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

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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 age of 4 years
- Caregivers of 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 IXDs
- Expect to initiate Phase 3 pivotal trial in 2020

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

Survey Methods and Results

- We performed a caregiver survey to obtain additional phenotypic information regarding the history of KCNQ2 DEE disease as well as Anti-Seizure Medication (ASM) use, with a focus on ezogabine
- Demographics, comorbidities, seizure onset with 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
  - 4 known GOF
  - 3 atypical phenotype

Locations (n)

- USA (n=31); Canada (n=5); UK (n=1); Australia (n=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 (D. 1-48), Day 2-24 (D. 3.5-109)
- Initial seizure frequency (n=49)
  - 63% had >10 seizures 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

Survey narratives

- We had full seizure control lasting months and only saw seizures with fevers and illness. He was showing gains of function
- Our children tolerated Potiga well and it seemed to improve EEG and attention/awareness.
- Child was not having seizures, but starting Potiga coincided with improvements in EEG and attention/awareness.
- Cognitive improvements documented by therapists who did not know the child was on Potiga and by parent
- Seizures wane by 4 years of age, can occur in clusters thereafter
- Seizures present during first week of life
- Infants inherited autonomic 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 1/37,000
- Dravet Syndrome 1/12,200 births
- 941 Invitae epilepsy panel tests (Trutty et al., Epilepsia 2019)
- 219 subjects with KCNQ2 genotyped (116 VUS; 103 LP/P)
- Further characterization of VUS likely to identify many more variants as LP/P
- Approach: Dravet Syndrome birth rate?
- Approximately half of KCNQ2 variants cause DEE
- 40% of BNFS 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

KCNQ2 Epilepsy Panel Screening

- 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 division) 100, 150, 375, 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
- Still taking as of survey
- No adverse effects due to adverse effects

Caregiver Narratives: Seizure Control and Quality of Life

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