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An Online Survey of Caregivers of Patients with KCNQ2 Developmental & Epileptic Encephalopathy (KCNQ2-DEE): Focus on Ezogabine

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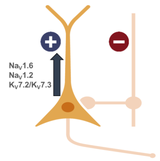
Informational Poster Prepared by Xenon Pharmaceuticals Inc.

BACKGROUND

Seeking Novel Disease Modifying Medicines for Developmental and Epileptic Encephalopathies

- Caused by single gene *de novo* mutations in voltage gated ion channels
- Severe phenotypes characterized by frequent refractory seizures, severe developmental delays, autistic features, motor disabilities, and increased SUDEP risk
- Selective ion channel modulators may directly target disease causal gene, with potential to treat epileptogenesis and improve long term outcomes

Mutation	EIEE	Drug Strategy
Partial GOF $Na_V1.6$	EIEE13	Selective inhibition $Na_V1.6$
Partial GOF $Na_V1.2$	EIEE11	Selective inhibition $Na_V1.2$
Partial LOF $K_V7.2$	EIEE7	Selective opener $K_V7.2/7.3$ tetramers
Partial LOF $K_V7.3$	Unassigned	Selective opener $K_V7.2/7.3$ tetramers
Partial LOF $Na_V1.1$	EIEE6	Selective opener $Na_V1.1$



About KCNQ2-DEE

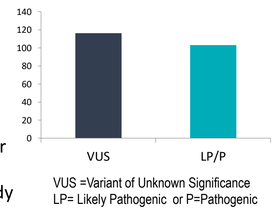
- Severe neurodevelopmental disorder caused by dominant negative missense mutations in the KCNQ2 causing significant loss of $K_V7.2$ mediated potassium current

> **"Our hope is that XEN496 could represent a genetically targeted treatment that improves the lives of children living with this debilitating disease."**
> Jim Johnson, President, KCNQ2 Cure Alliance

- Presents during first week of life
  - Frequent daily refractory tonic seizures, status common
  - Most often associated with severe developmental delay
  - Present with language/social impairment, outbursts, repetitive and self injurious behaviours
  - Motor disabilities
  - Seizures wane by 4 years of age, can occur in clusters thereafter
- Inherited autosomal dominant truncation mutations cause Benign Familial Neonatal Seizures
  - Often presents with multiple seizures without overt developmental delay

KCNQ2 Epilepsy Panel Screening

- Scottish national cohort study (Symonds et al., Brain 2019) birth rate of pathogenic KCNQ2 variants 1/17,000
  - Dravet Syndrome 1/12,200 births
- 9413 Invitae epilepsy panel tests (Truty et al., Epilepsia 2019)
  - 219 subjects with KCNQ2 genotype (116 VUS; 103 LP/P)
- Further characterization of VUS likely to identify many more variants as LP/P
  - Approaching Dravet Syndrome birth rates?
  - Approximately half of KCNQ2 variants cause DEE
  - 40% of BFNS families reported with delayed psychomotor development (Steinlein et al., Epilepsy Research 2007)
- Separate screen identified 159/8565 tests as pathogenic (Lindy et al., Epilepsia, 2018)
  - Dravet Syndrome 322/8565 tests



VUS =Variant of Unknown Significance
LP= Likely Pathogenic or P=Pathogenic

SURVEY METHODS AND RESULTS

- We performed a caregiver survey to obtain additional phenotypic information regarding the seizure history of KCNQ2-DEE disease as well as Anti-Seizure Medication (ASM) use, with a focus on ezogabine
  - Demographics, comorbidities, seizure onset and frequency, ASM use, and history of ezogabine use
- 30 question survey, conducted by Xenon in collaboration with The KCNQ2 Cure Alliance for KCNQ2 syndrome
- Implemented by M3 Global research and reviewed and approved by Veritas Independent Review Board
- Families recruited by targeted email outreach, social media campaign and an educational webinar
- Survey responses collected over a three-week period for each syndrome in late 2019

Preliminary Demographics and Seizure Burden of Survey Patients

Demographics	
Data available	67 complete responses for analysis; Exclusions as follows: • 8 non-English speaking origin • 6 known GOF • 3 atypical phenotype
Locations (n)	USA (31); Canada (5); UK (7); Australia (7)
Patient Age, n (%)	18 (36%) younger than 4 years 32 (64%) older than 4 years
Age of seizure onset after birth	Day 0=26%. Day 1=40%, Day 2=24% Days 3-5=10%
Initial seizure frequency (n=49)	63% had more than 10 seizures per day 35% had between 2-10 seizures per day 2% had 1 seizure per day
Current seizure frequency (n=50)	28% had seizures over past 30 days 38% had seizures over past 90 days 46% had seizures over past 180 days

- 7 patients had access to ezogabine*; one early in disease course
  - All on ezogabine for years: 5 for two years, 1 each for 3 and 5 years.
  - Total daily dose (in TID divisions) 105, 150 , 175, 187.5, 225 mg/day; 2 respondents did not remember dose.
- 1 had drug stopped by neurologists due to FDA warnings; 5 tapered off when drug no longer available; 1 still taking as of survey response
- No discontinuations due to adverse effects

* Patients used ezogabine and Potiga interchangeably in their responses

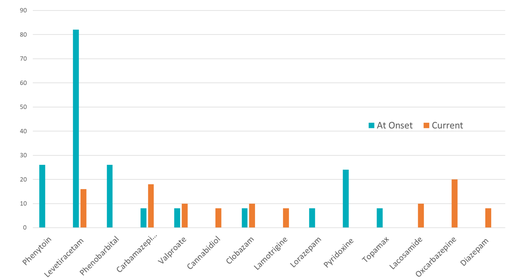
Caregiver Narratives: Seizure Control and Quality of Life

Which medication or combination of medications or treatments (current or previous) do you consider to be the best for your child's seizures and why?	Which medication or combination of medications or treatments (current or previous) do you consider to be the best for your child's overall quality of life and why?
"Ezogabine + Trileptol. Ezogabine may help with developmental defects."	"Potiga and Trileptal have been the best at controlling his seizures and Potiga seem to make him feel much better so that was the best at improving his quality of life."
"Ezogabine with onfi was the best [seizure] control we ever had."	"We thought Potiga was the best medication for cognitive improvements. Potiga was never taken for seizure control as seizures had stopped and EEG was normal."
"Potiga was a miracle drug in my opinion for his longer seizures which stopped about 2 months after he started Potiga. We've also noticed good improvements with Trileptal and Depakote which he is currently taking."	"Ezogabine And onfi. While on the combo he was trying to stand on his own which was amazing!"
	"Our children tolerated Potiga well and it seemed to improve EEG and awareness/alertness."

Caregiver Narratives: Ezogabine-Specific Effects

Did you see any improvements in your child's seizures, behaviour or development while they were taking ezogabine? ALL SEVEN RESPONDENTS ANSWERED "YES"
"Cognitive improvements documented [by] therapists who did not know the child was on Potiga and [by] parent observation."
"Started at 3 months old, achieved seizure freedom around 5 months old for approximately 6 months when infantile spasms started."
"Child was not having seizures, but starting Potiga coincided with improvements in EEG and attention/awareness."
"Seizure control and developmental gains - smiling, eating by mouth."
"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."
"Alertness, better development, EEG improved."
"His seizures immediately decreased in frequency and he stopped having longer seizures about 2 months after he started."

Current ASM Use in KCNQ2-DEE (reported by ≥4 respondents)



Mean number of ASMs used at onset = 2.6
Mean number of ASMs tried and stopped before current regimen = 4
Mean number of current ASMs used = 1.6

Behind the Seizure™ Program

- Behind the Seizure™ program is a collaboration with Invitae, Xenon, BioMarin and Stoke that offers no-cost testing to all children with seizures up to 60 months of age
- 180+ gene panel launched in February 2019
- Access to genetic testing allows identifying cause of seizures and implementation of specific treatments in many cases
- Supports patient ID for clinical studies
- Builds physician data base

CONCLUSIONS

- Survey was informative regarding clinical trial design and improved knowledge of disease course from a patient/family experience
- Survey identified significant proportion of patients seizing over the of age 4 years
- Caregivers reported children took ezogabine for both seizure control and other reasons and reported benefits for both
- Ezogabine was reported to be well tolerated by survey respondents
- Study limitations include retrospective report with possible memory bias as well as possible overlap with published cases

Next Steps:

- Phase 3 protocol being finalized with input from KOLs
- Expect to initiate Phase 3 pivotal trial in 2020

XENON