XENON

EILAT XVI Conference: New Antiepileptic Drugs and Devices

An Overview of XEN1101 and XEN496

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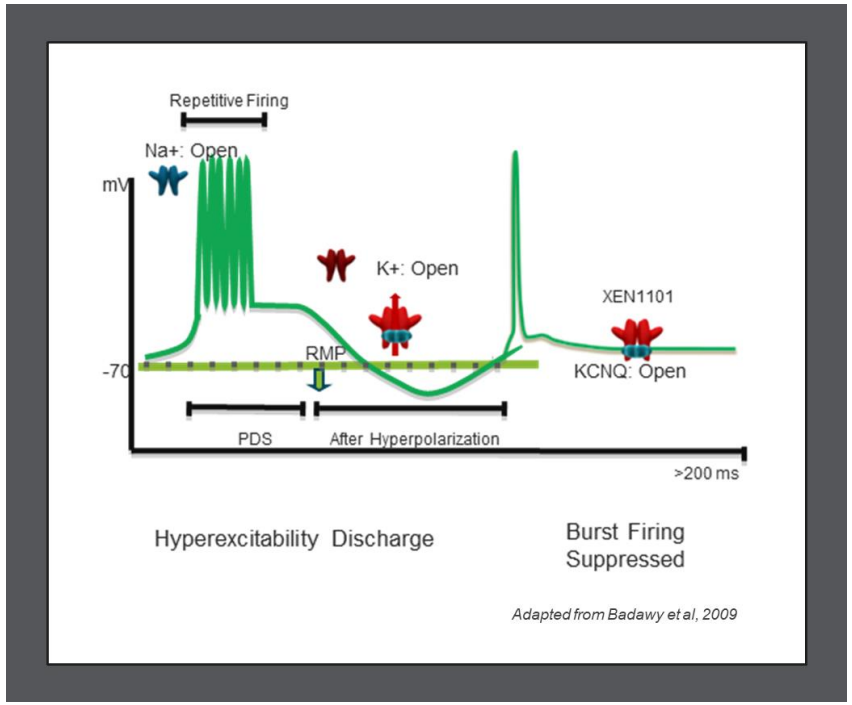
Xenon Pharmaceuticals: Ion Channel, Neurology-Focused Pipeline

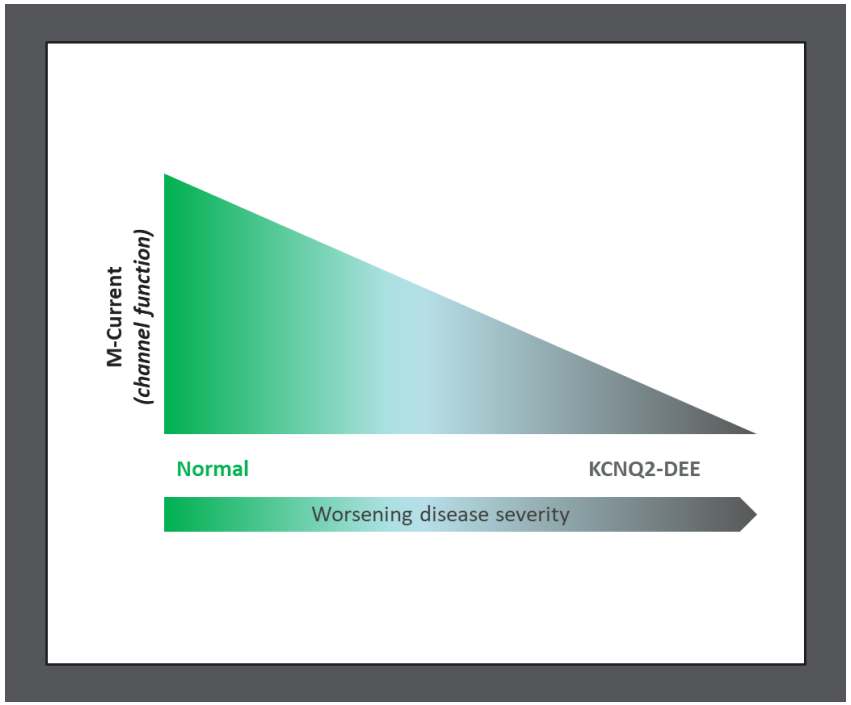
Therapeutic Program *Indication*	Pre-clinical	Phase 1	Phase 2	Phase 3
XEN496 (Potassium Channel Opener) *Orphan Pediatric Epilepsy: EPIK Clinical Trial*				
XEN1101 (Potassium Channel Opener) *Adult Focal Epilepsy: X-TOLE Clinical Trial*				
XEN1101 (Potassium Channel Opener) *Major Depressive Disorder (MDD): X-NOVA Clinical Trial*				
XEN1101* (Potassium Channel Opener) *MDD: Mount Sinai Collaboration*				
Ion Channel Modulators *Orphan Channelopathies*				
NBI-921352 (XEN901) *Rare Pediatric Epilepsy: SCN8A-DEE: Neurocrine Biosciences*			NEUROCRINE BIOSCIENCES	
NBI-921352 (XEN901) *Focal-Onset Seizures in Adults: Neurocrine Biosciences*			NEUROCRINE BIOSCIENCES	
PCRX301 (Topical $Na_V1.7$ Inhibitor) *Post-operative Pain: Pacira BioSciences*		PACIRA BIOSCIENCES, INC.		

*Investigator Sponsored Phase 2 Proof-of-Concept Study

The KCNQ2 Potassium Channel

- 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



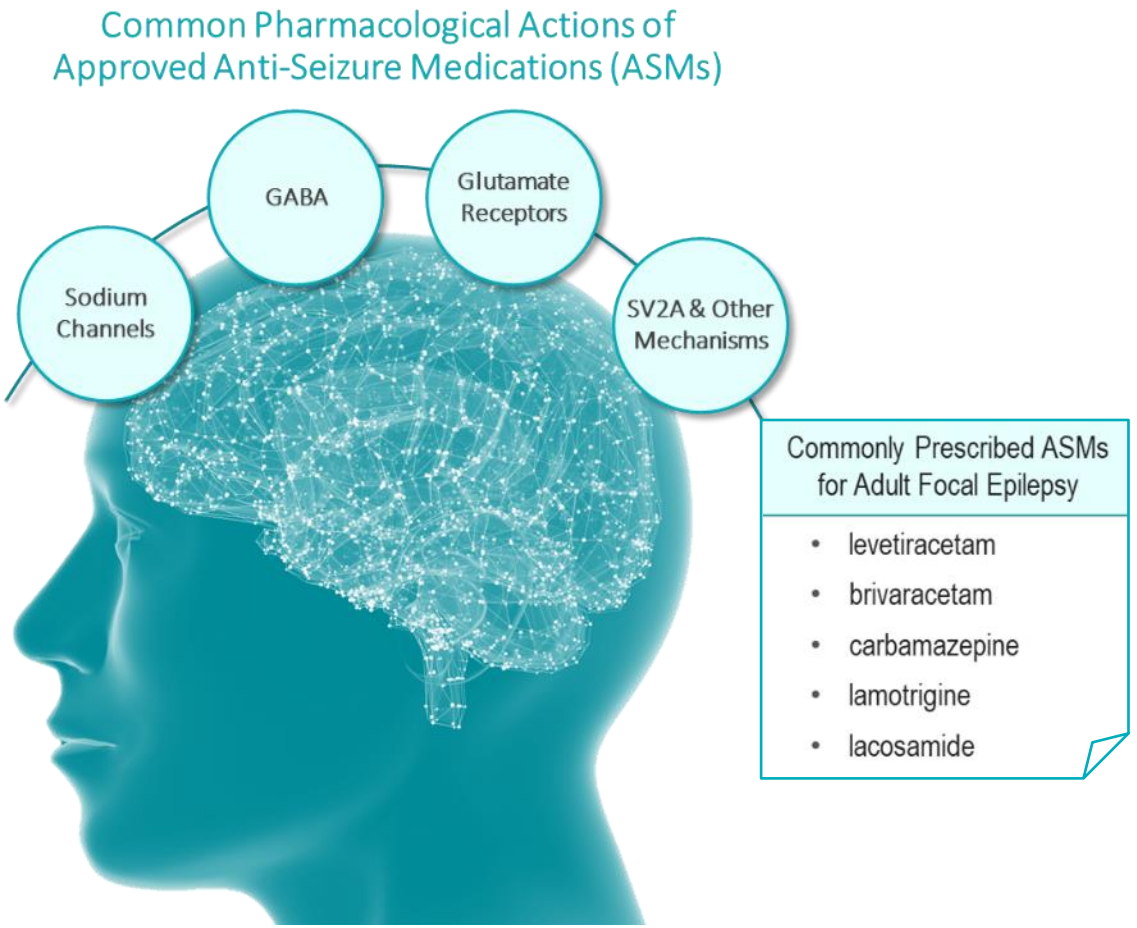


XEN1101

A NEXT-GEN KV7 CHANNEL OPENER

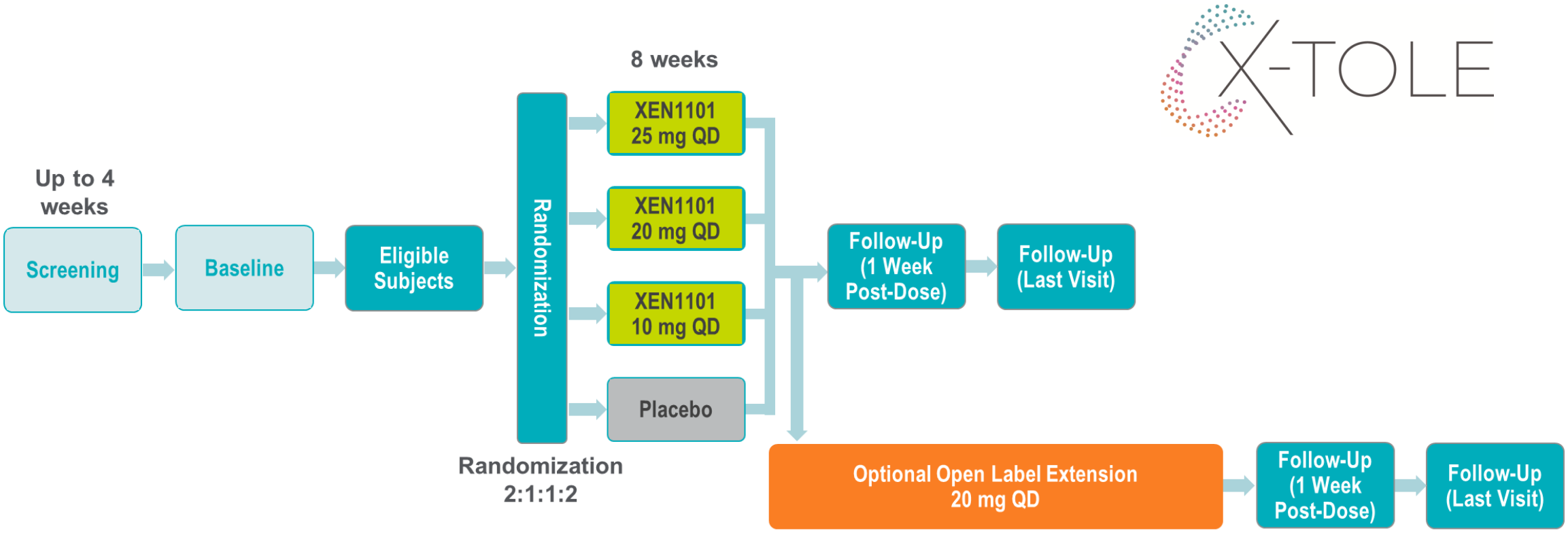
XEN1101 Next-Gen K_V7 Channel Opener

- Only-in-class K_V7 potassium channel modulator to treat adult focal seizures
- Novel MOA for rational polypharmacy
- Designed to address limitations of first-gen K_V7 modulator, ezogabine
  - Higher *in vitro* and *in vivo* potency
  - PK TID → QD
  - Lacks the chemical properties that could form pigmented dimers
- Potential to treat common comorbidities, such as depression



Addressing previous limitations, enhancing the K_V7 opportunity

“X-TOLE” Study Schema



Demographics and Baseline Characteristics (Safety Population)

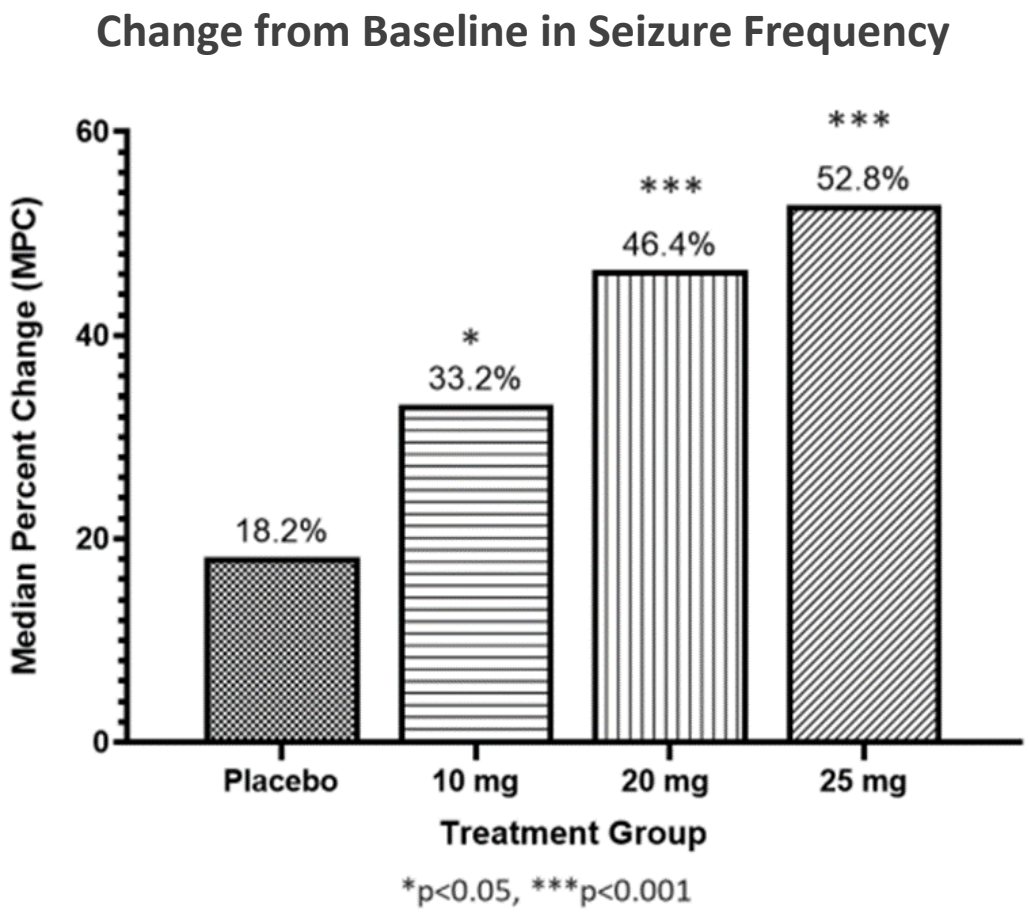
- Subjects had an average age of 40.8 ± 13.3 years
- 8.9%, 40.3%, or 50.8% of the subjects were on and continued taking 1, 2, or 3 stable background ASMs, respectively, throughout the study
- Subjects failed a median of 6 previous ASMs prior to study entry
- Median baseline seizure frequency across the study groups was approximately 13.5 per month

	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=114)	TOTAL (N=325)
Age in years, Mean (SD)	**42.9 (13.7)**	**40.0 (12.1)**	**41.7 (13.6)**	**38.7 (13.1)**	**40.8 (13.3)**
Age at study entry category					
≥ 65, n (%)	**5 (4.4)**	**2 (4.3)**	**4 (7.8)**	**1 (0.9)**	**12 (3.7)**
< 65, n (%)	**109 (95.6)**	**44 (95.7)**	**47 (92.2)**	**113 (99.1)**	**313 (96.3)**
Gender					
Female, n (%)	**61 (53.5)**	**27 (58.7)**	**26 (51.0)**	**54 (47.4)**	**168 (51.7)**
Male, n (%)	**53 (46.5)**	**19 (41.3)**	**25 (49.0)**	**60 (52.6)**	**157 (48.3)**
Region					
Europe, n (%)	**67 (58.8)**	**31 (67.4)**	**32 (62.7)**	**68 (59.6)**	**198 (60.9)**
North America, n (%)	**47 (41.2)**	**15 (32.6)**	**19 (37.3)**	**46 (40.4)**	**127 (39.1)**
Background ASM Use					
1, n (%)	**12 (10.5)**	**4 (8.7)**	**2 (3.9)**	**11 (9.6)**	**29 (8.9)**
2, n (%)	**46 (40.4)**	**18 (39.1)**	**20 (39.2)**	**47 (41.2)**	**131 (40.3)**
3, n (%)	**56 (49.1)**	**24 (52.2)**	**29 (56.9)**	**56 (49.1)**	**165 (50.8)**
Number of Pre-study ASMs failed					
Median [Q1, Q3]	**6.0 [3.0, 8.0]**	**5.0 [4.0, 9.0]**	**6.0 [4.0, 9.0]**	**5.5 [3.0, 9.0]**	**6.0 [4.0, 9.0]**

Subjects were randomized for an 8- week double-blind phase to placebo or one of three active treatment groups in a 2:1:1:2 ratio

Arms well balanced and representative of a difficult to treat adult FOS patient population

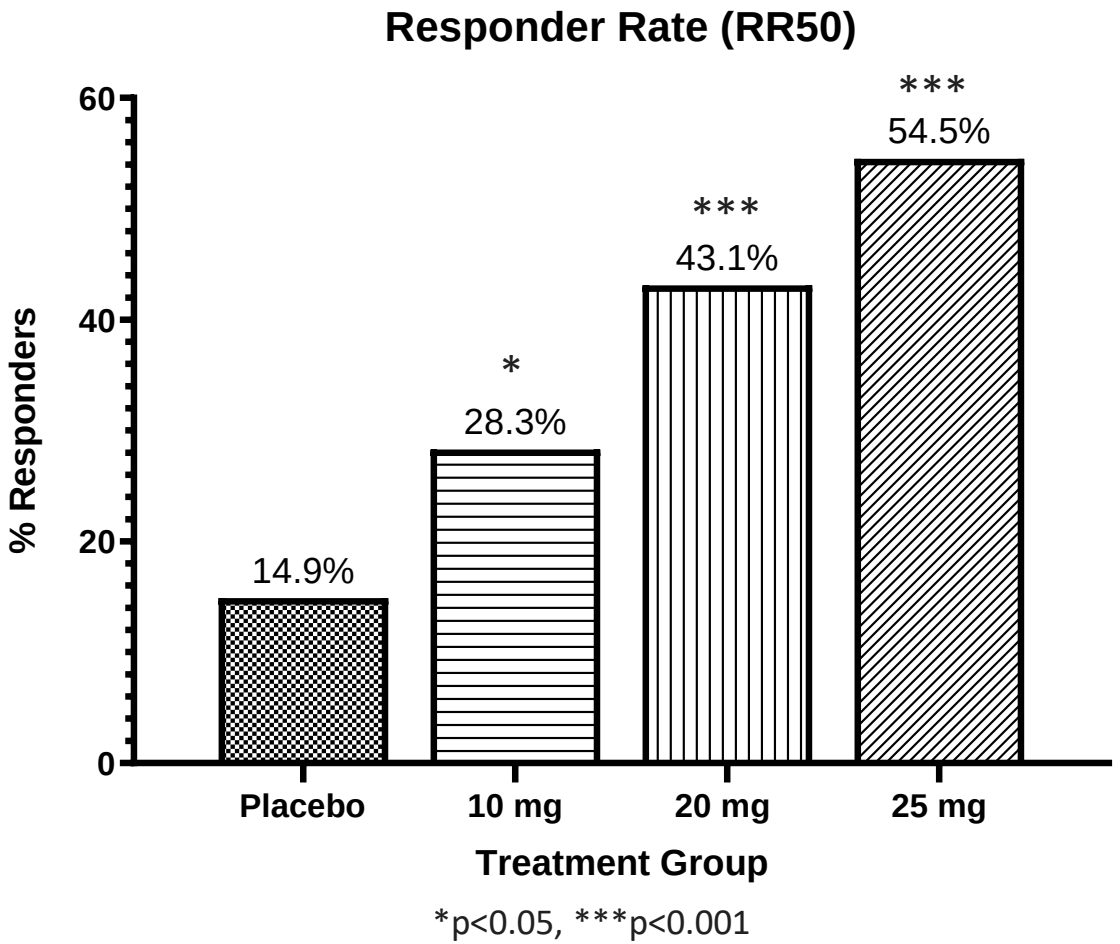
Efficacy Results: MPC from Baseline



	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=112)
Monthly Seizure Frequency in Baseline				
Median [Q1,Q3]	**13.4 [8.0, 30.1]**	**17.4 [8.0, 55.6]**	**14.5 [7.5, 36.4]**	**12.8 [8.4, 24.6]**
Monthly Seizure Frequency in the DBP				
Median [Q1, Q3]	**10.5 [5.4, 25.1]**	**10.9 [3.5, 41.2]**	**5.2 [3.0, 24.9]**	**5.3 [2.5, 13.6]**
Percent Change from Baseline to the DBP				
Median [Q1, Q3]	**-18.2 [-37.3, 7.0]**	**-33.2 [-61.8, 0.0]**	**-46.4 [-76.7, -14.0]**	**-52.8 [-80.4, -16.9]**
P-value from ranked ANCOVA model				
P-value for pairwise comparison vs. placebo (2-sided)		**0.035**	**<.001**	**<.001**
Primary Dose Response test p-value	**<.001**			

Highly significant and dose-dependent reduction in seizures

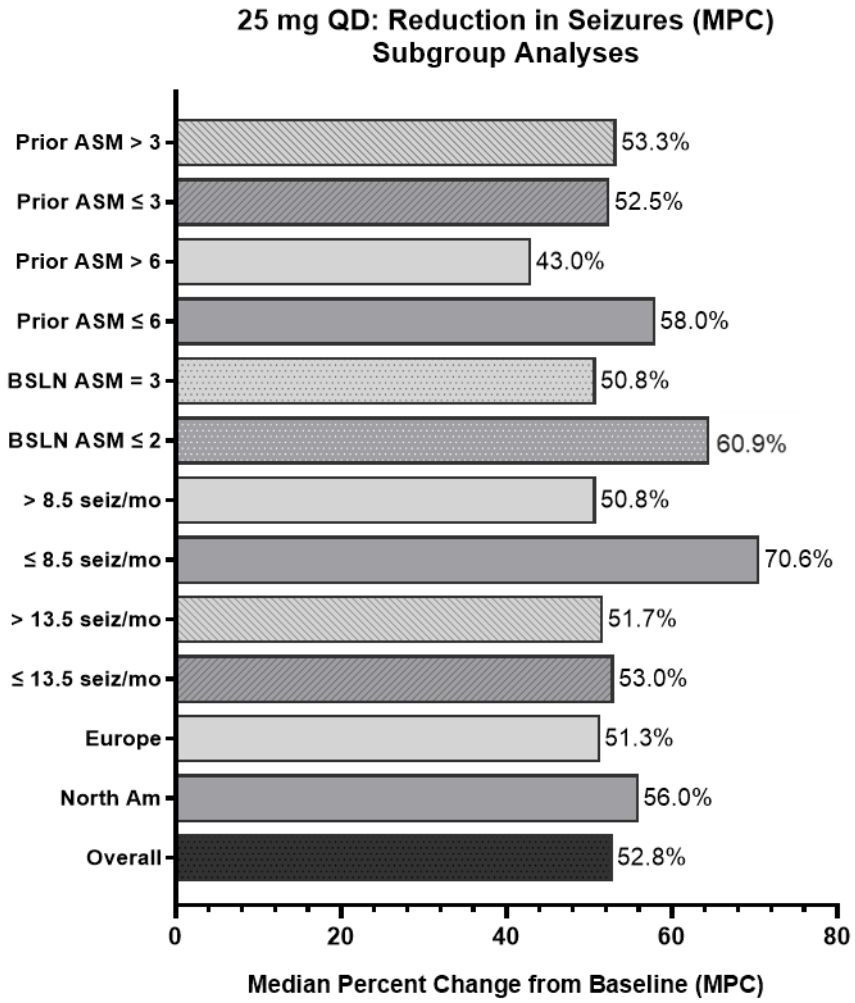
Response Rates and CGI-C/PGI-C
(Secondary Endpoints)

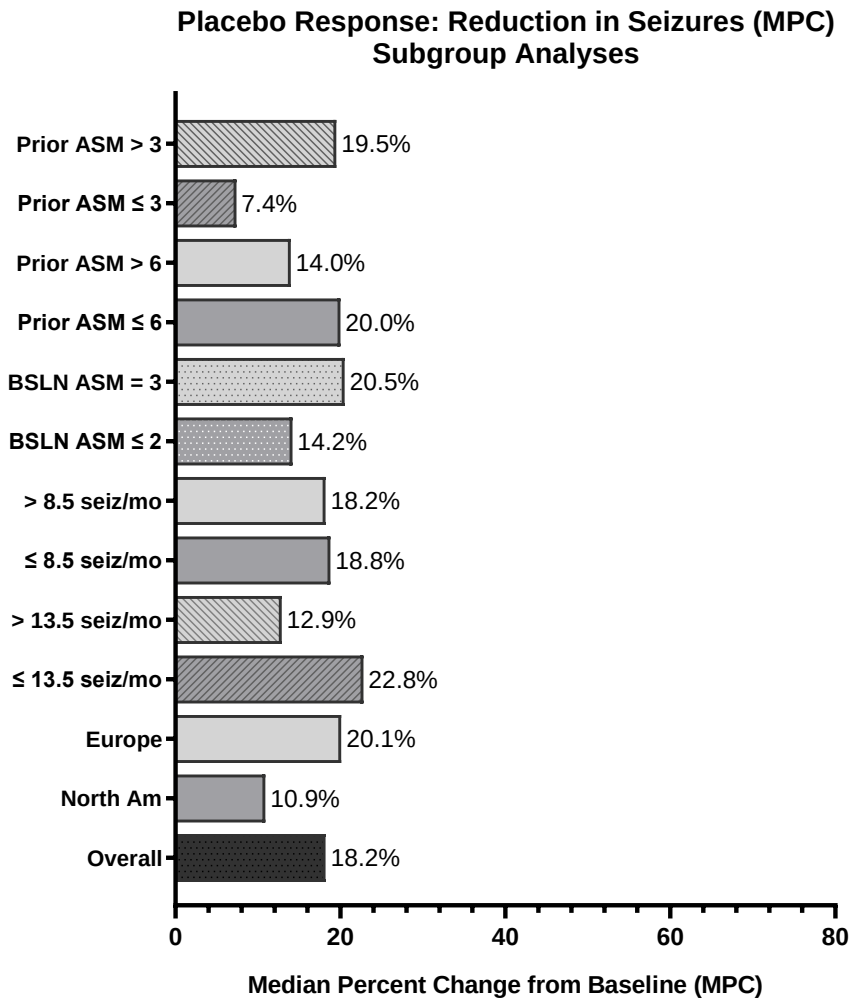


	XEN1101 25 mg (N=112)	Placebo (N=114)
CGI-C (Portion of Patients Much Improved or Very Much Improved)	46.4% (p<0.001)	22.8%
PGI-C (Portion of Patients Much Improved or Very Much Improved)	42.9% (p=0.001)	21.9%

Dose-dependent increase in the number of responders with >50% reduction in FOS

Subgroup Analyses of Seizure Reduction





Increased seizure reduction in patients with less disease severity

Summary of All TEAEs* in the DBP
(Safety Population)

Subjects with n(%)	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=114)	XEN1101 Any dose (N=211)
At least one TEAE	71 (62.3)	31 (67.4)	35 (68.6)	97 (85.1)	163 (77.3)
At least one serious TEAE	3 (2.6)	2 (4.3)	2 (3.9)	3 (2.6)	7 (3.3)
At least one TEAE leading to permanent treatment discontinuation	4 (3.5)	1 (2.2)	7 (13.7)	18 (15.8)	26 (12.3)
At least one serious TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*TEAE: Treatment Emergent Adverse Event i.e. AEs started or worsened in Double Blind Phase including 6 weeks of follow-up

- The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), gait disturbance (1.9%)

TEAE profile consistent with other ASMs, with majority of TEAEs within the CNS

Most Common TEAEs ≥5% in All Treatment Arms

System Organ Class/ Preferred Term	Placebo (N=114) n (%)	XEN1101 10mg (N=46) n (%)	XEN1101 20mg (N=51) n (%)	XEN1101 25mg (N=114) n (%)	XEN1101 Any dose (N=211) n (%)
Overall	**71 (62.3)**	**31 (67.4)**	**35 (68.6)**	**97 (85.1)**	**163 (77.3)**
Nervous System Disorders	**35 (30.7)**	**20 (43.5)**	**28 (54.9)**	**83 (72.8)**	**131 (62.1)**
Dizziness	8 (7.0)	3 (6.5)	13 (25.5)	36 (31.6)	52 (24.6)
Somnolence	8 (7.0)	5 (10.9)	11 (21.6)	17 (14.9)	33 (15.6)
Headache	9 (7.9)	6 (13.0)	6 (11.8)	9 (7.9)	21 (10.0)
Balance disorder	2 (1.8)	2 (4.3)	4 (7.8)	13 (11.4)	19 (9.0)
Tremor	2 (1.8)	3 (6.5)	3 (5.9)	12 (10.5)	18 (8.5)
Aphasia	1 (0.9)	1 (2.2)	1 (2.0)	8 (7.0)	10 (4.7)
Ataxia	1 (0.9)	3 (6.5)	1 (2.0)	5 (4.4)	9 (4.3)
Dysarthria	0 (0.0)	1 (2.2)	0 (0.0)	8 (7.0)	9 (4.3)
Memory impairment	1 (0.9)	1 (2.2)	2 (3.9)	6 (5.3)	9 (4.3)
Disturbance in attention	1 (0.9)	0 (0.0)	3 (5.9)	5 (4.4)	8 (3.8)
Psychiatric Disorders	**18 (15.8)**	**7 (15.2)**	**13 (25.5)**	**31 (27.2)**	**51 (24.2)**
Confusional state	1 (0.9)	1 (2.2)	3 (5.9)	6 (5.3)	10 (4.7)
Anxiety	6 (5.3)	0 (0.0)	5 (9.8)	2 (1.8)	7 (3.3)
Hallucination	0 (0.0)	0 (0.0)	3 (5.9)	0 (0.0)	3 (1.4)
General Disorders and Administration Site Conditions	**12 (10.5)**	**10 (21.7)**	**9 (17.6)**	**30 (26.3)**	**49 (23.2)**
Fatigue	6 (5.3)	5 (10.9)	4 (7.8)	14 (12.3)	23 (10.9)
Gait disturbance	1 (0.9)	2 (4.3)	2 (3.9)	8 (7.0)	12 (5.7)
Gastrointestinal Disorders	**10 (8.8)**	**10 (21.7)**	**5 (9.8)**	**19 (16.7)**	**34 (16.1)**
Nausea	3 (2.6)	1 (2.2)	1 (2.0)	7 (6.1)	9 (4.3)
Constipation	1 (0.9)	2 (4.3)	3 (5.9)	3 (2.6)	8 (3.8)
Eye Disorders	**6 (5.3)**	**3 (6.5)**	**5 (9.8)**	**18 (15.8)**	**26 (12.3)**
Vision blurred	1 (0.9)	0 (0.0)	1 (2.0)	7 (6.1)	8 (3.8)
Infections and Infestations	**13 (11.4)**	**6 (13.0)**	**6 (11.8)**	**6 (5.3)**	**18 (8.5)**
Urinary tract infection	4 (3.5)	4 (8.7)	3 (5.9)	2 (1.8)	9 (4.3)

TEAE profile consistent with other ASMs, with majority of TEAEs attributed to CNS

Vital Signs and Other Safety Outcomes

- There was no cardiovascular signal of concern based on vital signs from resting or orthostatic tests
- There were no safety signals of concern from physical or neurologic exams
- No signals of concern from ECGs, safety labs or urinalysis
- There was no evidence of urinary retention based upon mean differences across treatment groups in the total or individual items of the American Urological Associations Symptoms Index

- Weight changes were different from placebo only at the highest dose:

Dose arm	Mean changes from baseline ± SD (in kg)	Number (%) of subjects with >7% change in body weight
Placebo	0.2 ± 2.4	3 (2.6%)
10 mg/day	0.6 ± 2.3	2 (4.3%)
20 mg/day	1.6 ± 2.2	2 (3.9%)
25 mg/day	1.9 ±2.9	15 (13.2%)*

*Based on change from mean of Screening (V1), Baseline (V2) and Randomization (V3) compared to end of DBP (V8/ET). If last record prior to treatment is used for Baseline, 7 (6.1%) subjects met threshold for increase. One subject had a decrease of >7%.

Summary of Safety and AE Profile

- XEN1101 was generally well-tolerated in this study with AEs consistent with other commonly prescribed ASMs
  - SAE incidence was low and balanced across groups; similar low SAE incidence (3.3%) as seen in placebo (2.6%) and no deaths in the study
  - The most common (>10%) TEAEs across all XEN1101 dose groups were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%)
  - The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), gait disturbance (1.9%)
  - Two AEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and both subjects remained on drug with no other changes or intervention
  - TEAEs of weight increase were reported in 1 (0.9%) subject on placebo, 1 (2.2%) subject at 10 mg, 2 (3.9%) subjects at 20 mg and in 3 (2.6%) subjects at 25 mg
    - More subjects experienced >7% change in body weight in the 25 mg treatment group compared to placebo
  - There were no cardiovascular signals of concern in ECG or vitals signs
  - There have been no TEAEs of pigmentary abnormalities reported during the double-blind phase of the study, or in preliminary analysis during the ongoing OLE to date

X-TOLE Study Conclusions

- XEN1101 showed dose-dependent, consistent, highly statistically significant and clinically meaningful seizure reduction in "difficult-to-treat" patient population
  - Heavily pre-treated patient population failed a median of 6 ASMs; 50.8% were on 3 background ASMs
- In addition, XEN1101 demonstrated increased efficacy in patients with less severe disease at baseline
- XEN1101 was generally well-tolerated in this study with AEs consistent with other commonly prescribed ASMs
- Based on the strong Phase 2b topline results from the X-TOLE study, Xenon has sought input from the U.S. FDA and other regulatory agencies prior to initiation of Phase 3 studies of XEN1101 this year

XEN496

A PHASE 3 PRECISION MEDICINE FOR KCNQ2-DEE

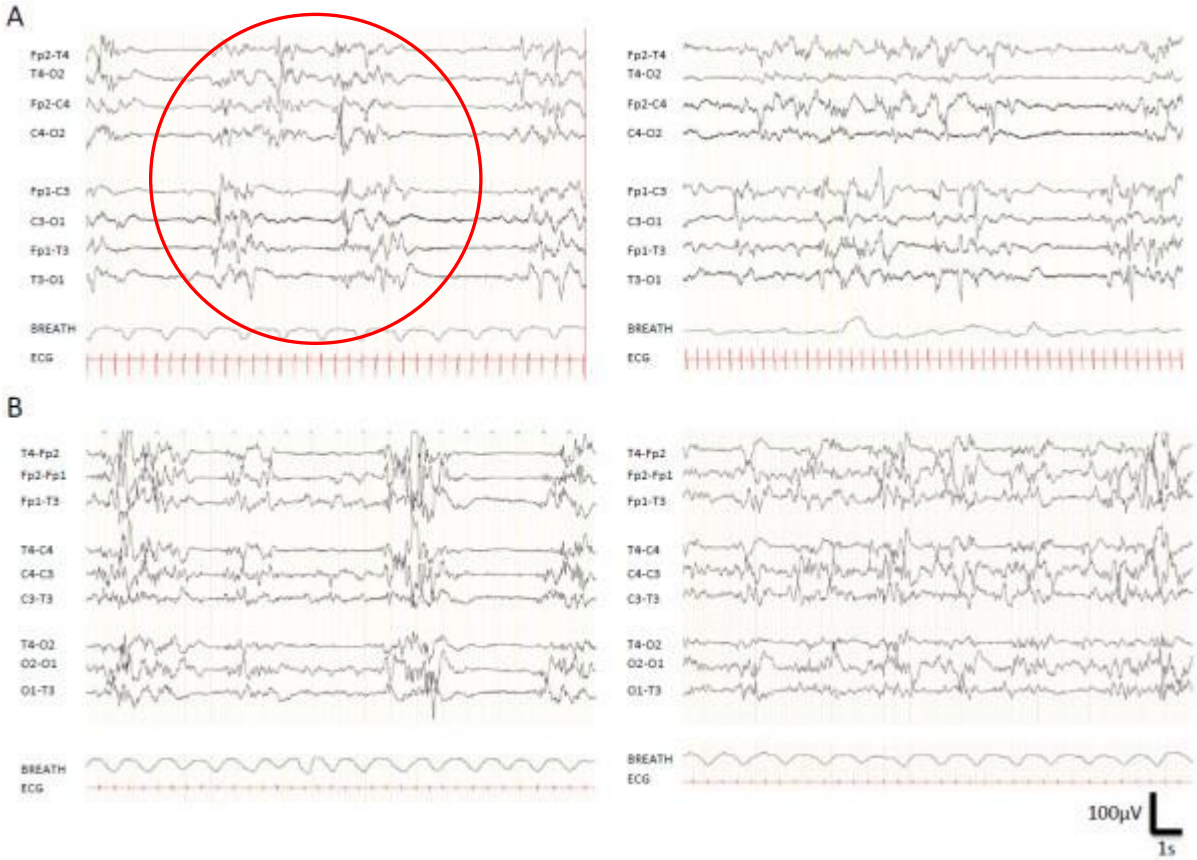
KCNQ2-Related Disorders

- The *KCNQ2* gene codes for a potassium (K^+) channel subunit ($K_V7.2$)
- Pathogenic variants in *KCNQ2* result in a spectrum of epileptic syndromes, which include:
  - Benign Familial Neonatal Epilepsy (BFNE) / Self-limited Familial Neonatal Epilepsy
    - Autosomal dominant and self-limiting: normal intellect, ready response to ASMs as neonate, and resolves with no sequelae including low incidence of seizures later in life
  - *KCNQ2* developmental and epileptic encephalopathy (KCNQ2-DEE) due to loss-of-function variants
    - Target disease for XEN496
    - Characterized by neonatal seizures, usually focal tonic, burst suppression on EEG initially and persistently abnormal, multidomain developmental arrest which may be severe
  - KCNQ2-DEE due to gain-of-function variants (rare)
    - Onset of seizures after neonatal period, non-epileptic myoclonus as neonate, infantile spasms, developmental delay

KCNQ2-DEE Disease Characteristics

- First described by Weckhuysen et al. in 2012
  - Differentiated the “developmental epileptic encephalopathy” from the self-limiting form of KCNQ2-associated familial neonatal seizures
  - Both forms have variants in *KCNQ2*; however, DEE variants confer a more severe dysfunction
- KCNQ2-DEE is characterized by:
  - Multiple, daily, refractory seizures presenting within the first week of life with a prominent tonic component and autonomic signs
  - The electroencephalogram (EEG) at onset of the disease shows a burst-suppression pattern later evolving into multifocal epileptiform activity
  - Mild to profound permanent intellectual disability

EEG in two neonates with KCNQ2-DEE

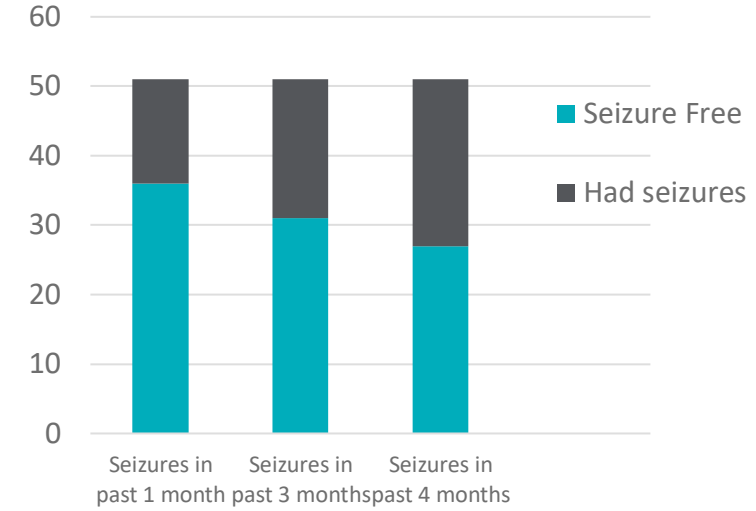


Understanding KCNQ2-DEE*

- **Onset**
  - Seizure onset was reported within the first 2 days of life for 90% of patients, and within the first 5 days of life for the remaining 10% of patients
- **Seizure type-described in recent publication**
  - Focal tonic seizures are characteristic
  - Comprise 80% of all seizures in case series
  - Are observable can be counted by caregiver observation
- **Course**
  - Patients may have an initial response to sodium-channel inhibitor antiseizure medications
  - Seizures decrease by approximately age 1-4 years
  - Several patients continue to have some seizures

*Informed by Xenon's survey of affected families through KCNQ2 Cure Alliance

Seizure Occurrence in KCNQ2-DEE Survey




Received: 23 June 2020 | Revised: 29 December 2020 | Accepted: 31 December 2020
DOI: 10.1002/epi4.12466
CRITICAL REVIEW
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Capturing seizures in clinical trials of antiseizure medications for *KCNQ2*-DEE

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KCNQ2-DEE Patients' Seizure Response to Ezogabine

- Case study use of ezogabine in the most refractory patients after multiple ASM failures
- Bias from overlapping subjects and gain-of-function variants removed from published data
- Physicians treated patients both for seizure control and/or for developmental outcomes
- 11/11 patients with reported seizures had a further response to ezogabine

Study Subject	Seizures Before Ezogabine	Seizure Response with Ezogabine	
OL #8	Daily	→	**Seizure free, then onset of spasms (controlled)**
OL #6	Daily	→	**Seizure free for 3 months then recurrence**
MI #12	50-60/day	→	**Less than 1 per week, with seizure free periods**
OL #1	Daily	→	**Weekly**
OL #5	Daily	→	**Less than monthly**
OL #7	Daily	→	**Seizure free**
OL #4	Several per week	→	**Less than monthly**
MI #16	2-3 daily clusters	→	**Less than 1 per day**
WE #M	Multiple daily	→	**"Strong" reduction in frequency to weekly**
MI #15	Not described	→	**Seizure free on high doses**
MI #22	Not described	→	**Improvement in seizures and EEG background**
OL #3	Seizure free	→	Seizure free (unchanged)
MI #11	Not described	→	Not described
MI #18	Seizure free	→	Seizure free (unchanged)
MI #14	Not described	→	No change (discontinued)
MI #3	Not described	→	No change
MI #9	Not described	→	No change

MI = Millichap et al. 2016; OL = Olson et al. 2017 AES; WE = Weckhuysen et al. 2013

KCNQ2-DEE Patients' Development Response to Ezogabine

- Bias from overlapping subjects and gain-of-function variants removed from published data
- Improvement in psychomotor development and alertness reported in 12/17 patients by the authors

Study Subject	Changes in Development with Ezogabine
OL #8	**Improved head control, visual tracking and vocalizations**
OL #6	**Improved grasp, motor skills (head control, rolling, sitting)**
MI #12	**Started to cry, hold head up, reach for objects, play with toys**
OL #1	**Improved head control, tone, vision, vocalizations, feeding**
OL #5	**Improved alertness**
OL #7	**Improved alertness**
OL #4	**Improved language, alertness/interaction and motor skills**
MI #16	**Increased alertness and tone**
WE #M	Not described
MI #15	**Improved responsiveness**
MI #22	**Improvement in development**
OL #3	**Rapid improvement in skills**
MI #11	**Improved development: alertness and interactions**
MI #18	No change
MI #14	No change (discontinued)
MI #3	No change
MI #9	No change

MI = Millichap et al. 2016; OL = Olson et al. 2017 AES; WE = Weckhuysen et al. 2013

XEN496: Potential Precision Medicine Approach for KCNQ2-DEE

- No drug has been specifically studied in and approved for KCNQ2-DEE
- Na^+ channel blockers reported to decrease seizure frequency in patients with KCNQ2-DEE with varying degrees of success, but several patients remain refractory, or have seizures return after a course of existing ASMs
- All have continued cognitive, developmental and motor impairments[1]
- There remains a high unmet medical need

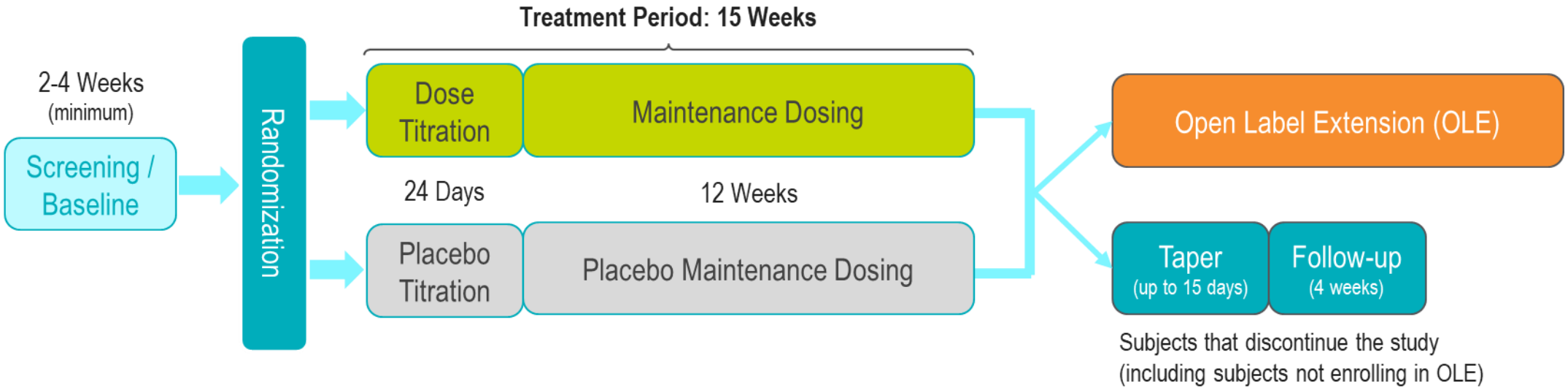
Development of Proprietary XEN496

- XEN496 is pediatric-specific, granule formulation of ezogabine to be presented as sprinkle capsules
- Ezogabine previously approved by FDA with proven mechanism in adult focal seizures
- MOA that potentiates K_V7-mediated potassium current
- Potential for precision medicine approach to treat rare KCNQ2-DEE pediatric epilepsy
- Fast Track designation and Orphan Drug Designation in U.S. and Orphan Medicinal Product Designation (Europe)

[1] Kuersten M, Tacke M, Gerstl L, Hoelz H, Stülpnagel CV, Borggraefe I. Antiepileptic therapy approaches in KCNQ2 related epilepsy: A systematic review. Eur J Med Genet. 2020 Jan;63(1):103628. doi: 10.1016/j.ejmg.2019.02.001. Epub 2019 Feb 14. PMID: 30771507.

Phase 3 Clinical Trial Underway

Primary Objective: evaluate the efficacy of XEN496 as adjunctive therapy in reducing seizure frequency from baseline, compared to placebo in pediatric subjects with KCNQ2-DEE



Indication:	Seizures in pediatric subjects with KCNQ2-DEE
Study population:	~40 patients, aged between 1 month and <6 years of age
Randomization:	Parallel group, 1:1, XEN496:Placebo
Screening/Baseline:	2-6 weeks, depending on current seizure frequency
Treatment period:	Minimum of 15 weeks on active treatment (24 days titration + 12 weeks maintenance)
Seizure frequency:	Caregiver-reported electronic seizure diary informed by video-EEG
Efficacy Outcomes:	Change in seizure frequency in subjects who received placebo in the primary study, after 15 weeks of OLE treatment

Key Eligibility Criteria

Inclusion Criteria

- Aged from 1 month to <6 years, with a body weight of ≥3.0 kg.
- Prior genetic test result consistent with a diagnosis of KCNQ2-DEE.
- Seizure onset within 2 weeks after birth and EEG and documented clinical history consistent with KCNQ2-DEE.
- Magnetic resonance imaging 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.
- Have ≥4 focal tonic or other countable motor seizures per 28 days.
- Taking 1 to ≤4 concomitant antiseizure medications (ASMs). All doses must be stable for at least 1 week prior to screening.
- Vagal nerve stimulation (VNS) is allowed and not counted as a concomitant ASM if implanted for ≥6 months, and settings are stable for ≥6 weeks prior to screening.
- Ketogenic diet is allowed and not counted as a concomitant ASM if ketosis is stable for at least 6 weeks prior to screening, and it is expected to be maintained throughout the study.

Exclusion Criteria

- Presence of a pathogenic or likely pathogenic variant in an additional gene associated with other epilepsy
- 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.
- Seizures secondary to infection, neoplasia, demyelinating disease, degenerative neurological disease, or central nervous system (CNS) disease deemed progressive, metabolic illness, or progressive degenerative disease.
- Confirmed diagnosis of infantile spasms within the past month prior to screening.
- QT interval corrected for heart rate by Fridericia's formula (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.
- Current disturbance of micturition or known urinary obstructions or history of bladder or urinary dysfunction.

Conclusions

- Xenon Pharmaceuticals has two potassium channel modulators for the treatment of epilepsy in late clinical development
- XEN496
  - Phase 3 EPIK Study in pediatric KCNQ2-DEE is ongoing
- XEN1101
  - Phase 2b X-TOLE Study in adult FOS completed
  - Phase 3 initiation anticipated H2 2022
  - Major Depressive Disorder Proof of Concept study ongoing
  - Indication expansion in epilepsy anticipated