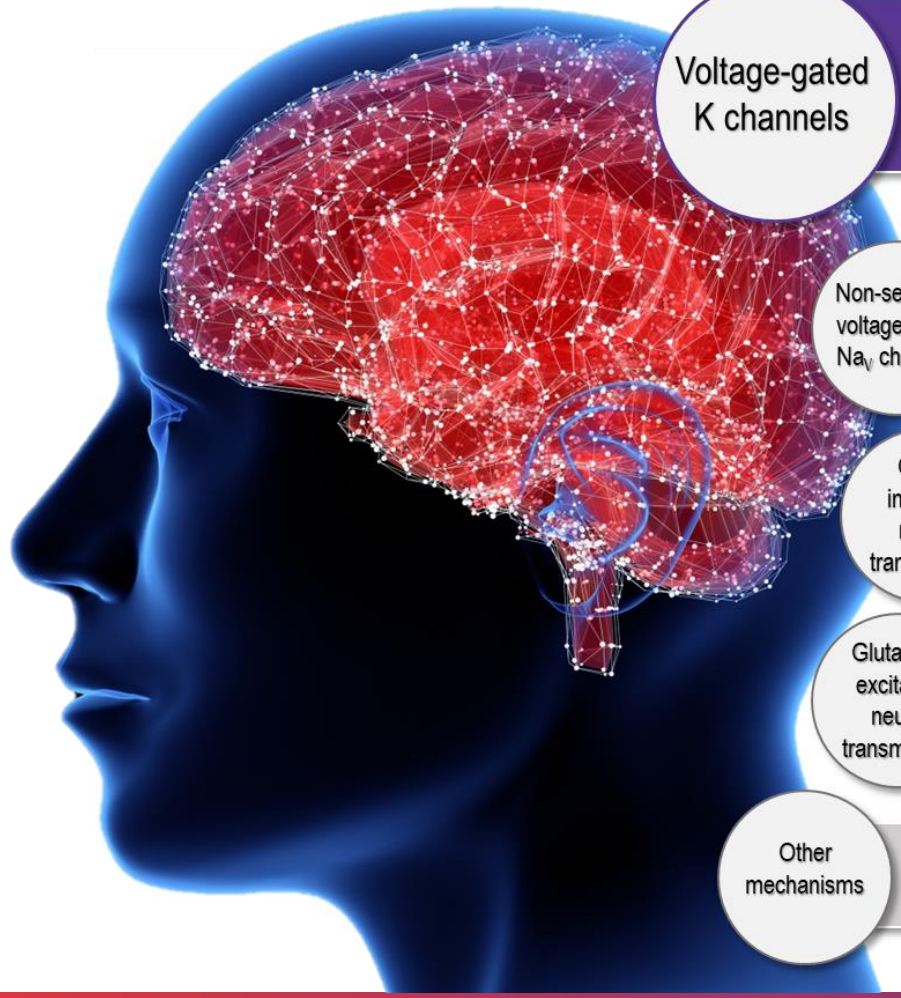
K_V7 Potassium Channel Modulators for the Treatment of Epilepsy

Ernesto Aycardi M.D.
Chief Medical Officer, Xenon Pharmaceuticals Inc.

Xenon's K_V7 Channel Modulators for Adult and Pediatric Epilepsies



Voltage-gated K channels

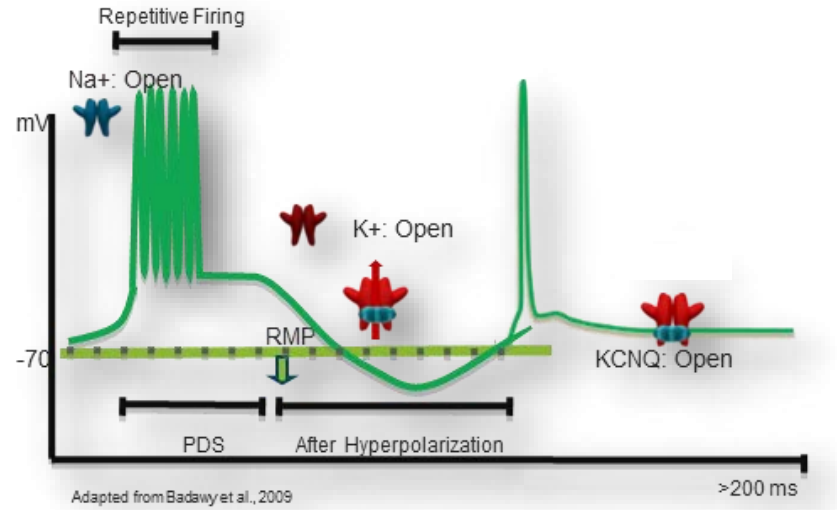
XEN496 (K_V7) | XEN1101 (K_V7)

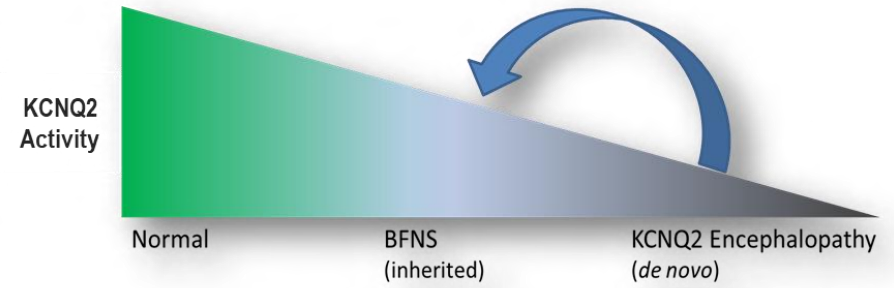
Major Classes Of Approved Anti-Seizure Medications (ASMs)

Non-selective voltage-gated Na_V channels	Phenytoin (Na+); Carbamazepine (Na+); Pregabalin (Ca^{2}+); Lacosamide (Na+)
GABA inhibitory neuro-transmission	Clobazam; Diazepam; Vigabatrin; Tiagabine
Glutamate excitatory neuro-transmission	Topiramate (KA); Perampanel (AMPA)
Other mechanisms	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

Case Study of KCNQ2-DEE Patients *Millichap 2016*	Medical Record Review/Parent Interviews *Olson 2017* (8 Families)
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

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

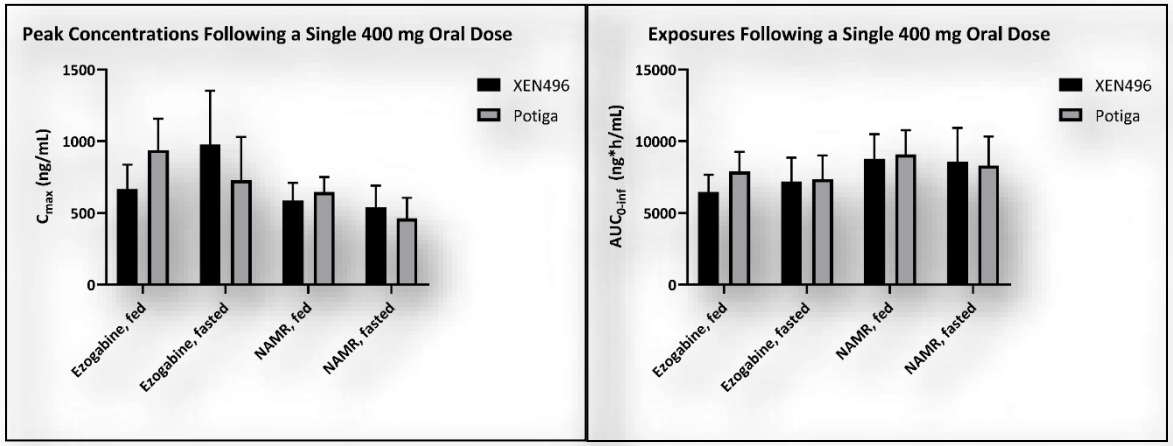
Millichap, John J et al. "KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients." Neurology. Genetics vol. 2,5 e96. 22 Aug. 2016.

Olson et al. 2017 AES Annual Meeting, Abstract 3.176.

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

Typical sprinkle capsule

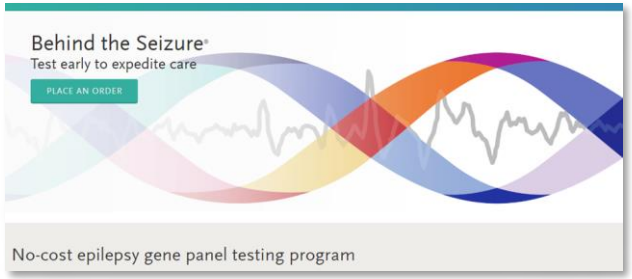


From a PK perspective, no dose adjustments arising from differences in formulation are anticipated for the upcoming efficacy study in KCNQ2-DEE

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

KCNQ2 Cure

unity love strength hope

- 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

Demographics
Data available 67 compete responses
Location (n) USA (31) – Canada (5) – UK (7) – Australia (7)
Patient age n (%) Younger than 4 years - 18 (36%) Older than 4 years – 32 (64%)
Age of seizures onset after birth Day 0 = 26% - Day 1 = 40% - Day 2 – 24% - Day 3-5 = 10%
Initial seizure frequency >10 seizures / day = 63% 2-10 seizures / day = 35% 1 seizure / day = 2%
Current seizure frequency 28% had seizures over past 30 days 38% had seizures over past 90 days 46% had seizures over past 180 days

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."

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

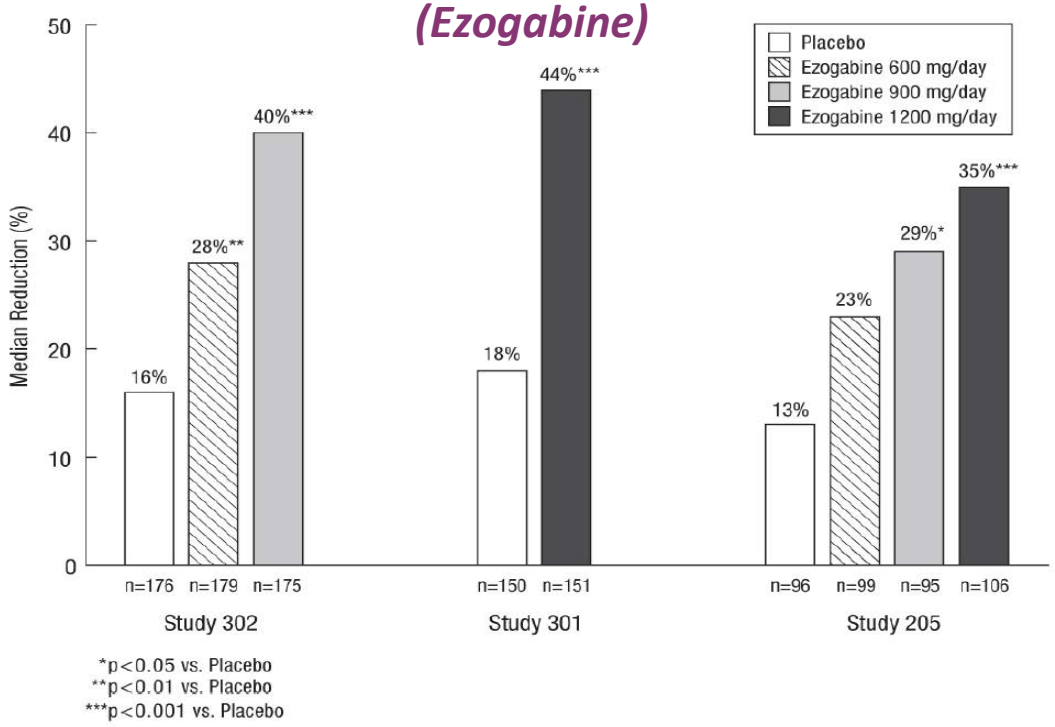
- Initiate Phase 3 clinical trial in 2020*
- Randomized, double-blind, placebo-controlled study
  - ***Anticipated primary endpoint***: median % change in seizure frequency from baseline compared to treatment period of active versus placebo
- ~40 KCNQ2-DEE patients (infants up to six years old)

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

XEN1101 “Next-Gen” KCNQ2 Modulator

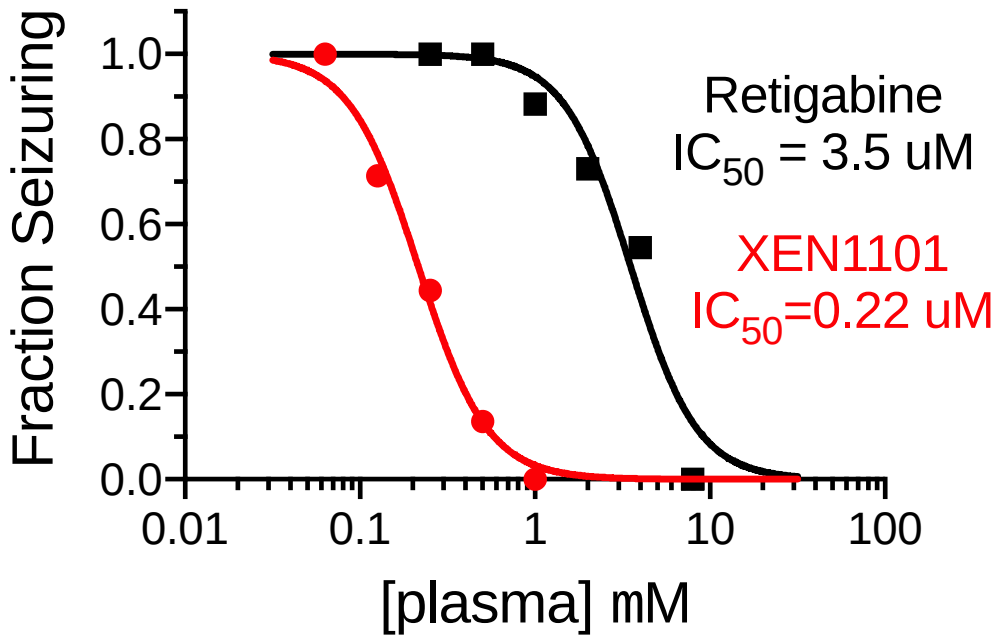
- Same mechanism of action as ezogabine, but with substantial improvements
  - More potent *in vitro* and *in vivo*
  - Improved PK
    - Once daily dosing and predicted better tolerability
- No predicted pigmentation liability
  - Does not form pigmented dimers
- Modulates cortical activity in healthy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

Proven ‘Mechanism of Action’ in Adult Epilepsy (Ezogabine)



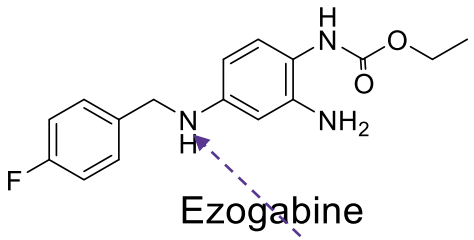
XEN1101: Anti-Seizure Activity vs Ezogabine

- 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)

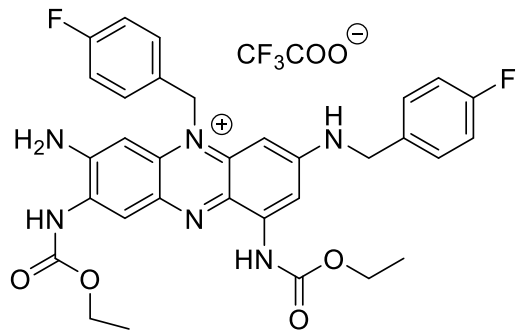


Ezogabine Dimerization

- 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



Ezogabine Phenazinium-Type Dimer

Sample of purified phenazinium-type dimer

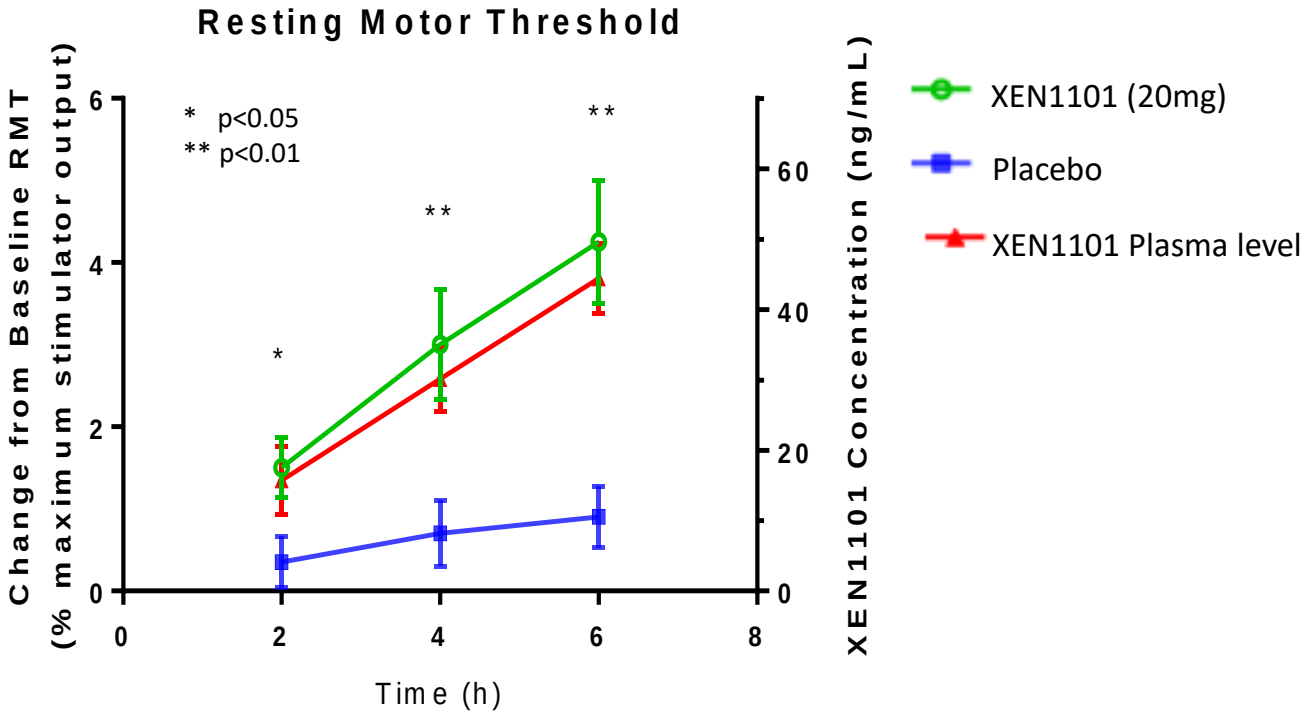
- Ezogabine has a secondary aniline function, which is key to forming phenazinium-type dimers.
- XEN1101 instead has a tertiary aniline at the corresponding position.
- **This key structural difference prevents XEN1101 from forming analogous dimers, as this would require a nitrogen atom with five chemical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

- 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.

(1) Groseclose *et al*. *Chem. Res. Toxicol.* 2019, 32:294-303

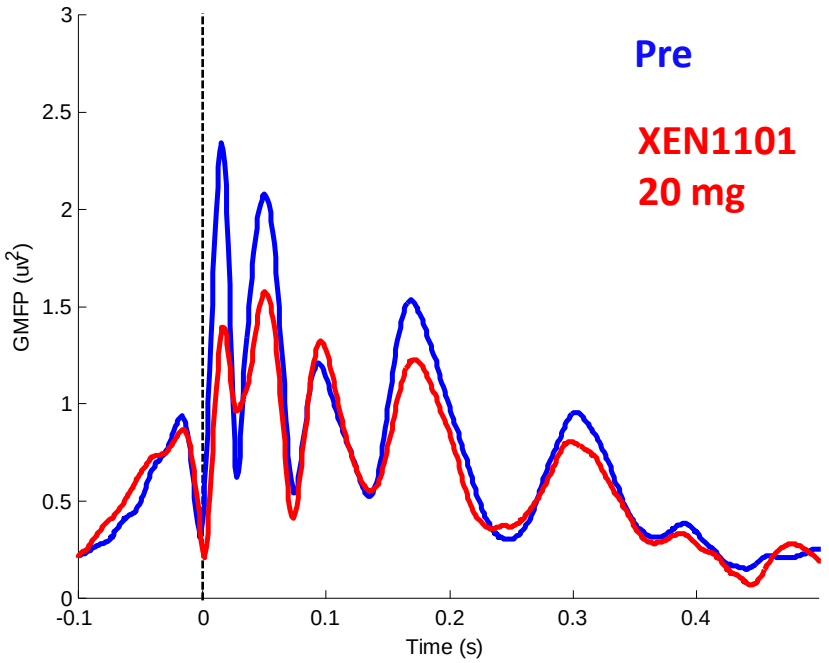
Reducing Cortical Excitability: TMS Results

TMS-EMG



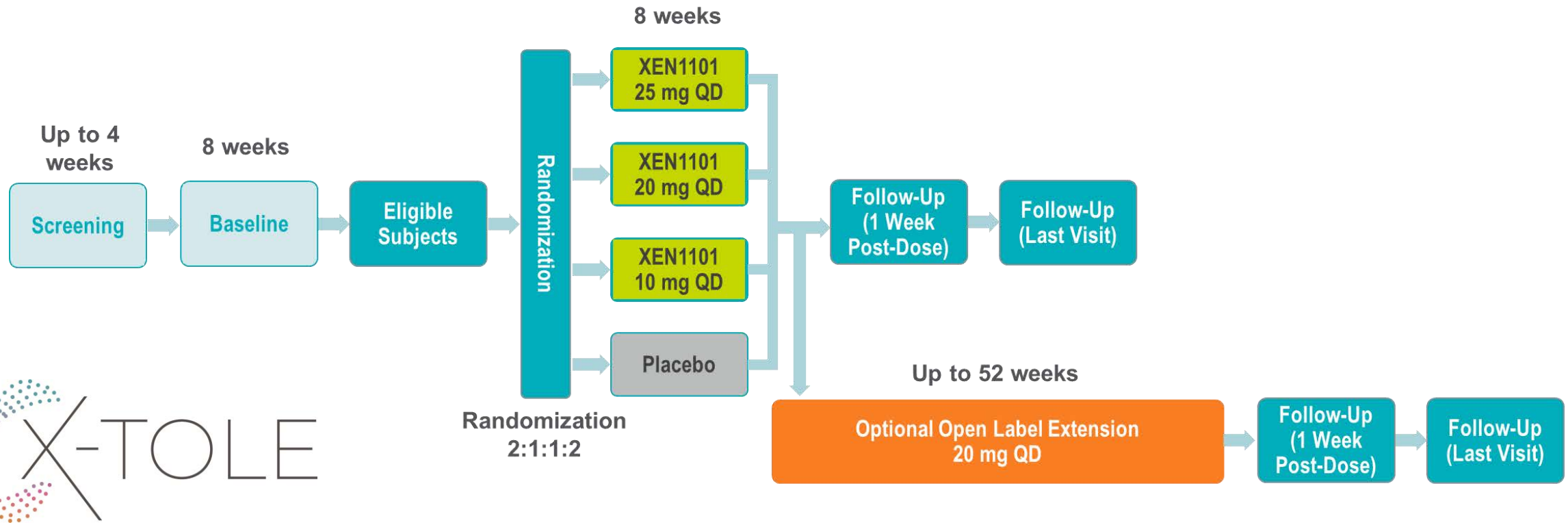
TMS-EEG

Global Mean Field Power (GMFP)



XEN1101: Phase 2b "X-TOLE" Clinical Trial Underway

- Phase 2b clinical trial is being conducted at approximately 90 sites in Europe and North America



X-TOLE

Summary & Acknowledgements

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

Special thanks to:

- KCNQ2 patients and families
- KCNQ2 Cure Alliance and other advocacy groups
- Expert physicians
- Xenon Pharmaceuticals Team
  - Greg Beatch, Noam Butterfield, Jay Cadieux, Alison Cutts, James Empfield, Cynthia Harden, Alix Helper, Celene Grayson, Heather Kato, Rostam Namdari, Simon Pimstone, Robin Sherrington

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