Design of a Clinical Trial to Determine the Efficacy of XEN496 in *KCNQ2*-Developmental and Epileptic Encephalopathy (*KCNQ2*-DEE)

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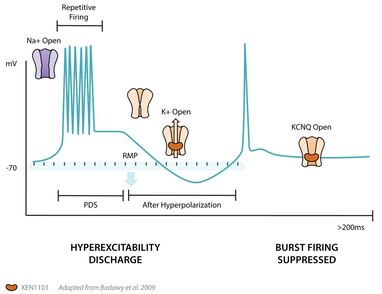
BACKGROUND

- *KCNQ2*-DEE is an ultra-rare, severe neurodevelopmental disorder characterized by multiple daily refractory seizures presenting within the first week of life, resulting in profound developmental impairment generally requiring life-long care.[1-4] There is currently no anti-seizure medication specifically indicated for patients with *KCNQ2*-DEE
- Strong human genetic validation and pharmacologic evidence[5,6] support the use of XEN496 (ezogabine), a $K_v7.2/7.3$ activator, as a potential treatment
- Ezogabine (previously approved for adult focal onset seizures but withdrawn from the market for commercial reasons) is a targeted therapy that has shown promise as a precision medicine for the treatment of KCNQ2-DEE[7,8]
- Xenon Pharmaceuticals Inc. is conducting an innovative clinical trial with a novel pediatric formulation of ezogabine developed for this indication
- However, clinical trials in this population are particularly challenging because the disorder is ultra-rare, occurs very early in life, has a spectrum of phenotypes, and treatment with available antiseizure medications has resulted in a wide range of clinical response

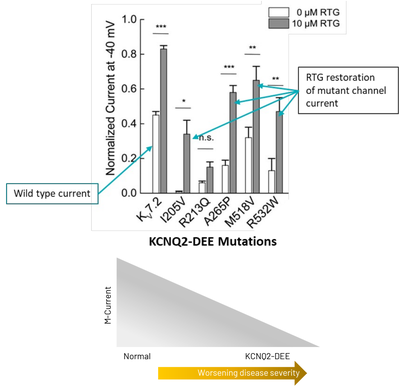
Why Ezogabine for *KCNQ2* Encephalopathy?

- The *KCNQ2* gene codes for the $K_v7.2$ voltage-gated subunit, which can form functional heterotetramers with $K_v7.3$ to form active $K_v7.2/7.3$ potassium channels
- KCNQ2 K_v channel activity dampens neuronal hyper-excitability, repolarizing membranes to end the action potential to maintain balance
- Certain missense (LOF) mutations in the *KCNQ2* gene cause an inability of the channels to modulate K_v current during neuronal firing, leading to an over-excitability of neurons which results in uncontrolled seizures; the hallmark of *KCNQ2*-DEE
- A K_v channel opener (enhancer) would *decrease* hyper-excitability in the brain as a treatment for *KCNQ2*-DEE



XEN496 is the First Precision Medicine to be Developed for *KCNQ2*-DEE

- XEN496, a novel, pediatric formulation of ezogabine, is being developed as a precision medicine to selectively address the etiology of *KCNQ2*-DEE
- Pharmacological profile of ezogabine is unique from all currently approved anti-seizure medications
- Ezogabine is a potent activator of K_v7 channels (including $K_v7.2$), potentiating the M-current[5]
- Ezogabine does not inhibit the cardiac $K_v7.1$ channel
- Ezogabine targets the root cause of *KCNQ2*-DEE loss-of-function (LOF)[7]
- *In vitro* ezogabine/retigabine (RTG) can restore the depleted $K_v7.2$ M-current caused by dominant negative *KCNQ2*-DEE missense mutations[5]
- Genotypic/phenotypic rationale supports potential to improve outcomes beyond seizure reduction

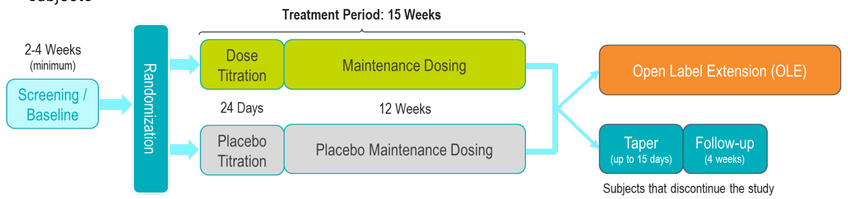


STUDY DESIGN AND OBJECTIVES

- The design is intended to maximize the number of eligible patients that can participate, minimize the burden to families/caregivers, and provide evidence of effectiveness
- Seizures continue to represent the primary endpoint for efficacy of anti-seizure medications, and seizures in *KCNQ2*-DEE are stereotyped, clinically evident, and do not occur without an observable clinical correlation
- Electronic seizure diaries for the caregivers are utilized as a key source of seizure frequency data, as well as allow collection of study medication compliance, and record other medication use, and any adverse events that may arise. Use of the diaries also ensures quality data and remote monitoring of compliance

EPIK Phase 3 Clinical Trial Underway

- A randomized (1:1), double-blind, placebo-controlled parallel group study with a total of ~40 *KCNQ2*-DEE subjects



EPIK Phase 3 Study's Primary Objectives and Endpoints

Primary Objective

- To evaluate the efficacy of XEN496 as adjunctive therapy in reducing seizure frequency compared to placebo in pediatric subjects with *KCNQ2*-DEE

Primary Endpoint

- % change from baseline in monthly (28 days) countable motor seizure frequency during the blinded treatment period - recorded by caregivers in a daily seizure diary

Secondary Endpoints

- 50% response rates in subjects taking XEN496 relative to placebo
- Changes from baseline in subject overall condition using Caregiver Global Impression of Change (CaGIC) and Severity scales (CaGIS)

Tertiary Endpoints

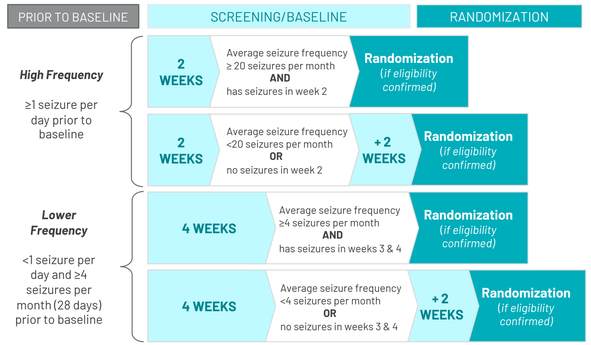
- Proportion of subjects achieving reduction in monthly seizure frequency from baseline (<25%, 25<50%, 50<75%, 75<100%)
- Number of seizure free days
- Use of rescue medications
- Plasma concentration of ezogabine and metabolite NAMR
- Quality of life (Peds-QL)
- Neurocognitive development and behavior (Adaptive Behavior Assessment System (ABAS-3) and Bayley Scales of Infant and Toddler Development (BSID-III))
- Change from baseline in subject overall condition using Clinician Global Impression of Change (CGIC)
- CaGIC in specific domains (subject's behavior, alertness, motor skills, visual function and communication)

Safety and Tolerability Endpoints

- Safety and tolerability of XEN496 (Severity and frequency of AEs and serious adverse events (SAEs), clinically significant changes in laboratory tests, vital signs, ECG, physical and neurologic examinations, urological examinations, and ophthalmology examinations)

Baseline Period: Variable Duration

- Baseline may vary from 2 to 6 weeks depending on the number of countable motor seizures experienced by the subject during this period
- If seizure frequency is below the specified thresholds for high frequency or lower frequency seizures, the baseline may be extended by 2 more weeks to obtain an accurate baseline and confirm eligibility



Use of eDiary

Caregiver Use of eDiary

- Complete diary each day
- Report seizure count
- Record urine output
- Record medication compliance
- Capture rescue medication use

Site eDiary Activities

- Set-up and train Caregivers on the eDiary
- Check the subject ePRO eligibility
- Deactivate the subject from the device
- Send data to TrialManager

Benefits of eDiary

- Facilitating accurate and timely data capture
- Record of data if diary lost (if paper diary is lost or destroyed, data unrecoverable)
- Compliance with eDiary is much easier to monitor
- eDiary alerts and reminders maximize compliance and increase safety
- Allows remote monitoring

CONCLUSIONS

- There remains a high unmet medical need for treatments for *KCNQ2*-DEE
- This trial design includes novel features intended to facilitate enrolment, such as the variable baseline period to allow those with high seizure burden to enter the study with a shorter baseline period, and flexibility in allowing various visits to be conducted at the patient's home
- The electronic seizure diary facilitates data capture, allows remote monitoring, and provides a tool to ease the burden for caregivers and increases safety oversight
- It is expected that the design, tools, and flexibility will overcome numerous challenges to facilitate enrolment and successful completion of this phase 3 trial of XEN496 in *KCNQ2*-DEE

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DISCLOSURES Noam Butterfield, Cynthia Harden, Celene Grayson, and Yi Xu are employees of and own stock or stock options in Xenon Pharmaceuticals Inc. Simon Pimstone is an officer or director and/or receives compensation from Xenon Pharmaceuticals Inc, XYON Health Inc., Eupraxia Pharmaceuticals, and Alpha9 Theranostics. John J. Millichap reports royalties from Up-To-Date; consulting fees from Eisai, Xenon, Biomarin, Greenwich, Praxis, Neurelis, Neurocrine, Biohaven; and grants from the National Institutes of Health.

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