A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

Protocol Number: XPF-009-301

IND Number: 138144

Eudra CT Number: 2020-002396-35

Clinical Study Identifier: EPIK

Compound: XEN496; Ezogabine (USAN); Retigabine (INN)

Sponsor: Xenon Pharmaceuticals Inc.
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Burnaby, British Columbia
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Version Number: 5.0

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the protocol, ICH-GCP guidelines, and applicable regulatory requirements.

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

INVESTIGATOR AGREEMENT

STUDY TITLE: A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

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 study drug and study procedures. I will let them know that this information is confidential and proprietary to Xenon and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Xenon, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with applicable local regulations, EC/IRB regulations, and ICH-GCP guidelines.

Investigator's Signature	Date
Investigator's Printed Name	

COORDINATING INVESTIGATOR AGREEMENT

STUDY TITLE: A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy

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. [redacted] to third parties. I understand that the study may be terminated or enrollment suspended at any time by Xenon, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to the assigned responsibility for the coordination of investigators at different centers participating in the multicenter trial.

I agree to conduct this study in full accordance with applicable local regulations, EC/IRB regulations, and ICH-GCP guidelines.

Coordinating Investigator's Signature	Date
Coordinating Investigator's Printed Name	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:	A Phase 3 Study of Adjunctive XEN496 in Pediatric Subjects With *KCNQ2* Developmental and Epileptic Encephalopathy
Protocol Number:	XPF-009-301
Protocol Identifier:	EPIK
Phase:	Phase 3
Investigational Medicinal Product (IMP)/Study Drug:	XEN496: IR, multiparticulate sprinkle capsule formulation of ezogabine (retigabine) for pediatric subjects. Placebo: Capsules matching XEN496 in appearance containing only inactive ingredients. The capsules are meant to be opened and the contents dispersed into soft foods or liquids for oral administration [redacted]. Herein and throughout the protocol, XEN496 and placebo are collectively referred to as "study drug".
Indication:	Seizures in pediatric subjects with KCNQ2-DEE.
Study Description:	Randomized, double-blind, placebo-controlled, parallel group study, to evaluate the efficacy, safety, and tolerability of XEN496 administered as adjunctive treatment in pediatric subjects with KCNQ2-DEE.
Main Objectives:	**Primary Objective:** • To evaluate the efficacy of XEN496 as adjunctive therapy in reducing seizure frequency compared to placebo in pediatric subjects with KCNQ2-DEE. **Key Secondary Objective:** • To evaluate the proportion of pediatric subjects with KCNQ2-DEE who achieve a ≥50% reduction from baseline in seizure frequency when taking XEN496, compared with placebo. **Additional Secondary Objective:** • To evaluate CaGI-C and CaGI-S scores in pediatric subjects with KCNQ2-DEE taking XEN496, compared with placebo. **Safety and Tolerability Objectives:** • Safety and tolerability of XEN496 in pediatric subjects with KCNQ2-DEE.

Study Population:	Approximately 40 subjects diagnosed with KCNQ2-DEE, aged 1 month to less than 6 years.
Study Duration:	Subjects will undergo: • Screening/Baseline period – Minimum of 2 or 4 weeks duration (based on seizure frequency). – Additional time (2 weeks) may be added to the screening/baseline period at the discretion of the investigator to ensure adequate establishment of baseline seizure frequency (see *Establishment of Baseline Seizure Frequency* below). • Treatment period – Up to approximately 15 weeks (titration and maintenance). – Titration period – 24 days. – Maintenance period – 12 weeks. • Taper period – Up to 15 days. The study drug should be tapered over a period of up to 15 days at any point a decision is made that a subject will discontinue study dosing, for any reason. This includes: – [redacted] • Follow-up – Approximately 4 weeks after subjects have tapered off of study drug. Total study duration per subject is estimated to be: • Approximately 17 to 21 weeks for subjects who complete the maintenance period and enroll in the OLE. • Approximately 23 to 27 weeks for subjects who complete the maintenance period and do not enroll in the OLE.
Study Design:	**Design:** Randomized, double-blind, placebo-controlled, parallel group. **Allocation:** Randomization 1:1 (XEN496: placebo). **Intervention:** Parallel assignment. **Blinding:** Including subject, parents/guardians, caregivers, outcomes assessors/adjudicators, investigators, and sponsor. Designated pharmacy staff may be unblinded as appropriate. **Baseline Period:** ***Screening:*** Subjects will be screened (Visit 1) prior to entering the study and starting the baseline period. The parent(s)/guardian(s) of each subject will receive verbal and written information followed by signing of the ICF

prior to any screening procedures taking place. [redacted]

***Establishment of Baseline Seizure Frequency*:**

Subjects will enter a baseline period that will vary in duration depending on the number of countable motor seizures experienced by the subject during this period.

The initial planned baseline duration will be based on previous medical history and seizure frequency as reported by the caregiver:

a. Subjects who typically experience ≥1 seizure per day prior to baseline will enter a minimum 2-week baseline period, after which they will be randomized, if all other eligibility criteria are met.

- The baseline period may be extended by 2 weeks for a total baseline duration of 4 weeks if either of the following occur:
  - [redacted]
  - [redacted]

b. Subjects who typically experience <1 seizure per day and ≥4 seizures per month (28 days) prior to baseline will enter a minimum 4-week baseline period.

- The baseline period may be extended by 2 weeks for a total baseline duration of 6 weeks if either of the following occur:
  - [redacted]
  - [redacted]

Following baseline, subjects that meet all remaining entrance criteria will be randomized to the study. [redacted]

	Randomization: Eligible subjects will be randomized 1:1 to receive either XEN496 or placebo and will be stratified by their age (<2 or ≥2 years) and seizure frequency category during baseline (high or low seizure frequency group). **Treatment Period:** ***Titration***: Subjects will receive a titration of the study drug over a period of 24 days, [redacted] to reach the top dose of 21 mg/kg/day (or placebo), [redacted] If subjects begin to experience any adverse effects raising tolerability concerns, the investigator may decide to stop the dose escalation and continue with the last dose used, or step down to the previous dose level, and continue with the lower dose over the remaining titration period and into the maintenance period. ***Maintenance***: Following titration, subjects will continue treatment at the optimal dose determined during titration for 12 weeks. **Taper Period and End of Study:** At the end of the maintenance period, subjects will be required to taper off study drug over a period of up to 15 days, unless they qualify and enroll in the OLE. Subjects who discontinue the study early, or who will not participate in the OLE, will be required to enter into the taper period at that time and will be expected to complete the end of study follow-up safety monitoring schedule. Subjects will be followed for safety monitoring for 28 days after the last dose of study drug has been administered. **Long-term OLE:** Subjects may be considered for an open-label long-term extension (under a separate study protocol) if they meet the protocol-specified requirements.
Main Criteria for Subject Selection:	**Main Criteria for Inclusion:** • Male or female subjects aged 1 month (44 weeks postmenstrual age) to less than 6 years, with a body weight of ≥3.0 kg, at screening (Visit 1). • Documented evidence of a genetic test result from an appropriately accredited laboratory, consistent with a diagnosis of KCNQ2-DEE (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support and an alternate diagnosis). • Seizure onset within 2 weeks after birth and EEG and documented clinical history consistent with KCNQ2-DEE. • MRI has been performed and is without evidence of structural abnormalities, including but not limited to, hypoxia, hypoxia-ischemia, ischemia (arterial or venous), stroke, sinovenous thrombosis, intracranial hemorrhage, or focal or

	global brain malformation. Brain MRI changes that are described as being associated with the KCNQ2-DEE and presumed to be secondary to the disease itself, will not be exclusionary. • Must have had [redacted] focal tonic or other countable motor seizures in the month (28 days) prior to screening, documented by caregiver report or investigator medical notes. • Subjects will be taking 1 and no more than 4 concomitant ASMs. All doses must be stable for at least 1 week prior to screening and expected to be maintained throughout the duration of the study (until the end of the treatment period). • VNS is allowed and will not be counted as a concomitant ASM. The VNS device must be implanted for at least 6 months before screening, and the device settings must be stable for at least 6 weeks prior to screening and throughout the duration of the study. Use of the VNS device magnet is allowed. • Ketogenic diet is allowed and will not be counted as a concomitant ASM. The subject must be on a stable dietary regimen that produces ketosis for at least 6 weeks prior to screening and is expected to maintain the regimen throughout the study. **Main Criteria for Exclusion:** • Presence of a pathogenic or likely pathogenic variant in an additional gene associated with other epilepsy syndromes. (Variants in other epilepsy-associated genes that are not known to be pathogenic or are not likely to be pathogenic based upon adjudication review will not be a basis for exclusion.) • Presence of a known gain-of-function variant in the KCNQ2 gene, or clinical characteristics consistent with previously reported pathogenic gain-of-function variants in the KCNQ2 gene, such as subjects with infantile spasms without a history of neonatal-onset seizures. • Seizures secondary to infection, neoplasia, demyelinating disease, degenerative neurological disease, or central nervous system disease deemed progressive, metabolic illness, or progressive degenerative disease. • Confirmed diagnosis of infantile spasms within the past month prior to screening. • History or presence of any significant medical or surgical condition or uncontrolled medical illness at screening including, but not limited to, cardiovascular, gastrointestinal,

	hematologic, hepatic, ocular, pulmonary, renal, or urogenital systems, or other conditions that would not justify the subject's participation in the study, as determined by the investigator's benefit-risk assessment. • QTcF of >440 msec. In addition, subjects with a history of arrhythmia, prolonged QT, heart disease or subjects taking medications known to increase the QT interval. • History of hyperbilirubinemia which lasts longer than 1 week will require exclusion of hepatic disease before entering the study. • History of bilirubin-induced neurological dysfunction. • Current disturbance of micturition or known urinary obstructions or history of bladder or urinary dysfunction including abnormal postvoid residual bladder ultrasound, vesicoureteral reflux, urinary retention or required urinary catheterization in the preceding 6 months. • Subjects who are planned to begin to follow a ketogenic or other specialized dietary therapy during the study. • Subjects using felbamate who have presented with clinically significant abnormalities and/or hepatic dysfunction during felbamate treatment, and subjects who have taken felbamate for less than 6 months prior to screening. • Subjects who are currently taking adrenocorticotropic hormone.
Randomization Criteria:	[redacted]
Dose Administration and Discontinuation:	**Dose Administration:** The study drug is supplied as capsules [redacted] and placebo. For blinding purposes, all capsules are the same size and color.

The daily dose of study drug should be administered orally mixed with food or drink TID in equally divided doses (as supplied by the pharmacy), based on body weight.

[redacted]

The entire contents of the capsules containing study drug should be added to [redacted] a liquid or a semisolid food prior to ingestion. Refer to the pharmacy and/or caregiver study drug manuals for a list of acceptable foods and liquids. For clarity, the capsules themselves are not intended to be ingested.

[redacted]

Refer to the pharmacy manual for additional instructions on dose administration.

Dose Titration Period:

The treatment period begins with a dose titration period. All eligible subjects will start with a dose of [redacted] of study drug. The dose will be escalated [redacted] to a maximum dose of [redacted] (21 mg/kg/day), [redacted].

The following dose titration scheme is approximate. The final dose and number of capsules using the weight-based dosing are detailed in the pharmacy manual.

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

TID: three times daily.

[redacted]

The investigator will be blinded to the treatment allocation. Assuming no moderate to severe treatment-related AEs are observed, the subject's dose will be escalated to the next dose level during titration according to the dosing regimen.

The investigator will assess the subject's tolerability and AE profile throughout the treatment period. [redacted]

	Pharmacy staff will prepare the appropriate dose of study drug in the event of a dose decrease. The maximum dose will not exceed [redacted] (21 mg/kg/day), [redacted] **Dose Maintenance Period:** The dose maintenance period is planned for 12 weeks after the titration period. During this period, the subject will be maintained on the optimally tolerated dose level established during the initial weeks of the treatment period. **Dose Taper Period:** The dose taper period is intended for subjects who exit the study, either because of early termination or because the caregiver has decided not to enter the subject in the OLE. During the dose taper period, the dose should be reduced in a stepwise manner [redacted] to mirror the dose escalation scheme during the dose titration period, but in reverse order.
Main Outcome Measures:	**Primary Endpoint:** • Percent change from baseline in monthly (28 day) countable motor seizure frequency during the blinded treatment period, as recorded by caregivers in a daily seizure diary. **Key Secondary Endpoint:** • Proportion of subjects with ≥50% reduction in monthly (28 day) seizure frequency from baseline. **Additional Secondary Endpoints:** • CaGI-C scores for the subject's overall condition and for seizures. • Change from baseline in CaGI-S for the subject's overall condition and for seizures. **Safety and Tolerability Endpoint:** • Severity and frequency of AEs and serious adverse events, clinically significant changes in laboratory tests, vital signs, ECGs, physical and neurologic examinations, bladder and urological examinations, and ophthalmology examinations.
Statistical Considerations:	[redacted]

	[redacted]
Sample Size Determination:	Approximately 40 subjects will be randomized (1:1) to either XEN496 or placebo. [redacted]

STATISTICAL ANALYSIS PLAN

Available upon request.