Kv7 Potassium Channel Modulators for the Treatment of Epilepsy

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Xenon’s $K_v7$ Channel Modulators for Adult and Pediatric Epilepsies

Voltage-gated $K$ channels

Non-selective voltage-gated $Na_v$ channels

GABA inhibitory neurotransmission

Glutamate excitatory neurotransmission

Other mechanisms

Major Classes Of Approved Anti-Seizure Medications (ASMs)

Phenytoin (Na+); Carbamazepine (Na+); Pregabalin (Ca$^{2+}$); Lacosamide (Na+)

Clobazam; Diazepam; Vigabatrin; Tiagabine

Topiramate (KA); Perampanel (AMPA)

Levetiracetam; Brivaracetam; Cannabidiol (CBD); Cenobamate
KCNQ2 is a Highly Validated Target

- KCNQ2 dampens neuronal hyper-excitability
- K+ channels have important inhibitory control over neuronal firing in the CNS
- Repolarize membranes to end the action potential
- K+ channel opener (enhancer) would decrease hyper-excitability in the brain

*M-Current Gradient Correlates with Disease Severity*
# Ezogabine and KCNQ2-DEE Experience

**KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE) is a severe neurodevelopmental disorder caused by dominant negative missense mutations in the KCNQ2 gene.**

<table>
<thead>
<tr>
<th>Case Study of KCNQ2-DEE Patients</th>
<th>Medical Record Review/Parent Interviews</th>
</tr>
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<tbody>
<tr>
<td><em>Millichap 2016</em></td>
<td><em>Olson 2017 (8 Families)</em></td>
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Ezogabine associated with improvements in seizures and/or development in:

- 3 of the 4 infants treated before 6 months old were seizure free or occasional seizures <1/week
- Improvement in seizures and/or development in 3 of the 4 patients treated before 6 months of age, and in 2 of the 7 patients treated later
- No serious adverse effects

Interviews/medical record review of KCNQ2-DEE patients prescribed ezogabine:

- Sustained improvement in seizure frequency in 5 of the 6 children with at least weekly seizures
- Improvements in development or cognition in all 8 children
- Urinary retention/hesitation in 3 patients, but overall well tolerated

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**Case Studies Suggest XEN496 May Be Efficacious in this Often Refractory Disease**


New, Proprietary, Pediatric-Friendly Formulation of XEN496

- XEN496 is a granule formulation, packaged as single-dose sprinkle capsules
  - Sprinkle capsules containing different weights of XEN496 will be manufactured based on patient’s weight/targeted drug level
  - Parents/caregivers open the capsules and disperse the granules into the chosen semi-solid or liquid food “carrier”
- Standard in vitro testing has shown that XEN496 acts as an “immediate-release” drug product
- PK study in 24 adult healthy volunteers is complete
  - 400 mg dose in fed or fasted states
  - XEN496’s absorption and elimination curves comparable to historical PK data for IR ezogabine tablets
  - Results support planned XEN496 Phase 3 trial in KCNQ2-DEE

From a PK perspective, no dose adjustments arising from differences in formulation are anticipated for the upcoming efficacy study in KCNQ2-DEE
Xenon’s Strategic Alliances

Behind the Seizure® Collaboration with Invitae, BioMarin, Xenon & Stoke

- Offers no-cost testing to any child < 8 years with an unprovoked seizure
- Launched Feb 2019, 190+ gene panel
- >320 institutions have participated
- Support patient ID for clinical studies
- ~150 positive tests to date
- ~3-4% of 0-2 year old children tested

- Working closely on Study design and feasibility
- Joining KOL meetings
- Supported patient surveys
- Involved in regulatory filings
- Funding a multicenter natural history study
Xenon-KCNQ2 Cure Alliance Survey Focus on Ezogabine

- 30 question survey, conducted by Xenon in collaboration KCNQ2 Cure Alliance Foundation
  - 7 Patients had access to ezogabine, one early in disease course
  - No discontinuations due to adverse effects

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Did you see any improvements in your child’s seizures, behaviour or development while they were taking ezogabine? ALL SEVEN RESPONDENTS ANSWERED “YES”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data available</td>
<td>“Cognitive improvements documented [by] therapists who did not know the child was on Potiga and [by] parent observation.”</td>
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<tr>
<td>Location (n)</td>
<td>“Started at 3 months old, achieved seizure freedom around 5 months old for approximately 6 months when infantile spasms started.”</td>
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<tr>
<td>Location (n) USA (31) – Canada (5) – UK (7) – Australia (7)</td>
<td>“Child was not having seizures, but starting Potiga coincided with improvements in EEG and attention/awareness.”</td>
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<tr>
<td>Patient age n (%) Younger than 4 years - 18 (36%)</td>
<td>“Seizure control and developmental gains - smiling, eating by mouth.”</td>
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<tr>
<td>Patient age n (%) Older than 4 years – 32 (64%)</td>
<td>“We had full seizure control lasting months and only saw seizures with fevers and illness. He was showing gains of function moving his limbs more and was more aware of his surroundings.”</td>
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<tr>
<td>Age of seizures onset after birth Day 0 = 26% - Day 1 = 40% - Day 2 – 24% - Day 3-5 = 10%</td>
<td>“Alertness, better development, EEG improved.”</td>
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<tr>
<td>Initial seizure frequency &gt;10 seizures / day = 63%</td>
<td>“His seizures immediately decreased in frequency and he stopped having longer seizures about 2 months after he started.”</td>
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<tr>
<td>Initial seizure frequency 2-10 seizures / day = 35%</td>
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<tr>
<td>Initial seizure frequency 1 seizure / day = 2%</td>
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<tr>
<td>Current seizure frequency 28% had seizures over past 30 days</td>
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<tr>
<td>Current seizure frequency 38% had seizures over past 90 days</td>
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<tr>
<td>Current seizure frequency 46% had seizures over past 180 days</td>
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Program Status

• FDA has indicated it is acceptable for Xenon to study XEN496 in infants and children up to 4 years of age with KCNQ2-DEE with appropriate safety monitoring
  • A single small pivotal trial may be considered adequate to demonstrate efficacy in KCNQ2-DEE

• Safety monitoring plans include long-term follow up monitoring for potential bladder or ocular side effects

• CRO selected for phase 3; site selection is in progress

NEXT STEPS

• Initiate Phase 3 clinical trial in 2020*
  • Randomized, double-blind, placebo-controlled study
    • Anticipated primary endpoint: median % change in seizure frequency from baseline compared to treatment period of active versus placebo
    • ~40 KCNQ2-DEE patients (infants up to six years old)

*Guidance is dependent upon the ability to initiate clinical sites and patient enrollment given the ongoing COVID-19 pandemic.
XEN1101 “Next-Gen” KCNQ2 Modulator

• Same mechanism of action as ezogabine, but with substantial improvements
  • More potent in vitro and in vivo
  • Improved PK
    • Once daily dosing and predicted better tolerability
• No predicted pigmentation liability
  • Does not form pigmented dimers
• Modulates cortical activity in healthy volunteers (TMS)
  • Within predicted efficacious exposures
• Well tolerated in Phase 1 studies

Proven ‘Mechanism of Action’ in Adult Epilepsy (Ezogabine)
XEN1101: Anti-Seizure Activity vs Ezogabine

- Maximal Electroshock Stimulus (MES) using 60 Hz bipolar stimulus with CF-1 mice
- Oral dosing, plasma concentration at time of efficacy measure.
- Data binned by [plasma]
- XEN1101 16-fold more potent than ezogabine (retigabine)
- 40% seizure reduction in humans (placebo, 16%) with plasma concentration of 3 μM retigabine (Gunthorpe, 2012)
Ezogabine Dimerization

- Ezogabine can form a number of dimeric species, including highly-coloured phenazinium-type dimers which have been implicated in the pigmentary abnormalities observed with long-term retigabine exposure.\(^{(1)}\)

![Ezogabine](image1.png)

- Ezogabine has a secondary aniline function, which is key to forming phenazinium-type dimers.
- XEN1101 instead has a tertiary aniline at the corresponding position.
- This key structural difference prevents XEN1101 from forming analogous dimers, as this would require a nitrogen atom with five chemical bonds.

![Ezogabine Phenazinium-Type Dimer](image2.png)

- This dimerization is an oxidative process.
- Treatment of ezogabine solutions with hydrogen peroxide leads to the characteristic purple colour of the phenazinium-type dimer forming within minutes.
- No such colour change is observed with solutions of XEN1101, even after several days.

Reducing Cortical Excitability: TMS Results

**TMS-EMG**

**Resting Motor Threshold**

- XEN1101 (20mg)
- Placebo
- XEN1101 Plasma level

* p<0.05
** p<0.01

**XEN1101 Concentration (ng/mL)**

- XEN1101 (20mg)
- Placebo
- XEN1101 Plasma level

**TMS-EEG**

**Global Mean Field Power (GMFP)**

- Pre
- XEN1101 20 mg
XEN1101: Phase 2b “X-TOLE” Clinical Trial Underway

- Phase 2b clinical trial is being conducted at approximately 90 sites in Europe and North America
Xenon has two potassium channel modulators for the treatment of epilepsy in late clinical development:

- **XEN496**: Initiation of Phase 3 clinical trial in pediatric KCNQ2-DEE anticipated in 2020*
- **XEN1101**: Phase 2b X-TOLE Study in adult focal seizures ongoing in Canada, U.S. and Europe
  - Top-line results anticipated in 1H:2021*
  - Planning indication expansion for XEN1101

*Guidance given is dependent upon patient enrollment rates and/or the ability to initiate clinical sites given the ongoing COVID-19 pandemic.

**Special thanks to:**
- KCNQ2 patients and families
- KCNQ2 Cure Alliance and other advocacy groups
- Expert physicians
- Xenon Pharmaceuticals Team