and prior to end of DBP treatment may be considered protocol deviations.
6. Use of seizure rescue medication (name of medication, total dose, and date of use) was to be collected after the baseline visit.

7. Seizure description information, for the purpose of eDiary data collection, will be collected at the baseline visit, and the corresponding seizure type for each subject will be assigned before an eDiary device is issued.

3.1.1.6 Other Baseline Parameters

Baseline values for other safety and efficacy parameters are discussed along with the post-baseline assessments in Section 3.1.3 and 3.1.4.

3.1.2 Prior or Concomitant Medications

Medications and therapies taken by the subject 30 days prior to screening and during the study will be recorded in the eCRF.

All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) using the version in effect at the time of database lock.

Prior medications are those that the subject used prior to the randomization date. Prior medications can be discontinued before the date of randomization or can be ongoing during the treatment phase. Subjects are expected to be treated on the randomization date.

Concomitant medications are any treatments received by the subject concomitantly to study drug, from randomization to the end of double-blind treatment period or start of OLE treatment (whichever is earlier). This can include those medications started prior to the randomization date and are ongoing. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (ie, after the end of the DBP).

Non-medication treatment (responsive neurostimulation, vagus nerve stimulator, deep brain stimulator, epilepsy surgery, ketogenic/low carbohydrate diet) will be recorded on the electronic case report form (eCRF) at the screening visit and they were not expected to be changed during the study.

3.1.3 Efficacy Endpoints for the DBP

3.1.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline period in monthly (28 days) focal seizure frequency to the double-blind treatment period.

In the DBP portion of the study, subjects are instructed to enter their seizure information daily using an electronic patient-reported outcomes (ePRO) device provided by sponsor. The ePRO device will be used for subjects to record seizures, daily study drug administration, and use of rescue medication. The data collected through the ePRO system is considered source data. Daily seizure information includes the date, occurrence of each seizure (up to 10 for the day), and seizure type, as well as additional details on the seizures that have occurred. This information was to be used as the basis for deriving all endpoints involving seizure frequency. Starting from Protocol Amendment 4.1, a paper seizure diary will be used as a backup to record daily seizure activity if a subject experiences documented technical issues when entering daily seizure(s) into the seizure diary on the ePRO device (see Protocol Section 8.2.2). These data will be combined for the assessment of primary efficacy endpoint to minimize missing data.

1. Baseline period window for seizure frequency assessment.

Each subject is expected to have a minimum 8-week baseline period. In cases where the baseline is longer than 8 weeks, all evaluable data prior to Visit 3 (randomization date) and after the start of the baseline visit (Visit 2) will be used to assess the baseline. If the Visit 3 date is different from the randomization date, the randomization date will be considered the start of DBP and baseline will end at the randomization date minus 1 day. Seizure information during this time may be used for assessment of the baseline seizure frequency. Note that this baseline analysis window may not be the same as the window used for eligibility criteria.

2. DBP analysis window for seizure frequency assessment.

   The DBP analysis window for seizure assessment will be based on the following:

   i) If a randomized subject completed the DBP treatment (with or without entering the OLE), the double-blind window will start from the randomization (Visit 3) date and end at the last visit of the DBP (Visit 8) date.

   ii) If a randomized subject had early treatment discontinuation or did not complete the end of DBP visit (Visit 8), the double-blind window will start from the randomization (Visit 3) date, and end at the last dose date in the DBP, as recorded on the disposition eCRF page.

3. Post-DBP analysis window.

   The post-DBP window will be the time after the end of DBP to the last follow-up visit (Visit F2a) or start of OLE. Evaluable seizure data during this period will be described in data listing.

Focal Seizure Types

The types of countable focal seizures include the following:

- Type 1 - Focal aware seizures with motor signs.
- Type 2 - Focal seizures with impaired awareness with motor signs.
- Type 3 - Focal seizures with impaired awareness with no motor signs.
- Type 4 - Focal seizures that lead to generalized tonic-clonic seizures.

Note that in the eDiary, subjects will be asked to assign a seizure type to each seizure that they experience, in accordance with their seizure key card designations agreed to with the investigator at the start of baseline. In addition to types 1 through 4 as defined above, subjects will also have the option to enter seizure type 5 (focal aware seizures with no motor signs), but this seizure type will not be considered a countable seizure for the purpose of the primary and secondary efficacy endpoints. If a subject only reports a type 5 seizure on a particular date, this subject will be considered to have no countable seizures on that day.

In order to help a subject classify their seizure types, each subject will be provided a list of their typical seizure descriptions, each assigned to a corresponding seizure type by the investigator and recorded on the seizure key card that is provided along with the eDiary device at the baseline visit.

If a subject experiences a new manifestation other than the pre-existing seizure types as described on the key card, the subject will select seizure type of ‘Other’ and provide a

description of the seizure to the investigator or study site. Based on the description, the event will be reclassified into types 1 through 5 or other appropriate classification by the investigator or sub-investigator, and recorded on a separate eCRF as soon as possible, but no later than the next study visit.

If the investigator determines that the "other" seizure is a new type 1 to 5 seizure not previously included in the subject's seizure key card, a new seizure key card and eDiary will be issued to the subject with the new seizure type included from that point onwards. For example, a subject who has a seizure key card and diary for type 1 seizures only, and who subsequently experiences a type 2 seizure, would be issued a new seizure key card with type 1 and 2 seizure descriptions and a new eDiary with options to select both type 1 and 2 seizures.

If the additional 'other' seizure reported in the eDiary cannot be classified as type 1 to 5, it will be checked as 'None of the above' on the eCRF and this event will not be counted for the purpose of analysis.

A new seizure key card may also be issued to the subject if the original seizure description was incorrectly classified by the site based on a review of all the subject's seizure description information. In this case, a new record will be created in the seizure description and eDiary assignment form, where the same description of the event will be copied (when applicable), but the correct seizure type will be assigned. Since the entries in the eDiary cannot be changed after they have been entered into the device, the incorrect seizure type(s) reported in the eDiary will be remapped based on a separate xls file created by sponsor clinical reviewers based on a blinded systematic review of all randomized patients. The process for documenting remapping is outlined in study Note-to-File (dated Aug 19, 2021). The resulting new seizure types will then be used to support the analyses related to seizure types for relevant subjects. The original (incorrectly assigned) seizure type will still be kept in the analysis dataset. The affected subjects or dates will also be documented in reviewer's guide and analysis data model (ADaM) specification.

Focal Seizure Frequency

Monthly (28 days) focal seizure frequency will be calculated separately for the baseline period and the DBP for each subject, based on above countable seizure types 1 to 4.

- Baseline monthly seizure frequency = ((sum of daily countable focal seizure counts during the baseline period window) / (number of days in the baseline analysis window with evaluable seizure data)) × 28.
- DBP monthly seizure frequency = ((sum of daily countable focal seizure counts in DBP analysis window) / (number of days in DBP analysis window with evaluable seizure data)) × 28.
- Percent change from baseline = ((DBP monthly seizure frequency – baseline monthly seizure frequency) / (baseline monthly seizure frequency)) × 100.

A negative value of percent change indicates a reduction in seizure frequency.

The monthly seizure frequency for the post-DBP period can be calculated separately in a similar manner for exploratory purposes only.

Evaluable Seizure Data

For all seizure frequency computations, seizure diary days with no data will be excluded from the denominator. Daily seizure records with a 'No' response will be included in the numerator as 0 seizures and the days will be included in the denominator. If all seizures reported for a subject on a particular day are not classifiable or not of a type 1 to 4, the number of countable seizures for that day will be 0.

The current derivation for the primary endpoint does not explicitly impute the missing data, but the approach is equivalent to using the average seizure frequency during the days with non-missing seizure data to impute the seizure frequency for days with missing seizure data. More detail on the handling of missing data is described in Section 3.4.9.1.

3.1.3.2 Secondary Efficacy Endpoints

The definitions for the secondary efficacy endpoints are as follows:

- Response (RR50) is defined as having achieved ≥50% reduction in monthly (28 days) focal seizure frequency from baseline to the DBP, based on percent change from baseline in monthly focal seizure frequency as defined for the primary endpoint (based on countable seizure types 1-4). Subjects who do not meet these criteria in the DBP analysis window will be treated as non-responders. For the purpose of statistical inference, this endpoint will be considered the key secondary endpoint for the DBP.
- Weekly change from baseline in seizure frequency to each of the week in DBP will be calculated using the following steps (based on countable seizure of types 1-4):
    - Baseline weekly seizure frequency = ((sum of daily focal seizure counts during the baseline period window) / (number of days in the baseline period window with evaluable seizure data))× 7 = baseline monthly seizure frequency / 4.
    - The analysis window for post-baseline weeks 1 through 8 is defined as Study Days 1-7, 8-14, 15-21, 22-28, 29-35, 36-42, 43-49, and 50-56 (if a subject completed DBP, use Visit 8 date for the upper limit of week 8 instead of Day 56). Only the seizure data within the DBP analysis window will be used (see Section 3.1.3.1 for DBP analysis window definition).

  If a subject has seizure total evaluable days in DBP window <4 days, then weekly seizure frequency variables will not be calculated for the subject. Otherwise, apply the following algorithm for each week:
    - For week 1, if this is NOT the last week with evaluable seizure data, if the number of evaluable days in week 1 is ≥1, then use the evaluable days in this week to calculate this week's seizure frequency as ((number of total type 1-4 in week 1) / (number of evaluable days in week 1)) × 7. Otherwise, if evaluable days in week 1 is 0 (very unlikely scenario), but this is not the week with last evaluable data, this week seizure frequency will be imputed by the baseline weekly seizure frequency.
    - For week 1, if this is the last week with evaluable seizure data, then the number of evaluable days should be at least 4. The seizure frequency for week

1 will be defined as ((number of total type 1-4 in week 1) / (number of evaluable days in week 1)) × 7.

- For each of the remaining week z (ranges week 2 to 8), do the following:
  - if the number of evaluable days Y in week z is ≥4, then use the evaluable days in this week to calculate this week's seizure frequency: ((number of total type 1-4 in week z) / (number of evaluable days in week z)) × 7.
  - If the number of evaluable days Y in week z is between 1- 3, then define the current week seizure frequency as a weighted average (w) of current and the previous week seizure frequency: w1 × previous week's seizure frequency + w2 × current week's observed seizure frequency, where w1 = (4 - Y) / 4, and w2 = Y / 4.
  - If the number of evaluable days Y in week z is 0, and this is not the last week when seizure data is evaluable, then the current week seizure frequency can be imputed by the previous week seizure frequency. However, if there is no more evaluable data beyond this week, current week seizure frequency will not be calculated in this case and will be treated as missing.

- Change from baseline in weekly seizure frequency for post-baseline week y = seizure frequency for week y – baseline weekly seizure frequency.
- The percent change from baseline in weekly seizures frequency for post-baseline week y = (change from baseline in weekly seizures for week y) / (baseline weekly seizure frequency) × 100.

- CGI-C and PGI-C

  The CGI-C (Forkmann et al. 2011) is a brief clinician-rated instrument that measures overall comparison of the subject's baseline condition with their current state. The following 7 categories are used to assess the change from baseline:

  1. Very much improved.
  2. Much improved.
  3. Minimally improved.
  4. No change.
  5. Minimally worse.
  6. Much worse.
  7. Very much worse.

  The PGI-C is the patient-reported outcome counterpart to the CGI-C. It consists of the items taken from the CGI-C and adapted to the subject.

  Subjects will be assessed in the DBP at the end of Week 8 or early termination (ET) visit, as well as at follow-up Visit F2a (second follow-up visit for the DBP).

The endpoint for the DBP will be based on the CGI-C or PGI-C performed at Week 8 (target Day 56). In the case of missing Visit 8 data, the non-missing value obtained at ET will be used.

3.1.3.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints related to the DBP are described below.

Quality of Life in Epilepsy Inventory

The 31-item Quality of Life in Epilepsy Inventory (QOLIE-31) (Cramer et al. 1998) contains 7 multi-item scales that cover the following health concepts:

- Emotional well-being.
- Social functioning.
- Energy/fatigue.
- Cognitive-functioning.
- Seizure worry.
- Medication effects.
- Overall quality of life.

The QOLIE-31 derived overall score is obtained using a weighted average of the multi-item scale dimensional scores.

The QOLIE-31 will be assessed in the DBP at the randomization visit, and at the end of Week 8 (Visit 8) or ET visit, as well as the follow-up Visit F2a (second follow-up visit for the DBP).

The analysis of DBP for QOLIE-31 will be based on baseline and change from baseline to the end of the DBP, based on assessment performed at Week 8 (target Day 56). In the case of missing Visit 8 data due to ET, the non-missing value obtained at ET visit will be used.

Details on how to calculate dimensional and derived overall scores are provided in Appendix B.

Change in Seizure Frequency per Month (28 days) for Each Seizure Subtype From Baseline to DBP or Occurrence of New Seizure Types

For each subject, monthly seizure frequency will be calculated for baseline and the DBP for each of the countable subtypes (1-4) as follows:

- Baseline monthly seizure frequency for subtype Z = (sum of daily seizure count of type Z during the baseline period window) / (number of days in the baseline period window with evaluable seizure data) × 28.
- DBP monthly seizure frequency for subtype Z = (sum of daily seizure count of type Z in DBP analysis window) / (number of days in double-blind analysis window with evaluable seizure data) × 28.
- The percent change from baseline in seizure subtype Z = (DBP monthly seizure frequency for subtype Z – Baseline monthly seizure frequency for subtype Z) / baseline monthly seizure frequency for subtype Z, when the baseline seizure for subtype Z is >0.

In addition, a subject is considered to have developed a new seizure type if he/she recorded a new seizure type post-baseline that was not observed during the baseline period.

Change in Number of Seizure-Free Days per Month (28 days) From Baseline to the DBP

A seizure-free day is a day without any reported seizure of types 1 to 4. This does not include the day when no seizure information is collected. Seizure-free days per month will be calculated separately for the baseline and the DBP as follows:

- Monthly seizure-free days in the baseline (or DBP) period = (total number of days without seizure of types 1-4 in the baseline [or DBP] analysis window) / (total number of days seizure information is available in the baseline [or DBP] analysis window) × 28.
- Change in seizure-free days per month = (monthly seizure-free days in the DBP – monthly seizure-free days in baseline).

Proportion of Subjects Experiencing Response During the DBP

Each subject will be classified into a response category based on their derived percent change from baseline in monthly seizure frequency as defined for the primary endpoint into the following categories:

- 100% reduction (seizure free).
- 75% to <100% reduction.
- 50% to <75% reduction.
- 25% to <50% reduction.
- 0% to <25% reduction.
- <0% (worse than baseline).

An alternative response definition of ≥75% and 100% will be derived from the above categories.

Time to Reach the Baseline Monthly Focal Seizure Count Through the DBP

Time to reach baseline monthly focal seizure (types 1-4) count is defined as follows:

- Baseline monthly focal seizure frequency is defined in Section 3.1.3.1 based on countable seizure types 1-4. This monthly seizure frequency will be used to assign the baseline monthly seizure count.
- If the total number of countable focal seizures (types 1-4) through end of DBP is ≥baseline monthly focal seizure count, then, time to baseline monthly seizure count is defined as the duration between randomization to the earliest date when the cumulative focal seizure count (types 1-4) from randomization is ≥baseline monthly seizure count.
- If the total number of countable focal seizure (types 1-4) through end of DBP is <baseline monthly focal seizure count, then the time to baseline monthly seizure count is censored at the end of the DBP analysis window.

Use of Rescue Medication

The following parameters will capture the use of rescue medication for baseline, as well as the DBP.

- Number and percent of subjects who used any rescue medication in the baseline and the DBP period, based on seizure diary data (both eDiary and paper diary).
- Average number of days per month (28 day) any rescue medication was used by a subject. Each day of use of rescue medication will be counted and the total occurrence for a subject will be based on all reported occurrences during the baseline and the DBP separately. Note that these analyses will be based on those days when seizure data is evaluable and using the analyses window for the baseline and DBP periods as used for seizure endpoints.

Early Study Withdrawal Due to Lack of Efficacy

- Number and percent of subjects who withdraw the DBP due to lack of efficacy. A subject will be considered a dropout due to lack of efficacy if the primary reason for discontinuation of DBP is 'Lack of efficacy' from the disposition form.
- Time of withdrawal is defined as the number of days from the date of randomization to the date of last IMP in the DBP, obtained from the disposition eCRF.

3.1.4 Safety Endpoints

3.1.4.1 AEs

AE Observation Period

Treatment-emergent adverse events (TEAEs) are AEs with an onset after the initiation of study drug or randomization date (whichever is earlier) and within 6 weeks after the last dose of IMP for those subjects who were treated with study drug. This will also include any AE with onset prior to initiation of study drug that increased in severity during the treatment period. TEAEs for the DBP will exclude those AEs that started after the OLE treatment.

Pretreatment AEs are AEs that are not treatment-emergent and with event onset prior to the initiation of study drug.

Post-treatment AEs in the DBP are AEs that developed, worsened, or became serious during residual post-treatment epoch in the DBP.

All AEs (including serious adverse events [SAEs]) will be coded to a lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and associated primary system organ class (SOC) will be coded according to the Medical Dictionary for Regulatory Affairs (MedDRA) Version 21.1.

SAEs

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

- Results in death.
- Is life-threatening.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered medically important (medical and scientific judgement should be exercised in deciding whether other AEs are to be considered serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above).

AEs by Relationship to Study Drug

The causality/relationship 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.

All AEs should be assigned with a relationship as above and missing relationship will be queries for resolution.

For analysis purposes, all AEs will be reclassified into 2 categories of related (includes 'definitely related' and 'possibly related') and non-related (includes 'not related' and 'unlikely related') to IMP.

AEs by Severity

The investigator will also assess the severity (intensity) of each AE as below.

- Mild: Events that are easily tolerated, require minimal or no treatment and do not interfere with the subject's usual daily activities.
- Moderate: Events that are sufficiently discomforting to interfere with subject'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.

All AEs should be assigned with severity as above and missing severity will be queries for resolution.

For analysis purpose, all AEs will be reclassified into 3 categories of mild, moderate, or severe (including life-threatening and fatal).

3.1.4.2 Deaths

The observation period for deaths is per the observation periods defined above.

- On-study: Deaths occurring during the on-study observation period. This includes any time after the informed consent date.
- On-treatment: Deaths occurring during the on-treatment epoch.
- Post-treatment: Deaths occurring during the residual epoch.

3.1.4.3 Laboratory Assessments

Clinical laboratory data consists of blood analysis, including hematology and clinical chemistry, and urinalysis. Laboratory determinations will be performed centrally by Medpace Reference Laboratories, located in Cincinnati, Ohio, USA and Leuven, Belgium. Subjects with laboratory samples that were not obtained or cannot be analyzed, may be requested to return for an unscheduled visit.

In some cases, clinical laboratory tests may be performed in local laboratories.

Clinical laboratory events will be expressed in SI units. Out of reference range values will be flagged as high (H) or low (L) in the listings. For analysis purposes, values preceded by a '<' or '>' sign will be considered equal to the lower or upper limit of quantification, respectively, unless otherwise specified.

Baseline is defined the last non-missing value prior to the first administration of study drug (in most cases this will be the value obtained at the randomization on Day 1).

Blood samples for clinical laboratory assessments will be taken as specified in Appendix A. The laboratory parameters are listed in Table 2.

Table 2 Clinical Laboratory Assessments

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)	

3.1.4.4 Vital Signs

Vital signs include weight (kg), body temperature (ºC), semi-supine and standing pulse rate (bpm), as well as semi-supine and standing systolic and diastolic blood pressure (mmHg).

Blood pressure and pulse will be measured in a semi-supine position after the subject has rested comfortably for at least 5 minutes; 3 measurements should be taken within 15 minutes and the average result entered in the eCRF. After the resting measurements, an orthostatic blood pressure test should be performed, ie, blood pressure and heart rate measured within 2 to 5 minutes after standing up.

Baseline for vital signs is defined the average of the available values recorded at screening visit, baseline visit and randomization visit (V1-V3).

The criteria for substantial change (or potentially clinically significant abnormality) are described in Table 3.

Table 3 Criteria for Substantial Change in Vital Signs

Parameter	Substantial Change Category
Vital signs	
Semi-supine systolic BP	≤90 mmHg and decrease from baseline ≥20 mmHg
	≥180 mmHg and increase from baseline ≥20 mmHg
Semi-supine diastolic BP	≤50 mmHg and decrease from baseline ≥15 mmHg
	≥105 mmHg and increase from baseline ≥15 mmHg
Semi-supine pulse rate	<50 bpm and absolute decrease from baseline ≥20 bpm
	≥120 bpm and increase from baseline ≥20 bpm
Weight	≥7% change from baseline
Orthostatic vital signs	
Standing systolic BP	≤90 mmHg and decrease from semi-supine ≥20 mmHg
	≥180 mmHg and increase from semi-supine ≥20 mmHg
Standing diastolic BP	≤50 mmHg and decrease from semi-supine ≥15 mmHg
	≥105 mmHg and increase from semi-supine ≥15 mmHg
Standing pulse rate	<50 bpm
	≥120 bpm

BP: blood pressure.

3.1.4.5 12-Lead Electrocardiograms

Twelve-lead ECG recordings will be taken after the subjects have been resting in a semi-supine position for at least 10 minutes. The subjects should avoid postural changes during the ECG recordings and site staff will ensure that subjects are awake during the ECG recording. The following will be assessed: heart rate, rhythm, interval from start of the Q-wave to the end of the S-wave (QRS), interval between the peaks of successive QRS complexes (RR), interval from the beginning of the P-wave until the beginning of the QRS complex (PR), interval between the start of the Q-wave and the end of the T-wave (QT), Fridericia's corrected QT (QTcF) interval.

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

Baseline for ECG is defined the average of the available values recorded at screening visit, baseline visit and randomization visit (V1-V3).

Substantial change categories are described in Table 4. Substantial change value will use both scheduled and unscheduled visits.

Table 4 Criteria for Substantial Change in ECG Parameters

ECG Parameter	Substantial Change Category
PR	≥200 ms and increase from baseline ≥25%
QRS	≥120 ms and increase from baseline >10%
QTcF	Absolute values (ms)
	>450 ms, >480 ms, >500 ms
	Increase from baseline
	30-60 ms, >60 ms

ECG: electrocardiogram; QTcF: Fridericia corrected QT interval.

3.1.4.6 Physical and Neurological Examinations

A complete physical examination and complete neurological examination will be performed at each study visit as described in Section 3.1.1.4. Any clinically significant abnormalities will be documented in the medical history or AE eCRF. After approval and implementation of Protocol Amendment 4.1, all subjects will receive a dilated ophthalmic exam prior to randomization and after the end of study drug treatment.

3.1.4.7 American Urological Association Symptom Index

The American Urological Association (AUA) symptom index includes 7 questions covering frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. Items 1 to 6 are rated from 0:'Not at all' to 5:'Almost always'; and Item 7, referring to nocturia, ranges from 0:'None' to 6: '5 or more times'. The total score is derived as the total sum of all items (1 to 7), and ranges from 0 to 35 (asymptomatic to very symptomatic).

An AUA symptom index will be completed for the subject by the investigator at the baseline and end of each month in DBP, as well as the OLE with longer intervals.

3.1.4.8 Columbia-Suicide Severity Rating Scale

The Columbia Protocol, also known as the Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2011), supports suicide risk assessment through a series of simple, plain-language questions that anyone can ask. The answers help users identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs.

Subjects 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 the protocol.

Based on the C-SSRS Scoring and Data Analysis Guide (Nilsson et al. 2013) the following outcomes are C-SSRS categories with binary response (yes/no). The categories have been reordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

- Category 1 – Wish to be Dead.
- Category 2 – Non-specific Active Suicidal Thoughts.
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act.
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan.
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent.
- Category 6 – Preparatory Acts or Behavior.
- Category 7 – Aborted Attempt.
- Category 8 – Interrupted Attempt.
- Category 9 – Actual Attempt (non-fatal).
- Category 10 – Self-injurious behavior without suicidal intent

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each subject. This will be defined for the baseline period (including assessment from both baseline and the screening visit), as well as the post-baseline DBP, respectively.

- Suicidal ideation score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.

Composite endpoints based on the above categories are defined as follows:

- Suicidal ideation: A “yes” answer at any time during baseline period (or DBP respectively) to any 1 of the 5 suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior: A “yes” answer at any time during baseline period (or DBP respectively) to any one of the 5 suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A “yes” answer at any time during baseline period (or DBP respectively) to any 1 of the 10 suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

3.1.5 PK Endpoints

Evaluation of the steady-state PK of XEN1101, as well as exposure response relationship, will be performed using a population PK approach. Detailed analysis will be addressed in a separate analysis plan.

3.1.6 Pharmacogenomic Endpoints

The relevant exploratory endpoints will not be analyzed for the DBP.

3.2 Analysis Populations

3.2.1 mITT Population (Full Analysis Set)

The mITT population (or Full Analysis Set) will include those randomized subjects who received at least 1 dose of IMP during the DBP and provided at least 1 day of post-treatment seizure information during the DBP. The mITT will be the main population for baseline, efficacy, and

exploratory analyses for the DBP. Subjects will be analyzed according to the group to which they were randomized.

3.2.2 Per Protocol Population

The per protocol population will consist of mITT subjects who meet all of the following criteria:

1. Completed at least 80% of expected diary records during the DBP.
2. No major protocol deviations that will potentially impact the primary study objective.

The following criteria have been identified a priori as major deviations that will potentially impact the primary study objective. Additional major deviations may be identified during the study. These will be reviewed and approved by the sponsor prior to database lock and unblinding of treatment assignment.

1. Deviation from key inclusion/exclusion criteria for DBP.
2. Receipt of treatment different from the randomized treatment assignment.
3. Receipt of prohibited medication per protocol in the DBP.

The reason for excluding subjects from the per-protocol population will be summarized by randomized treatment group and presented in a data listing.

The per protocol population will be used for sensitivity analysis of the efficacy endpoints.

3.2.3 Safety Population

The safety population will include all subjects who receive at least one dose of IMP. Subjects will be analyzed under the treatment which they received.

3.2.4 Additional Analysis Populations

Additional analysis populations related to analysis of the OLE, PK, genetic, or biomarker analyses will be defined in a separate SAP.

The pre- and post–COVID-19 analysis populations will include as those subjects who were randomized prior to or after 15 January 2020. The cutoff date was selected so that subjects in the pre–COVID-19 population would have completed more than at least 6 weeks of double-blind treatment as of 1 March 2020. These populations will be used to perform selected safety subgroup analysis.

3.3 Disposition of Subjects

This section describes subject disposition for both study status and the analysis populations.

Screened subjects will include all subjects who signed the informed consent form.

Randomized subjects will include all subjects who were provided a treatment assignment that was recorded in the interactive response technology database, regardless of whether the treatment kit was used.

The safety experience of subjects who were treated, but not randomized will be reported separately, and these subjects will not be included in the safety population. Subjects treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For subject study status, the total number of subjects in each of the following categories will be presented in the CSR using a flowchart diagram or summary table:

- Screened subjects.
- Screen failure subjects.
- Subjects entering baseline period.
- Baseline failures.
- Nonrandomized but treated subjects (if applicable).
- Randomized subjects.
- Randomized but not treated subjects (if applicable).
- Randomized and treated subjects.
- Completed DBP and entered OLE.
- Completed DBP and did not enter OLE.
- Number and percentage of subjects who did not complete the DBP treatment, with corresponding reasons.

For all categories of subjects (except for the screened, baseline only and nonrandomized categories) the summaries will be provided by randomized treatment arms, and percentages will be calculated using the number of randomized subjects as the denominator.

The number (%) of subjects randomized will also be summarized by country and region.

A listing of subjects with population assignment including individual reasons of exclusion from the respective analysis populations will be provided. Data listings for ET reasons will be also provided.

Additionally, the analysis populations for safety and efficacy (defined in Section 3.2) will be summarized in a table by number of subjects in the randomized population.

3.3.1 Randomization and Drug Dispensing Irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as: a) an ineligible subject is randomized; b) a subject is randomized based on an incorrect stratum; or c) a subject is randomized twice, or
2. A subject is dispensed an IMP kit not allocated by the protocol defined randomization, such as: a) a subject at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct as randomized IMP); or b) a nonrandomized subject is treated with IMP reserved for randomized subjects.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the CSR. Whether any of these constitute a major protocol deviation is deferred to the decision by the clinical team before the database lock. Nonrandomized treated subjects will be described separately.

Randomization and drug dispensing irregularities to be prospectively identified include, but are not limited to:

- Kit dispensation without interactive response technology transaction.
- Erroneous kit dispensation.
- Kit not available.
- Randomization by error.
- Subject randomized twice.
- Stratification error.

3.3.2 Other Protocol Deviations

Protocol deviations will be collected by the clinical team and the final version will be provided to the biostatistics contract research organization (Pivotal) prior to the DBP database lock. Important deviations will be identified by the sponsor and project team prior to database lock.

All the important deviations will be summarized by deviation type and listed in the CSR. A separate summary will be provided for COVID-19 related to protocol deviations.

3.4 Statistical Methods

3.4.1 General Considerations

Since the study is designed as a phase 2 study, 1-sided testing at the 0.05 level of significance based on trend test is proposed to assess the efficacy of XEN1101 to support further program development. The study will be considered to have achieved proof-of-concept to support phase 3 development when the 1-sided p-value is <0.05 for the trend test. Subsequent pairwise tests will be carried forward with the same level of significance. Besides 1-sided p-values, 2-sided p-values will also be presented as references for the primary and the key secondary efficacy endpoint (RR50), including both 90% and 95% CIs (2-sided) when applicable.

Unless otherwise specified, efficacy analyses will use the mITT population. Safety analyses will use the safety population. All p-values will be rounded to 3 decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999 it will be reported as ">0.999".

In general, continuous variables will be summarized using the number of observed cases, mean, SD, median, minimum, and maximum. Furthermore, when the median is provided as a measure of central tendency, 25th and 75th percentiles will also be provided. Categorical variables will be summarized using frequency counts and percentages in each category. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise noted.

3.4.2 Demographic and Baseline Characteristics

Demographic characteristics, including geographic region and randomization strata as described in Section 3.1.1, will be summarized with descriptive statistics by randomized treatment group and overall in the mITT population. Summaries for the safety population will be included in the appendices if the safety population is different from the size of mITT population, or if the randomized treatment for any subject is different from the actual treatment received.

Medical, psychiatric and surgical history, as well as baseline disease characteristics, will be summarized by MedDRA SOC, PT (if coded), randomized treatment group, and overall in mITT population.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

3.4.3 Prior or Concomitant Medications

Prior and concomitant medications will be summarized by treatment group according to the WHO-DD, considering the first digit of the anatomic and therapeutic category (ATC) class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and subjects will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, subjects may be counted several times for the same medication. Prior and concomitant medications will be summarized separately and will use the safety population.

Separate summaries for pre-study and baseline (concomitant) AED will be provided respectively for the safety population. For pre-study AEDs (stopped prior to study), descriptive summary of number of pre-study AEDs will be summarized. For baseline AEDs, the number and percent of subjects taking 1, 2, 3, or >3 AEDs will be summarized. See Section 3.1.1.5for definition and determination of pre-study and baseline AEDs. Pre-study AEDs are collected in the anti-epileptic drug history CRF, while the baseline AEDs will be obtained from the concomitant medication form.

All prior and concomitant AEDs will be listed by subject. A separate by-subject listing will also be provided for non-medication treatment (responsive neurostimulation, vagus nerve stimulator, deep brain stimulator, epilepsy surgery, ketogenic/low carbohydrate diet).

3.4.4 Study Drug Exposure and Compliance

3.4.4.1 Extent of Drug Exposure

The study drug exposure will be listed for each subject and summarized for the mITT and safety populations (if different between the 2). Duration of study drug exposure in the DBP is defined below:

- Duration of double-blind treatment is defined as the last date of IMP – first IMP date + 1. The first IMP date will be based on the earliest date after randomization when a dose taken was confirmed by the subject from the eDiary data. The last double-blind IMP date will be based on the last IMP date on the double-blind disposition eCRF.
- The duration of study treatment will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum), as well as categorical variable (eg, <2 weeks, 2 to <4 weeks, 4 to <6 weeks, 6 to <8 weeks) for the DBP. This will be summarized by treatment group.
- The number and percentage of subjects with dose reduction in DBP will be summarized by treatment group based on the dose reduction eCRF.

3.4.4.2 Compliance

A given administration will be considered noncompliant if the subject did not take the planned dose of treatment as required by the protocol. Compliance to the treatment regimen will be

monitored by site personnel during the study. Treatment noncompliance will be considered a protocol deviation.

Drug accountability (dispensed and returned) will be listed by visit for the DBP. Overall compliance during the DBP will be computed for each subject as (total number of capsules used / total number of capsules expected to be used) × 100% for the DBP. The total number of capsules used can be calculated as total number of capsules dispensed – total number of capsules returned. The number of expected capsules to be used during the DBP = Last dose date – first dose date + 1, adjusting for dose modifications. Number (%) of subjects with <80% compliance in the DBP will be summarized by treatment group in the mITT population. Depending on the completeness of the data collected, the compliance rate calculated from these sources may not be reliable and should be interpreted with caution. Handling of data anomalies will be described in the data specification document.

3.4.5 Analyses of Primary Efficacy Endpoints

All efficacy analyses will be performed using the mITT population. Corresponding analyses will also be performed for the per protocol population. Additional sensitivity analyses for the primary endpoint are described in Section 3.4.9.

As defined in Section 3.1.3, the primary endpoint of percent change from baseline will be calculated based on (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.

The primary objective of the study is to demonstrate efficacy of XEN1101 to support further clinical development. To test that, the primary null hypothesis is that all three dose groups are not different from placebo in median percent change in monthly (28 days) focal seizure frequency (MPC), as 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 three dose arms and the placebo (H_a: $MPC_{plac} \geq MPC_{10mg} \geq MPC_{20mg} \geq MPC_{25mg}$ with at least 1 inequality), where more negative values indicate better efficacy.

The primary null hypothesis will be tested with an ANCOVA model. The dependent variable will be the ranks of monthly (28 days) focal seizure frequency percent change from baseline, and the independent variables in the model will be the rank of baseline monthly (28 days) focal seizure-frequency, treatment arm (placebo, 10 mg, 20 mg, 25 mg), region (North America, eastern Europe, western Europe), and background use of CYP3A4 inducer medication (yes/no).

If the number of subjects in the eastern Europe region is too small (<10% of total sample size), then both eastern and western Europe regions will be combined into one category in the ANCOVA model.

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}) 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 mg, 20 mg, and 25 mg) within the framework of the ranked ANCOVA model. Ties will be handled using ties = mean. Since only a positive dose response trend is of interest to demonstrate treatment effect, a 1-sided test will be used.

If a significant result is achieved ($p < 0.05$) under H_{0123}, and the observed treatment effect is clinically meaningful for at least 1 dose level, the study will be considered positive for the proof-of-concept to support further phase 3 clinical development.

After the proof-of-concept criteria is achieved (null hypothesis H_{0123} is rejected under 1-sided 5% level of significance), pairwise comparison will be performed to compare each of the dose levels with placebo with the same level of significance. The corresponding hypothesis will be tested in sequential order: H_{03}: $MPC_{plac} = MPC_{25mg}$, H_{02}: $MPC_{plac} = MPC_{20mg}$ and H_{01}: $MPC_{plac} = MPC_{10mg}$ ($H_{03} > H_{02} > H_{01}$), within the same ranked ANCOVA model as the overall trend test. The Hodges-Lehman estimate (based on SAS proc npar1way) for each dose versus placebo will be calculated accompanied by the associated 2 sided 90% and 95% CIs. Note that the key secondary endpoint of 50% response rate will be incorporated into the above testing sequence, before moving to next low dose level pairwise comparison.

Section 3.4.8 describes the study-wide fixed sequence hierarchical testing procedure to control type I error, based on both the primary efficacy endpoint and the key secondary endpoint. If the prior null hypothesis is not rejected, then additional hypothesis will not be tested formally. However, the nominal 1-sided p-value comparing each of the doses versus placebo will still be provided for exploratory purposes.

3.4.5.1 Programming Specification for the Ranked ANCOVA Analysis

The detailed steps to get 1-sided unadjusted p-values for hypothesis tests are as follows:

a. Calculate the rank for the primary efficacy endpoint of percent change from baseline in monthly seizure frequency (rank_mpc), as well as the rank for baseline monthly seizure frequency (baseline_rank). Ties will be handled using mean value.

b. Perform the rank ANCOVA, with following example SAS codes.

```
Proc mixed data = rankdat;
    class CYP3A4 region studyarm;
    model rank_mpc = CYP3A4 baseline_rank region studyarm;
    lsmestimate  studyarm
      'h0123' -3 -1  1  3 divisor = 3,
      'h03'   -1  0  0  1,
      'h02'  -1  0  1  0,
      'h01'   -1  1  0  0,
      / lower;
      run;
```

3.4.6 Analyses of Secondary Efficacy Endpoints in the DBP

3.4.6.1 Response Rate Based on 50% Reduction in Seizure Frequency – key secondary endpoint

The definition of this endpoint is provided in Section 3.1.3.2. The proportion of subjects experiencing a monthly (28 days) focal seizure frequency improvement from baseline of ≥50%

will be compared using a logistic regression model with study arm (placebo, 10 mg, 20 mg, 25 mg), region (North America, Europe), background use of CYP3A4 inducer medication (yes/no) and log-transformed baseline monthly (28 days) focal seizure count as covariates.

Pairwise comparisons between each of the dose arms and placebo will be performed to assess the dose effect and incorporated into the fixed-sequence hierarchical testing procedure. Odds ratios and the corresponding 2-sided 90% and 95% CIs for each of the dose arms versus placebo will be calculated. One-sided and two-sided p-values for each of the pairwise comparison between each of the XEN1101 dose arms and placebo will be provided.

Formal statistical test taking consideration of multiplicity is described in Section 3.4.8.

3.4.6.2 Weekly Change from Baseline in Seizure Frequency in the DBP

The definition of this endpoint is provided in Section 3.1.3.2. Weekly seizure frequency for baseline and each of the post-baseline week in the DBP will be summarized descriptively over time by treatment arm. Change and percent change from baseline to each week will be summarized descriptively as well. The median over time for these parameters will be presented graphically by treatment groups to assess potential trend over time. This information may provide insight into the onset of treatment effect within each dose arm. If the descriptive data suggest a clear trend, additional exploratory analyses may be performed.

3.4.6.3 CGI-C and PGI-C Scores

The following analyses will be performed for CGI-C and PGI-C separately at the end of the DBP treatment (compared to baseline).

1. Number (%) of subjects with at least minimally improved global impression scores (including minimally, much, and very much improved) by treatment group.
2. Number (%) of subjects with at least much improved global impression scores (including much and very much improved) by treatment group. Those subjects without evaluable data will be assumed as not achieving this endpoint.
3. CGI-C or PGI-C scores in each dose group will be compared to placebo using an ANCOVA, including log-transformed baseline monthly seizure count, region, and background use of CYP3A4 inducer medication as covariates. Pairwise comparison between each of the dose arms and placebo will be performed using linear contrast. Least square mean difference between each of the dose arm versus placebo will be provided with 2-sided 95% CIs.
4. Number (%) of subjects in each response category by treatment group.
5. The proportion of subjects with at least much improved global impression of change scores will be compared using a logistic regression model with study arm (placebo, 10 mg, 20 mg, 25 mg), region, background use of CYP3A4 inducer medication as covariates. Odds ratios and the corresponding 2-sided 95% CIs for each of the dose arms versus placebo will be calculated. Similar comparison will be made for the proportion of subjects with at least minimally improved global impression of change scores.
6. Correlation between the primary efficacy endpoint of percent change in monthly focal seizure frequency from baseline versus CGI-C/PGI-C score will be explored using box

plots with percent change from baseline in y-axis and CGI-C category in the x-axis, separated by treatment group, as well as all subjects combined into 1 group.

The handling of missing data is described in Section 3.1.3.2. Due to the expected few number of subjects completing Visit F2a for the DBP (majority of subjects will rollover to OLE directly after Visit 8), no specific analysis will be performed for the follow-up Visit F2a. But these data will be included in the by-subject listing.

3.4.7 Analyses of Additional Efficacy Endpoints in the DBP

3.4.7.1 QOLIE-31

QOLIE-31 will be summarized descriptively at baseline and at the end of the DBP by treatment group. This will include absolute value and change from baseline for each of the dimensions (seizure/worry, overall quality of life, emotional well-being, energy/fatigue, cognitive, medication/effects, social function) and the overall score. The derived overall score and dimension scores at the end of the DBP treatment will be compared for each of the XEN1101 dose arms and the placebo based on least square mean difference under an ANCOVA model with treatment arm, background use of CYP3A4 inducer medication, log-transformed baseline monthly (28 days) focal seizure count as covariates, and baseline scores of QOLIE-31 (for the corresponding endpoint) as a covariate. Missing data will not be imputed.

Box plots will be presented by treatment arms for the change from baseline for derived overall score, and dimensional scores based on evaluable data.

The handling of missing data is described in Section 3.1.3.3. Due to expected limited number of subjects completing Visit F2a for the DBP (majority of subjects will rollover to OLE directly after Visit 8), no specific analysis will be performed for the follow-up Visit F2a. But these data will be included in the by-subject listing.

3.4.7.2 Change in Seizure Frequency per Month (28 Days) by Seizure Type

The percent change from baseline in monthly seizure frequency for each of the countable seizure types (1-4) will be summarized descriptively by seizure type and treatment arms. Note that for each type, only those subjects with baseline seizures of the corresponding type will be included in the summary, since the denominator for the percent change from baseline needs to be non-zero. Corresponding summary of monthly seizure frequency and percent change from baseline for this type will be based on the same subpopulation (or sample size) for this analysis.

In addition, the number (%) of subjects with a new seizure type that occurred at any time during the DBP that were not reported in the baseline period will be summarized by treatment arm. The specific new seizure type will also be summarized descriptively. It is possible that the seizure types only occurred in the DBP period, but not in baseline, may have occurred prior to study or in screening period.

Subject-level seizure type details will be included in the listings.

3.4.7.3 Proportion of Subjects Experiencing Response During the DBP

To further characterize the response on seizure reduction, the percent reduction in monthly focal seizure frequency from baseline to the DBP as defined for the primary efficacy endpoint will be further categorized as listed below, in addition to the 50% reduction category. The number and

percentage of subjects in each of the response categories will be summarized descriptively by treatment arm.

- 100% reduction (seizure free).
- 75% to <100% reduction.
- 50% to <75% reduction.
- 25% to <50% reduction.
- 0% to <25% reduction.
- <0% (worse than baseline).

3.4.7.4 Time to Reach Baseline Monthly Focal Seizure Frequency Through the DBP

A Kaplan-Meier analysis will be performed for the endpoint defined in Section 3.1.3.3, where the events (or treatment failure) are defined as reaching baseline monthly focal seizure counts.

The median time to event as well as the estimated percent of subjects without event during the 8-week post-baseline period will be estimated based on Kaplan-Meier method for each treatment group. A log-rank test will be performed to compare each of the XEN1101 dose arms to placebo.

3.4.7.5 Use of Rescue Medication and Early Dropout Rate Due to Lack of Efficacy

The following descriptive summaries related to rescue medication use and discontinuation during the DBP due to lack of efficacy will be provided:

- Number and percent of subjects who used rescue medication in the DBP. Note: The use of rescue medication will be based on the seizure diary data (both eDiary and paper diary).
- Average number of days per month (28 day) when any rescue medications were used by subject. Note: Each daily use of rescue medication will be counted once per day, and total occurrence for a subject will be based on all reported occurrences during the baseline and DBP separately, using the same analyses window as defined for the primary efficacy endpoint (see Section 3.1.3.1).
- Number (%) of subjects who withdrew from the DBP due to lack of efficacy. Note: A subject will be considered as a dropout due to lack of efficacy if the primary reason for discontinuation of DBP is 'Lack of efficacy.'
- Number of days from first administration of IMP to withdrawal from DBP due to lack of efficacy (if there are applicable subjects in the study).

3.4.8 Multiplicity Issues

A sequential test strategy for the primary efficacy and the key secondary endpoint in the DBP will be used to adjust multiplicity as described below.

Overall testing for primary efficacy endpoint of MPC on whether at least one dose of XEN1101 is better than placebo will be tested with null hypothesis H_{0123}: $MPC_{plac} = MPC_{10mg} = MPC_{20mg} = MPC_{25mg}$ vs alternative hypothesis of a monotonic (non-decreasing) dose response trend (H_a: $MPC_{plac} \geq MPC_{10mg} \geq MPC_{20mg} \geq MPC_{25mg}$ with at least 1 inequality), where a more negative value indicates better efficacy.

If a significant result is achieved (1-sided p <0.05) under H_{0123}, and the observed treatment effect is clinically meaningful for at least 1 dose level, the study will be considered to have achieved the primary objective.

For selecting the optimal dose level, statistical tests will be based on pairwise tests, and this will be performed after the above proof of concept goal (rejecting null hypothesis H_{0123} under 1-sided alpha of 5%) is achieved.

Pairwise comparison will proceed in a sequential fashion and will stop if there is a non-significant comparison.

- Comparison between 25 mg vs placebo on primary efficacy endpoint of MPC (H_{03}: $MPC_{plac} = MPC_{25mg}$ vs H_{a3}: $MPC_{plac} > MPC_{25mg}$).
- Comparison between 25 mg vs placebo on key secondary endpoint RR50 (H_{03}: $RR50_{plac} = RR50_{25mg}$ vs H_{a3}: $RR50_{plac} < RR50_{25mg}$).
- Comparison between 20 mg vs placebo on primary efficacy endpoint of MPC (H_{02}: $MPC_{plac} = MPC_{20mg}$ vs H_{a2}: $MPC_{plac} > MPC_{20mg}$).
- Comparison between 20 mg vs placebo on key secondary endpoint RR50 (H_{02}: $RR50_{plac} = RR50_{20mg}$ vs H_{a2}: $RR50_{plac} < RR50_{20mg}$).
- Comparison between 10 mg vs placebo on primary endpoint MPC (H_{01}: $MPC_{plac} = MPC_{10mg}$ vs H_{a1}: $MPC_{plac} > MPC_{10mg}$).
- Comparison between 10 mg vs placebo on key secondary endpoint RR50 (H_{01}: $RR50_{plac} = RR50_{10mg}$ vs H_{a1}: $RR50_{plac} < RR50_{10mg}$).

All tests will be based on 1-sided alpha of 0.05.

The overall 1-sided type I error is controlled at 0.05 level by the sequential test procedure described above. Analyses of additional secondary endpoints will be considered for exploratory purposes and will not be adjusted for multiplicity.

3.4.9 Sensitivity/Supportive Analyses for the Primary Efficacy Endpoint

All sensitivity or supportive analyses will be performed using the mITT population, unless otherwise specified.

3.4.9.1 Handling of Missing Data for the Primary Efficacy Endpoint

The primary efficacy endpoint will be derived from the days with non-missing seizure data as described in Section 3.1.3.1. Missing data may take the form of missing interim data prior to the end of follow-up or missing data from a certain date due to early withdrawal of double-blind treatment before the planned end of the DBP. Since those subjects who withdraw from the double-blind treatment early will be expected to change their background ASMs, seizure data collected beyond study treatment discontinuation will not be included in the primary endpoint assessment. The most common reasons for intermittent missing data are technical issues related to use of the eDiary or compliance (eg, subjects forgetting to complete the seizure diary within the 48-hour window). The current derivation for the primary endpoint does not explicitly impute the missing data, but the approach is equivalent to using the average seizure frequency during the days with non-missing seizure data to impute the seizure frequency for days with missing seizure data. In other words, days with missing seizure data will be assumed to have the same average seizure frequency as those days with non-missing data.

The following descriptive summaries will be provided to characterize the missing data pattern:

1. Descriptive summary of duration of follow-up within the DBP within each treatment arm, to assess the overall follow-up time for seizure data.
2. Descriptive summary of number and percent of days with missing seizure information within the baseline and DBP analysis period, within each treatment arm.

If significant imbalance was observed between treatment arms on missing data pattern, additional sensitivity analyses may be needed.

The following pre-specified sensitivity/supportive analyses will be performed to assess the impact of missing data:

1. Monthly seizure frequency will be calculated in first (from Day 1 to Day 28) and second (from Day 29-Visit 8/ET) 4-week period separately in the DBP. The same ranked ANCOVA model applied to the primary efficacy analysis will be applied to the percent change from baseline for the first and second 4-week period separately to compare the treatment effect. Those subjects in the mITT population with at least 1 evaluable seizure during the corresponding 4-week period will be included in the analyses.
2. The primary efficacy endpoint of percent change from baseline will be performed in the per-protocol population to assess the robustness of the results.
3. The primary efficacy endpoint of change from baseline in monthly seizure frequency will be modified by also including those evaluable diary data collected after the double-blind treatment end date for those early treatment discontinuations (up to the targeted 8 weeks post-randomization). Those subjects with less than 8 weeks of total evaluable days will be imputed by the estimated daily seizure count based on the last 7 evaluable days within the DBP window for the subject.
4. The primary analysis endpoint of percent change from baseline in monthly seizure will be based on data from the eDiary only, without using any data from the backup paper diary form (implemented after Protocol Amendment 4.1 for when there are technical issues with the eDiary device after site approval).

3.4.9.2 Sensitivity Analyses With an Alternative Distribution Assumption

The following sensitivity or supportive analysis will be performed to address potential deviation from the primary model assumption. The analyses will be performed for the mITT population.

An ANCOVA model will be performed for the response variable of log-transformed monthly focal seizure count during the DBP instead of ranked percent change from baseline in monthly seizure count. To avoid the log of 0 in seizure count, the response variable will be log (seizure count + 0.5). The ANCOVA model will include factors of log-transformed baseline monthly (28 days) focal seizure count, arm (placebo, 10 mg, 20 mg, 25 mg), region, and background use of CYP3A4 inducer medication (yes/no). Overall p-value based on linear trend test and pairwise comparison using the same contrast as described for the primary efficacy analysis will be applied, but the response variable will be log (monthly seizure frequency + 0.5).

The least square means from the model in log scale will be back transformed to the original scale to get the estimated % reduction in monthly seizure frequency relative to placebo, using following formula:

$$\%reduction\ relative\ to\ PBO = 100 \times \frac{\exp\left[LSMean(PBO)\right] - \exp\left[LSMean(XEN)\right]}{\exp[LSMean(PBO)] - 0.5}$$

3.4.9.3 Sensitivity Analysis to Address the Censoring Due to 10 Seizure Limitation for the Daily Seizure Count in Diary Data

The primary efficacy endpoint of monthly focal seizure frequency was based on daily seizure counts averaged over the baseline and the DBP period respectively, using the eDiary as the primary source. At the time of the eDiary design, it was assumed that subjects would not have more than 10 seizures in a given day and hence the eDiary was designed to accommodate a maximum value of 10 seizures per day. However, during the study, it was observed that ~10% of patients reported 10 seizures in a day at some point during the study. As a result, there is a potential for an under-estimation of the true daily seizure count for those subjects on those days when more than 10 seizures occurred. To address the impact of this censoring on the primary analysis of the study (which will remain unchanged) and its conclusion on treatment effect, additional sensitivity analyses proposed here will be conducted.

A descriptive summary of the percent of subjects with such potential censoring will be provided to assess the balance between arms.

a. Descriptive summaries of the number of subjects that reported 10 seizures in a day in eDiary by treatment group in the baseline period, including the number of days when 10 seizures were reported.

b. Descriptive summaries of the number of subjects that reported 10 seizures in a day in eDiary by treatment group in the DBP period, including the number of days when 10 seizures were reported.

For those subjects who reported 10 as the seizure count for only 1 day during either the baseline period or the DBP period (representing ~2% of total days on average), a noteworthy consideration is that the actual seizure count could probably be 10 as was reported. As such, we assumed that those subjects who reported only a single day with a seizure count of 10 will be considered to have experienced 10 seizures.

A tipping point analysis may be performed to assess the impact of data censoring due to 10-seizure limitation on estimated treatment effect, by applying imputation rules selectively for those subjects reporting >1 day with 10-seizure counts in the DBP period for the active groups, representing a conservative analysis:

> Imputation will be made pessimistically for those subjects on active treatment arms (XEN1101) who reported >1 days of 10-seizure counts in the diary data. This imputation for the DBP will be made by assuming that their actual seizure counts was 10 + delta, with delta ranging from 1 to 9 for each analysis. There will be no change to the seizure counts for placebo subjects. In addition, days reported with 10 seizures in the baseline period will not be imputed. This approach is a conservative approach since it will only result increased seizure counts of the subjects randomized to the active (XEN1101) treatment arm and only in the DBP thereby potentially decreasing treatment effects. Specifically, the following imputation rules will be applied with a selected delta:
>
> i) Seizure counts of 10 in the baseline period will not be changed, in either arm.

ii) For placebo subjects in the DBP (post-baseline), those days with 10-seizure count will remain at 10.

iii) For actively treated subjects in DBP, those days with 10-seizure count will be imputed as 10 + delta.

Note that since it was possible for a subject to report 10 seizures total, but only some of these (<10) were countable seizures (type 1-4). Therefore, the actual seizure counts for analysis purpose will only include those of type 1-4 (out of 10 total seizures reported) + delta.

Repeat rules i-iii for delta = 1, … 9 creating nine (9) imputed data sets, in addition to the original dataset with no imputation.

For each value dataset with a different delta of imputed delta (ranging from 1 to 9), the rank ANCOVA analysis as in the Primary Analysis will be performed, as well, and the pairwise comparisons of each of the active treated arm vs placebo will be calculated. The median difference between the active arm and the placebo arm will also be presented with corresponding confidence intervals for the median difference estimated with Hodges-Lehmann estimate.

The purpose of this analysis is to evaluate how the estimated treatment effect difference between XEN1101 vs placebo in primary analysis will be affected under a conservative scenario. If remarkable changes are apparent for small values of delta, it is possible that the results are influenced by the censoring mechanism and thus additional exploratory analyses may be performed.

3.4.10 Subgroup Analyses for the Primary and Key Secondary Efficacy Endpoint in DBP

The following subgroups will be considered for the primary efficacy endpoint of MPC and the key secondary endpoint of RR50:

1. Randomization strata: Use of CYP3A4 inducer medication (yes/no).
2. Geographic region: North America, Europe.
3. Number of prior AEDs: 1, 2, ≥3.

Since the study will have limited power to detect a difference in treatment effect within a subgroup, these subgroup analyses will be descriptive in nature, where summary statistics for baseline and percent change from baseline in monthly seizure frequency will be provided for each treatment arm within the subgroup. No statistical testing will be provided.

If a particular subset has <10% of the total subjects, they will be combined with another category as appropriate.

3.4.11 Analyses of Safety Data

Safety analyses will be carried out for subjects by actual treatment received, irrespective of the treatment to which the subject was randomized.

3.4.11.1 Summary of AEs

The primary focus of AE reporting will be on TEAEs. Pretreatment and post-treatment AEs will be described separately. All reported AEs (regardless of TEAE or not) will be included in a by-subject AE listing. Subsets of AEs of interest will also be listed.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as treatment-emergent or not. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of AEs with missing or partial-onset dates are provided in Section 3.5.3.

AE summaries will include number (n) and percentage (%) of subjects experiencing an AE within each treatment group. The denominator for computation of percentages is the number of subjects in the safety population within each treatment group. The number of events will be included in some summaries as well whenever appropriate.

Unless otherwise specified, sorting order will follow the internationally agreed SOC order, and further by decreasing number of events in PTs within SOCs based on total subjects. When more than one PT has same number of events, the order of presentation will be alphabetical in PTs.

Multiple occurrences of the same event in the same subject will be counted only once in the tables within a treatment phase.

Summary of All TEAEs in the DBP

The following TEAE summaries will be generated for the safety population:

- An overview of TEAEs in the DBP. Number (%) of subjects will be provided by treatment group to include following:
    - TEAEs.
    - Severe TEAEs.
    - Serious TEAEs.
    - Treatment-related AEs (defined as those events other than ‘not related’ and ‘unlikely related’ as assessed by the investigator).
    - TEAEs leading to death.
    - TEAEs leading to permanent treatment discontinuation.
    - TEAEs leading to dose interruption or dose reductions.
- All TEAEs during the DBP by primary SOC sorted by internationally agreed order and decreasing frequency of PT (based on combined XEN1101 subjects) within each SOC.
- All TEAEs during the DBP presented by PT.
- All treatment-related AEs in the DBP presented by primary SOC and PT.
- All TEAEs during the DBP by maximal severity (ie, mild, moderate, or severe), presented by primary SOC and PT.

Summary of TEAEs by Subgroup

The primary analysis of TEAE (by SOC and PT) will also be performed in the following subgroups:

- Randomization strata: Use of CYP3A4 inducer medication (yes/no).
- Geographic region: North America, Europe.
- Number of baseline/concomitant AEDs: 1, 2, ≥3.
- Pre- and post–COVID-19 Population (Section 3.2.4).

Summary of Potentially Important TEAEs in the DBP

- Most common TEAEs during the DBP by primary SOC and PT. The most common TEAEs are defined as those PTs with incidence of ≥5% in any of the treatment arms. This cutoff maybe adjusted based on clinical judgement.
- TEAEs with potential difference between treatment arms during the DBP, by primary SOC and PT. The events with potential difference are defined as those PTs with a difference in incidence rate of >10% between any of the XEN1101 dose arms and the placebo. This cutoff maybe adjusted based on clinical judgement.

Summary of SAEs or TEAEs Leading to Treatment Change in the DBP

- All treatment-emergent SAEs during the DBP by primary SOC and PT.
- All treatment-emergent SAEs during the DBP that are at least possibly related to the study drug, by primary SOC and PT.
- All treatment-emergent SAEs during the DBP by severity, and by primary SOC and PT.
- Summary of all TEAEs resulting in treatment interruption or discontinuation in the DBP.
- TEAEs leading to treatment discontinuation during the DBP, by primary SOC and PT, defined as those AEs in the DBP with action taken of treatment ‘Stopped permanently’.
- TEAEs leading to treatment interruption during the DBP, by primary SOC and PT, defined as those AEs in the DBP with action taken of treatment ‘interrupted and resumed at reduced dosing frequency’ or ‘interrupted and resumed at same dosing frequency’.
- Listing of TEAEs leading to treatment interruption or discontinuation during the DBP, including details on dose, severity, relationship, and outcome, etc.

Summary of Pretreatment and Post-Treatment AEs

- All pretreatment (or baseline) AEs by primary SOC and PT.
- All pretreatment (or baseline) SAEs by primary SOC and PT (can be replaced by listing if number of events are less than 5).
- All pretreatment (or baseline) AEs by maximal severity (ie, mild, moderate, or severe), presented by primary SOC and PT.
- All AEs with an onset during the residual period of the DBP by primary SOC and PT.

3.4.11.2 Summary of Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of subjects who died by study period (on study, DBP treatment epoch, residual treatment epoch) and reason(s) for death.
- Deaths in nonrandomized subjects or randomized but not treated subjects.
- TEAEs leading to death (death as an outcome in the AE eCRF as reported by the investigator) by primary SOC and PT. A corresponding listing will be provided.
- Listing of deaths with details on demographics, treatment, and cause of death.

3.4.11.3 Summary of Laboratory Parameters

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all quantitative laboratory variables (laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline and each post-baseline time point), by treatment group. Only evaluable data will be used and missing data will not be imputed.

In addition, a line plot of mean and/or median will be presented for every quantitative laboratory parameter by study arm and visit. This may also be presented with box plots (showing median and quartiles) for illustration purpose.

The number (%) of subjects with abnormal results (out of normal range) during the DBP for each of the laboratory variables will be summarized by treatment group.

Shift tables for baseline versus worst value post-baseline in DBP will be presented for all chemistry and hematology laboratory parameters based on categories of low, normal, and high (for numerical results) or abnormal and normal (for categorical results). The baseline value is defined as the last available measurement prior to or equal to the randomization date (based on the protocol, the assessments performed on the randomization date should occur prior to the administration of the first dose of study drug).

The proportion of subjects with substantial change in laboratory values (see Appendix C for criteria) during the DBP (based on worst value in the DBP analysis period) will be displayed by treatment group. The corresponding data listings will be provided.

Safety data from local laboratories will be summarized separately based on available data.

A listing of subjects with laboratory abnormalities will be provided, including subject identification number, age, gender, treatment arm, assessment date and visit, lab results, and normal ranges.

Drug-Induced Liver Injury

Liver function tests, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The following analyses will be performed:

1. A graph of distribution of peak values of ALT versus peak values of total bilirubin (in logarithmic scale or in the scale of × upper limit of normal [ULN] if appropriate) will also be presented. The graph will be divided into 4 quadrants with a vertical line corresponding to 3× ULN for ALT and a horizontal line corresponding to 2× ULN for total bilirubin.

2. A listing of possible Hy's law cases identified by treatment group (eg, subjects with any elevated ALT ≥3× ULN, and associated with an increase in bilirubin ≥2× ULN) with ALT, AST, alkaline phosphatase, and total bilirubin.

3.4.11.4 Summary of Vital Signs

A summary of vital signs (weight [kg], BMI [kg/m^2], temperature [ºC], including semi-supine and standing pulse rate [bpm], as well as semi-supine and standing systolic and diastolic blood pressure [mmHg]) including change from baseline, presented by descriptive statistics, will be displayed by time point and study arm. For orthostatic tests (heart rate, diastolic blood pressure, and systolic blood pressure) change upon standing, will also be summarized similarly. Only evaluable data will be used and missing data will not be imputed.

In addition, a line plot of mean and/or median will be displayed for every parameter in vital signs by study arm and visit. Box plots may be provided for illustrative purposes.

The percentage of subjects with substantial changes in the DBP from baseline for vital sign parameters will be summarized by study arm. For this analysis, the worst post-baseline value for each subject during the DBP will be used (regardless of scheduled or unscheduled visit). The criteria for substantial change is described in Section 3.1.4.4 and Appendix C.

All vital signs measures and details of substantial changes will be listed.

3.4.11.5 Summary of ECGs

Summary statistics (including number, mean, median, SD, minimum, and maximum) for all ECG intervals (actual values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point) by treatment group. Only evaluable data will be used and missing data will not be imputed.

The incidence and percentage of subjects with substantial changes in PR, QRS, and QTcF interval based on worst value post-baseline in the DBP will be summarized by treatment group. The criteria for substantial change is described in Section 3.1.4.5 and Appendix C.

All ECG results will be listed on a by-subject basis.

3.4.11.6 Physical, Neurological and Ophthalmologic Examinations

For the 15 items in the complete physical examination and 42 items in the complete neurological examination, the number and percentage of subjects with normal or abnormal results will be presented by treatment and study visit. Nominal visit will be used.

Within the incidences of abnormalities in neurological and ophthalmologic exam, the number and percentage of subjects with clinically significant abnormalities (if collected) will be presented by treatment and study visit.

3.4.11.7 Summary of AUA Symptom Index

Each item of the AUA symptom index will be presented using descriptive statistics by treatment group, with clear footnotes for different scale-meanings. Both raw scores and change from baseline will be summarized by response category by treatment group at each scheduled visit. Only evaluable data will be used and missing data will not be imputed.

Summary statistics will also be presented for each question by using bar graph for each response category and study visit compared between treatment groups.

Total scores will be summarized by treatment group and study visit (baseline through end of the DBP).

3.4.11.8 Summary of C-SSRS

The following analyses will be performed for the derived variables as described in Section 3.1.4.8:

- Number of subjects with suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the C-SSRS during the DBP, summarized by treatment group and study visit, including specific suicidal ideation and behavior. The denominator will be based on subjects in the safety population who have at least one post-baseline assessment.
- Shift table for change in C-SSRS categories from baseline to post-baseline during DBP. The categories will include no suicidal ideation or behavior, suicidal ideation, and suicidal behavior, based on worst outcome during the baseline and post-baseline period respectively. Each subject is counted in one category only. Subjects with both suicidal ideation and suicidal behavior are included in the suicidal behavior category.
- Shift table of change in C-SSRS suicidal ideation scores from baseline compared to maximum suicidal score during the DBP, ranging from 0 to 5.

The shift tables will include only those subjects in the safety population and evaluable data for both baseline and post-baseline DBP periods.

Subject-level data including additional details will also be listed.

3.4.12 Analyses of PK Data

A separate population PK analysis plan will be generated to support the population PK analysis in subjects with focal epilepsy. PK parameters for individual subjects will be derived from population PK analysis using the data from this study pooled with other studies if necessary. The population PK will be characterized by nonlinear mixed-effects modeling. A separate report to the CSR will be written to cover the population PK analysis.

3.5 Data Handling Conventions

3.5.1 General Conventions

In general, the baseline value is defined as latest value prior to the first study drug/IMP. In cases where an assessment is performed on the same date as the date of first IMP administration, but it is impossible to determine the evaluation time relative to first IMP start time, the evaluation time will be assumed to be following the protocol-defined schedule. Based on the protocol schedule, typically the data obtained on the randomization date can be considered as the baseline value. If such data is missing, the evaluable data prior to randomization date can be used.

Due to inherent variability and susceptibility to artefacts (eg, noise) in ECG and vital signs with time and in order to provide a more representative and stable reference, the average of the available values recorded at V1 (screening), V2 (start of baseline period) and V3 (randomization visit) will be used to calculate the "Baseline" value for use in "Change from Baseline" calculations for ECG and vital signs and not just the pre-drug value as previously planned.

3.5.2 Data Handling Related to eDiary Data

Based on the design of the eDiary, subjects were required to enter daily seizure information within a 48-hour window, covering the previous 24 to72 hours, using a provisioned eDiary device. Subjects entered their seizure occurrence 1 at a time, with a maximum of 10 seizures that could be entered per day. Subjects who answered 'Yes' to a specific seizure incidence, but without seizure type will be treated as missing for analysis purpose.

Note that when a subject reported seizures that appeared to be different from what was described in the seizure key card, a seizure type of 'Other' was to be selected by the subject in the eDiary. These 'other' seizures were then to be reclassified by the investigator through a separate eCRF. This additional information from the 'Other' eCRF will be incorporated in the overall seizure assessment for the subject, in addition to eDiary entries. If the 'Other' seizure is not classified as type 1 to 5 as used for analysis, it will be considered as no countable seizure for that occurrence.

In the cases of documented technical issues with a subject's eDiary that prevented data entry, subjects were permitted to provide seizure information in a backup paper diary, only for those days when the eDiary device was documented as not working (implemented under Protocol Amendment 4.1 [27 March 2020]). Seizure information from the backup paper diary could then be entered in the eCRF by the sites and be combined with the eDiary data for the primary analyses.

All data handling conventions will also be documented in the ADaM specification. Those records collected from paper diary will be identified in the ADaM dataset using appropriate flag variables.

3.5.3 mITT Analysis Flags

The mITT analysis population includes all randomized subjects who took at least 1 dose of study drug and completed at least 1 seizure assessment day. The analysis flag will be defined if both of these criteria were met:

- Treated with at least 1 dose of study drug (eg, at least 1 dose record in the seizure diary with dosing date ≥ randomization date, or other indication of treatment from drug accountability and disposition eCRF), and
- At least 1 day with evaluable seizure information (either yes or no for seizure information) during the double-blind period (DBP).

3.5.4 Missing Data and Handling in Data Presentation

Missing data for primary and secondary efficacy endpoints are described in Section 3.1.3 and Section 3.4.9.1. This section only addresses the handling of missing data for presentation purposes, as well as missing data commonly encountered for safety and baseline variables.

In general, missing baseline data will not be imputed. The following approaches are default methods for missing data handling in summary tables.

- Categorical data at baseline will be summarized for each treatment group using counts (n) and percentages (%). The denominator will be the analysis population specified for the summary, unless otherwise specified. Missing data may be presented as a separate category.

- Continuous data: The analyses and summaries for variables with continuous scales will be based on observed data only.

3.5.4.1 Handling of Missing/Partial Dates for AEs or Concomitant Medications

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

No imputation for medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

3.5.4.2 Handling of Missing Assessment of Relationship of AEs to IMP

If the assessment of the relationship to IMP is missing, then the relationship to IMP in the frequency tables is considered as possibly related, but no imputation should be done at the data level.

3.5.4.3 Handling of Missing Severity of AEs

If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

3.5.4.4 Handling of Potentially Clinically Significant Abnormalities

If a subject has a missing baseline, the subject will be grouped in the category "normal/missing at baseline".

For potentially clinically significant abnormalities with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the potentially clinically significant abnormalities will be based only on the second condition.

3.5.5 Study Day Calculation

Study day for a given assessment is defined as the assessment date – reference date + 1 if the assessment date is on or after the reference date, or assessment date – reference date if the assessment date is before the reference date, where the reference date is the date of randomization for this study. However, study day will not be defined if a subject was never treated in the DBP. The use of randomization date as a reference instead of first IMP date was due to potential inaccuracy of first IMP date obtained from the eDiary data.

3.5.6 Windows for Time Points

The visit windows for the by-visit analyses are defined in Table 5. This will include analysis of safety laboratory tests, vital signs, ECG, C-SSRS, and AUA symptom index. For analysis purpose, a larger window (comparing to the protocol visit window) will be used. This will be applicable for those analyses requiring visit information.

Table 5 Study Visit Windows for DBP

Scheduled Visit	Visit Window for Analysis Purpose in Study Days (Target Day)
Visit 1 (Screening)	Visit 1 < Visit 2 (Visit 1)
Visit 2 (prior to randomization)	Visit 2 < Visit 3 (Visit 2)
Visit 3 (randomization visit)	Visit 3
Week 1	Day 2-12 (Day 8)
Week 2	Day 13- 22 (Day 15)
Week 4	Day 23-36 (Day 29)
Week 6	Day 37-49 (Day 42)
Week 8	Day 50-64 (Day 57)
Follow-up 1	Visit F1a
Follow-up 2	Visit F2b

Note: The last available assessment prior to treatment (≤randomization date) is used as the "baseline" value for analysis of change from baseline and characterization of the population, with the exception of ECG and vital signs, the average of Visit 1, Visit 2 and Visit 3 was used for baseline definition.

The analysis visit will be defined by comparing the actual visit date with the nominal (or target) date and the corresponding analysis window. If more than one non-missing values are assigned to the same visit, then the one closest to the target date will be used in the by visit analysis. Multiple values on the same date will be averaged first. If 2 assessments are on different date but equal distance from the target date, the later date will be used. For those subjects who had early treatment discontinuation, their value obtained at ET visit may be mapped to the corresponding visit window defined above. However, if a subject has the F1a assessment that is also within the Week 8 window (but the F1a occurred after the last IMP as planned), it will be counted as the Follow-up 1 visit, not the Week 8 visit.

3.5.7 Unscheduled Visits

Unscheduled visit laboratory tests, vital signs, and ECGs may also be included in the by visit summaries, if the data is within the corresponding visit window and closest to the target day.

3.5.8 Pooling of Centers for Statistical Analyses

Due to potential differences of background treatment in different countries, sites were pooled to form the following 3 regions for the efficacy analyses: North America, eastern Europe, and western Europe (including the UK). If the number of subjects in the eastern Europe region is too small (<10% of total sample size), then both eastern and western Europe regions will be combined into one category in the analysis model.

In addition, descriptive summaries for primary and key secondary endpoint will also be provided by country, which may involve pooling multiple sites.

4.0 INTERIM ANALYSIS

No interim efficacy analysis is planned for this study.

Safety data will be assessed periodically, in blinded manner through a Safety Review Committee (SRC). This periodic review will include AEs, laboratory tests, vital signs, and ECGs. If the blinded data suggests a potential safety or tolerability issue for XEN1101, an external group will

perform an un-blinded interim review of safety to provide further recommendations to sponsor. The external independent reviewer may request additional trial data to better assess the benefit-risk of the subjects in the study. The process of safety review is documented in the SRC charter.

5.0 DATABASE LOCK

The database lock for the primary efficacy analyses is planned to be approximately 3 weeks after the last subject completed the last visit in the DBP.

6.0 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Version 9.4 or higher.

7.0 REFERENCES

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Appendix A Schedule of Assessments (DBP)

Study Period	**Screening**	**Baseline**	**Double-blind Treatment**						**Post-Tx Follow-up**		
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 exam[b]	X[b]	X[b]							X[b]		X[b]
Vital signs[b]	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

Study Period	**Screening**	**Baseline**	**Double-blind Treatment**						**Post-Tx Follow-up**		
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**	
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
Dispense study drug to subject			X			X		return			return
Study drug compliance check					X	X		X			X

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.

a. The dose of background AEDs must be unchanged for at least a month before screening and remain stable throughout vaseline and double-blind treatment phase. (The screening period may be completed as soon the subject 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 exam, a dilated fundoscopic exam 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 subjects not continuing on to the OLE). For subjects continuing on to the OLE that did not complete a dilated fundoscopic exam prior to randomization (ie, randomized prior to this requirement) a dilated fundoscopic exam 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 exam requires more than 1 week from Visit 8 to be completed in these subjects, 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 subject has rested comfortably for at least 5 minutes; three 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 2-5 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 postmenopausal 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 setup 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. Subjects 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 subjects 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. Subjects 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 subjects who 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. Subjects who discontinue early from the study should have all ET evaluations performed on the last day of receiving study drug, or as soon as possible thereafter.
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 subject from PI or designee.

Appendix B QOLIE-31 Scoring

The QOLIE-31 (Cramer et al. 1998) contains seven multi-items scales that tap the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive-functioning, seizure worry, medication effects, and overall quality of life. The QOLIE-31 overall score is obtained using a weighted average of the multi-item scale scores and also includes a single item that assesses overall health. The scoring form is as follows:

Scale/Item Numbers	Response 1	2	3	4	5	6	Subtotal	Final Score, 0-100 point scale
Seizure Worry								
11.	0	20	40	60	80	100	____	
21.	0	33.3	66.7	100	—	—	____	
22.	0	50	100	—	—	—	____	
23.	0	33.3	66.7	100	—	—	____	
25.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 5 = ____
Overall Quality of Life								
1.	(multiply response by 10)						____	
14.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 2 = ____
Emotional Well-Being								
3.	0	20	40	60	80	100	____	
4.	0	20	40	60	80	100	____	
5.	100	80	60	40	20	0	____	
7.	0	20	40	60	80	100	____	
9.	100	80	60	40	20	0	____	
						TOTAL:	____	÷ 5 = ____
Energy/Fatigue								
2.	100	80	60	40	20	0	____	
6.	100	80	60	40	20	0	____	
8.	0	20	40	60	80	100	____	
10.	0	20	40	60	80	100	____	
						TOTAL:	____	÷ 4 = ____
Cognitive								
12.	0	20	40	60	80	100	____	
15.	0	33.3	66.7	100	—	—	____	
16.	0	20	40	60	80	100	____	
17.	0	20	40	60	80	100	____	
18.	0	20	40	60	80	100	____	
26.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 6 = ____
Medication Effects								
24.	0	33.3	66.7	100	—	—	____	
29.	100	75	50	25	0	—	____	
30.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 3 = ____
Social Function								
13.	0	20	40	60	80	100	____	
19.	0	25	50	75	100	—	____	
20.	0	25	50	75	100	—	____	
27.	100	75	50	25	0	—	____	
28.	100	75	50	25	0	—	____	
						TOTAL:	____	÷ 5 = ____

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that as noted in the text "Scoring Rules," pages 2-3.

Precoded numeric values for responses on some items are in the direction that such that a higher number reflects a more favorable health state whereas for other some items, are in the direction that a lower number reflects a more favorable health state. Indeed, it should also be noted that different items may have different ranges of precoded numeric values. To account for these differences, the scoring procedure for QOLIE-31 need for the following steps:

1. First, group different items into different dimensions and convert the raw precoded numeric values of items to 0-100-point scores (subtotal column), with higher converted scores always reflecting better quality of life (see QOLIE-31 Scoring Form above).
2. The following step is to sum the subtotal scores and obtain the total value for each dimension.
3. Each total score in each dimension needs to be divided by the number of items that the respondent answered within each to get the final score. The possible range is 0 to 100 points. Higher scores reflect better quality of life, lower ones worse.
4. Note that in the scoring form, the divisors are to be used only in situations where every item within a given dimension has been answered. For example, if item 11 in the Seizure Worry dimension was left blank and the other four items in the scale were answered, then the total score for this dimension would be divided by 4 instead of 5.
5. After calculating the score for each dimension, total score is derived based on the weight as described below.

FORMULA FOR CALCULATING QOLIE-31 OVERALL SCORE

QOLIE-31 Scale	Final Scale Score		Weight		Subtotal
Seizure worry	____	×	.08	=	____ (a)
Overall quality of life	____	×	.14	=	____ (b)
Emotional well-being	____	×	.15	=	____ (c)
Energy/fatigue	____	×	.12	=	____ (d)
Cognitive functioning	____	×	.27	=	____ (e)
Medication effects	____	×	.03	=	____ (f)
Social functioning	____	×	.21	=	____ (g)
OVERALL SCORE: Sum subtotals (a) through (g)				=	____

Appendix C Criteria for Potentially Clinically Significant Abnormalities (Substantial Change) in Laboratory Tests, Vital Signs and ECG Parameters

Parameter	PCSA Category (Adults)
Clinical Chemistry	
ALT	>3 -5 ULN >5 -10 ULN >10 ULN
AST	>3 -5 ULN >5 -10 ULN >10 ULN
Alkaline phosphatase	>1.5 ULN
Total bilirubin	>1.5 -2 ULN >2 ULN
ALT and total bilirubin	ALT ≥3 ULN and Total Bilirubin ≥2 ULN
Hematology	
WBC	<3.0 10^9/L (non-Black), <2.0 10^9/L (Black) ≥16.0 10^9/L
Lymphocytes	>4.0 10^9/L
Neutrophils	<1.0 10^9/L
Eosinophils	>0.5 10^9/L
Hemoglobin	Males: ≤115 g/L, ≥185 g/L Female: ≤95 g/L, ≥165 g/L or Decrease from baseline: 20 g/L
Hematocrit	Male: ≤0.37 v/v, ≥0.55 v/v Female: ≤0.32 v/v, ≥0.5 v/v
Platelets	<100 10^9/L ≥700 10^9/L
ECG	
PR	≥200 ms and increase from baseline ≥25%
QRS	≥120 ms and increase from baseline >10%
QTcF	Absolute values (ms): >450 ms, >480 ms, >500 ms Increase from baseline: 30-60 ms, >60 ms
Vital Signs	
Semi-supine systolic BP	≤90 mmHg and decrease from baseline ≥20 mmHg ≥180 mmHg and increase from baseline ≥20 mmHg
Semi-supine diastolic BP	≤50 mmHg and decrease from baseline ≥15 mmHg ≥105 mmHg and increase from baseline ≥15 mmHg
Semi-supine pulse rate	<50 bpm and absolute decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
Weight	≥7% change from baseline

Parameter	PCSA Category (Adults)
Orthostatic Vital Signs	
Standing systolic BP	≤90 mmHg and decrease from semi-supine ≥20 mmHg
	≥180 mmHg and increase from semi-supine ≥20 mmHg
Standing diastolic BP	≤50 mmHg and decrease from semi-supine ≥15 mmHg
	≥105 mmHg and increase from semi-supine ≥15 mmHg
Standing pulse rate	<50 bpm
	≥120 bpm

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; CPK: creatine phosphokinase; ECG: electrocardiogram; LLN: lower limit of normal; PCSA: potentially clinically significant abnormalities; ULN: upper limit of normal; WBC: white blood cell.

Signature Manifest

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