XENON

ASENT 2021

VIRTUAL NEUROTHERAPEUTICS CONFERENCE

"Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel K_V7 Modulator"

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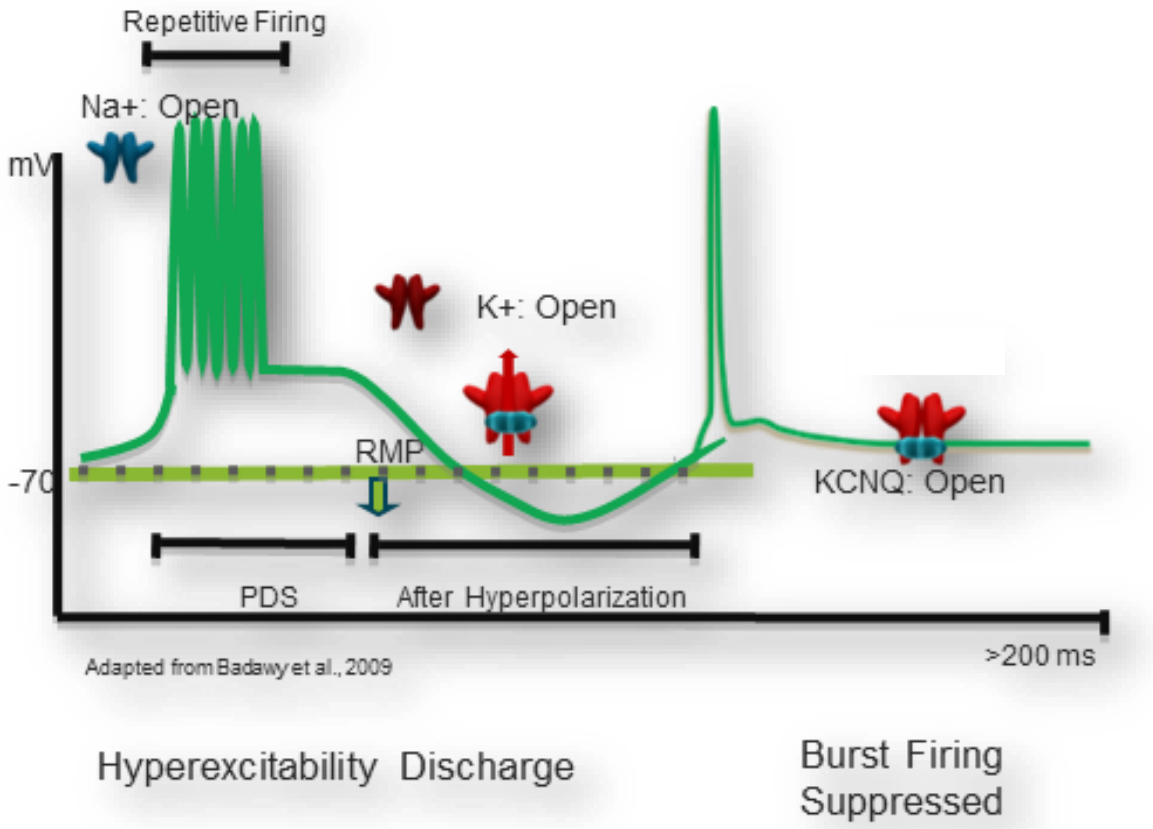
Xenon's Ion Channel, Neurology-Focused Pipeline

Therapeutic Program *Indication*	Pre-clinical	Phase 1	Phase 2	Phase 3
XEN496 (Potassium Channel Modulator) *Orphan Pediatric Epilepsy*				
XEN1101 (Potassium Channel Modulator) *Adult Focal Epilepsy*				
XEN007* (Calcium Channel Inhibitor) *Childhood Absence Epilepsy*				
Ion Channel Modulators *Orphan Channelopathies*				
NBI-921352 (XEN901) and $Na_V1.6/1.2$ Sodium Channel Inhibitors *Epilepsy (Orphan Pediatric and Adult Focal)*		Neurocrine Biosciences		
FX301 *Post-operative Pain*		flexion		
$Na_V1.7$ Inhibitors *Pain*		Genentech A Member of the Roche Group		

*A physician-led, Phase 2 proof-of-concept study is ongoing to examine XEN007 as an adjunctive treatment in pediatric patients diagnosed with treatment-resistant childhood absence epilepsy (CAE).

KCNQ2 is a Highly Validated Target

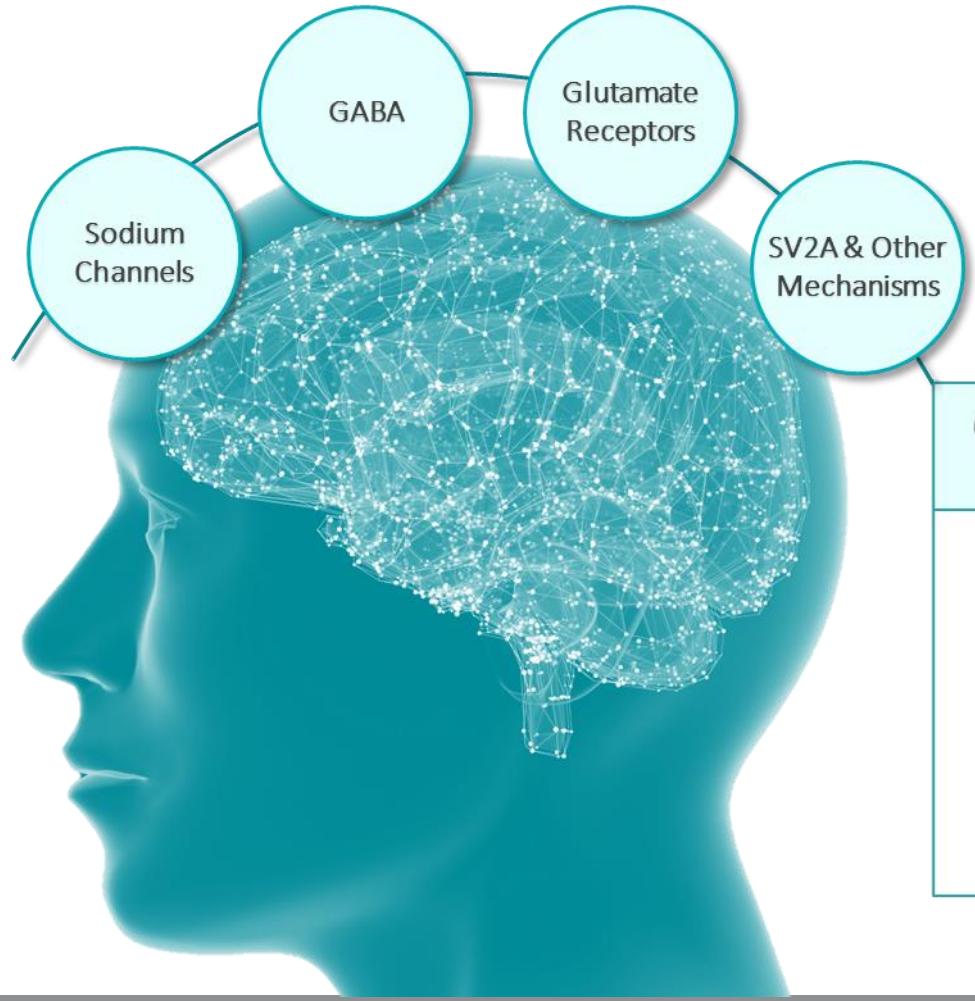
- KCNQ2 dampens neuronal hyper-excitability
- K^+ channels have important inhibitory control over neuronal firing in the CNS
- Repolarize membranes to end the action potential
- K^+ channel opener (potentiator) decreases hyper-excitability in the brain
- Mechanism validated clinically with first-generation K_V potentiator, ezogabine



XEN1101 is a Novel, "Next-Gen" K_V7 Channel Modulator

- Potential "only-in-class" K_V7 potassium channel modulator to treat adult focal seizures
- Addresses limitations of first-gen K_V7 modulator, ezogabine
  - No pigmentation or urinary symptoms observed
  - PK addressed (TID ⟶ QD)
- Novel MOAs needed for rational polypharmacy approach
- Potential efficacy for common comorbidities, such as depression

Common Pharmacological Actions of Approved Anti-Seizure Medications (ASMs)



Commonly Prescribed ASMs for Adult Focal Epilepsy

- levetiracetam
- brivaracetam
- carbamazepine
- lamotrigine
- lacosamide
- sodium valproate

XEN1101's Differentiated Profile in Adult Focal Epilepsy

- Potential for a **highly differentiated profile** within the **adult focal epilepsy space**:

Ease of Use

- ☑ Once daily (QD) dosing
- ☑ No titration; at efficacious doses immediately
- ☑ No significant DDI predicted
- ☑ Low daily dose
- ☑ No drug allergic reactions observed
- ☑ Slow elimination could provide coverage for missed doses

Efficacy

- ☑ Proven anti-seizure mechanism of action
- ☑ Broad efficacy in multiple pre-clinical seizure models as monotherapy or in combination with other ASMs
- ☑ Greater effect on TMS target engagement
- ❑ Phase 2b trial modeled for median monthly seizure reduction in the range of currently used ASMs

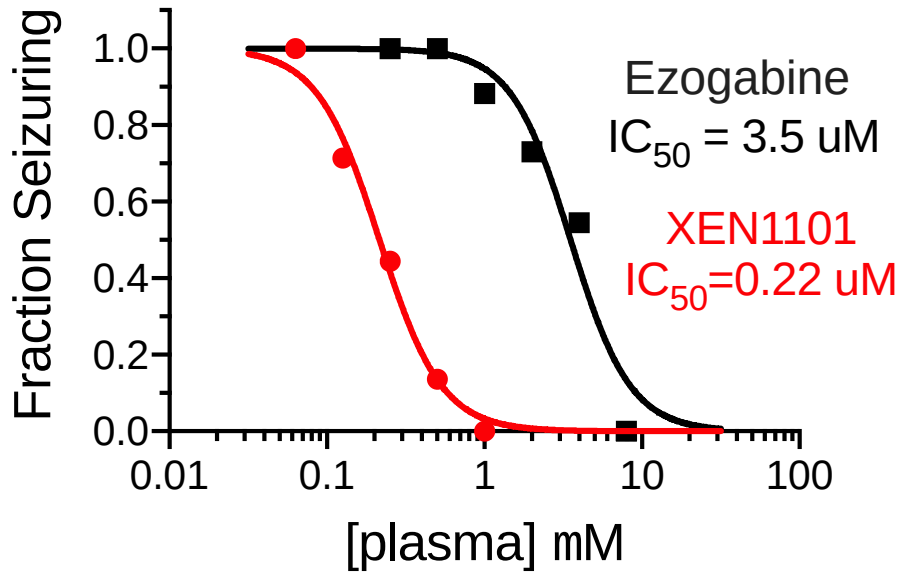
Safety / Tolerability

- ☑ Favorable safety profile and well-tolerated in Phase 1
- ☑ Evening QD dosing with C_{max} (and related CNS AEs) during sleeping hours
- ☑ Low C_{max} to C_{min} provides better tolerability
- ☑ To date, low drop out rates and high conversion rates to OLE in ongoing blinded Phase 2b trial

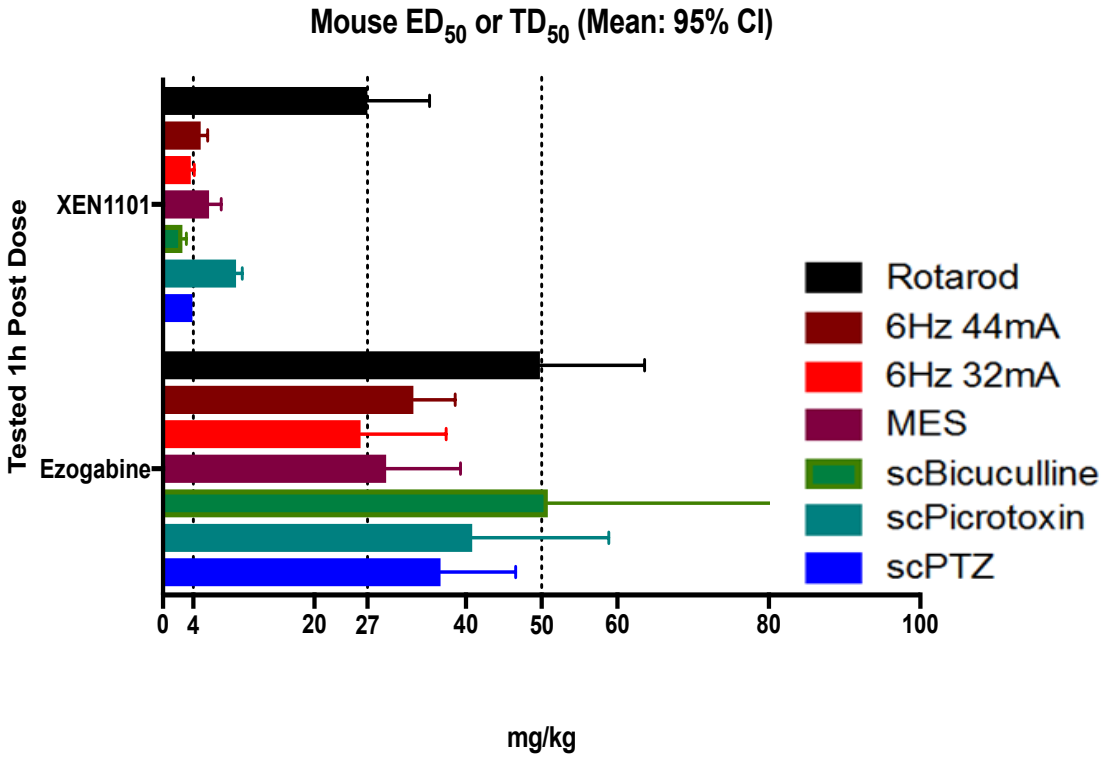
XEN1101: Anti-Seizure Activity (vs Ezogabine)

- Maximal Electroshock Stimulus (MES) using 60 Hz bipolar stimulus with CF-1 mice

XEN1101 is 16-fold more potent than ezogabine

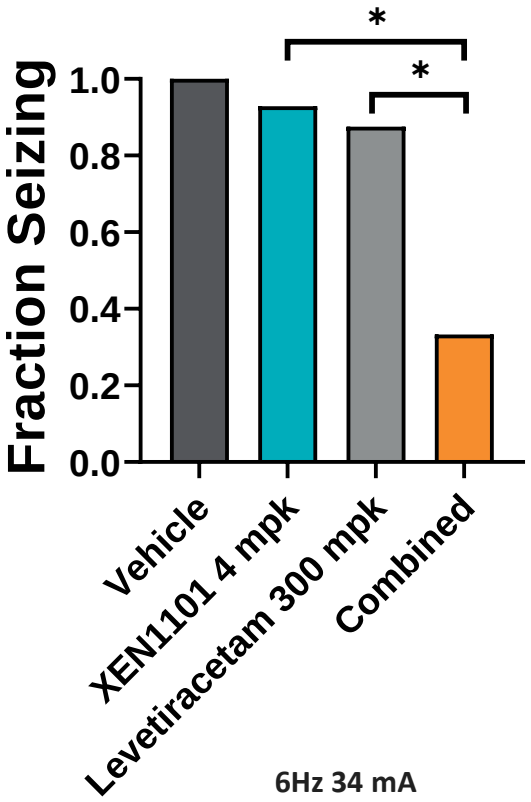


- Improved Therapeutic Index of XEN1101 versus Ezogabine

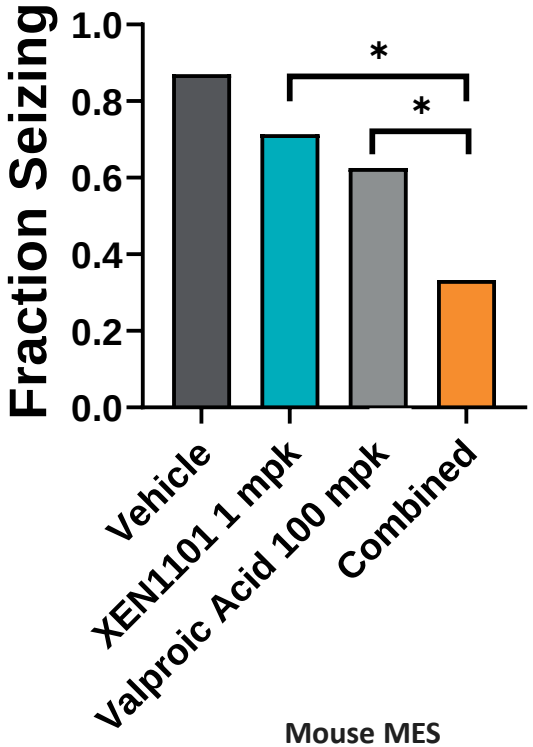


Combining XEN1101 with Common ASMs Provides Robust Seizure Protection

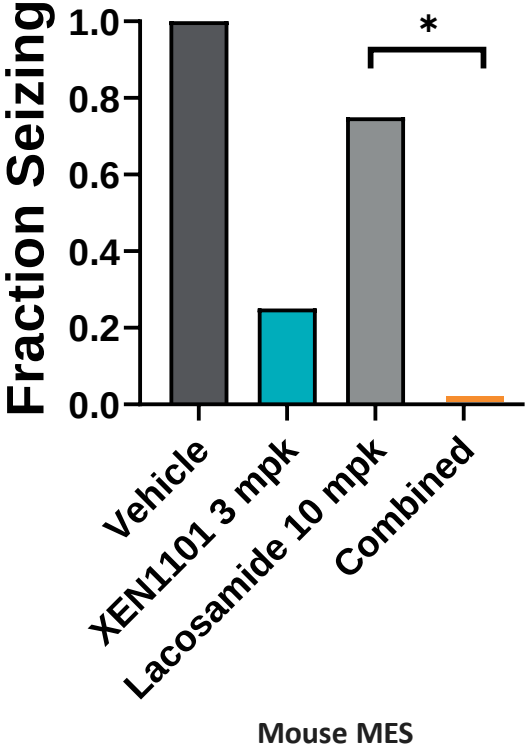
- Combining ineffective or weakly active doses of XEN1101 and common ASMs enhances robust seizure protection
- Enhanced efficacy is not a drug-drug interaction phenomenon; not explained by changes in plasma levels
- Combination doses were well tolerated



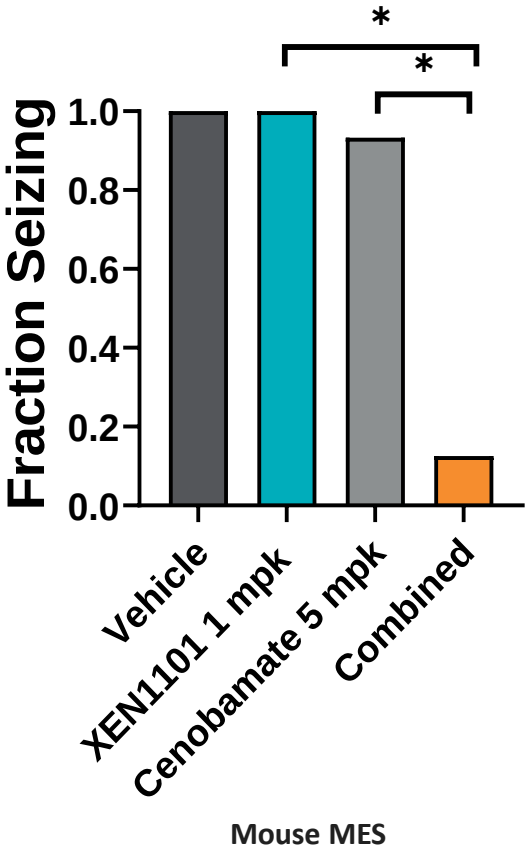
6Hz 34 mA



Mouse MES



Mouse MES



Mouse MES

XEN1101 Phase 1 Adaptive Integrated Design

SAD

placebo n=8

5 mg, n=3 — Cohort 1

15 mg, n=3 — Cohort 2

20 mg, n=6 — Cohort 3

30 mg, n=6 — Cohort 4

food effect, 20 mg, n=10 — Cohort 5

Fed 25 mg, n=6 — Cohort 6

Optional

MAD

placebo n=6

Cohort 1 — fasted, 15 mg, n=6

Cohort 2 — fed, 15 mg, n=6

Cohort 3 — fed, 25 mg, n=6

Optional

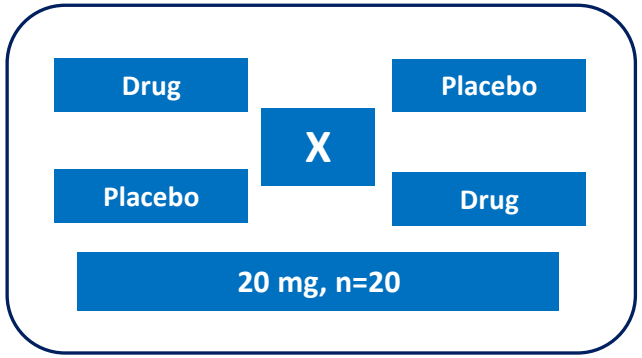
TMS Pilot

Cohort 1 — 15 mg, n=3

Cohort 2 — 20 mg, n=3

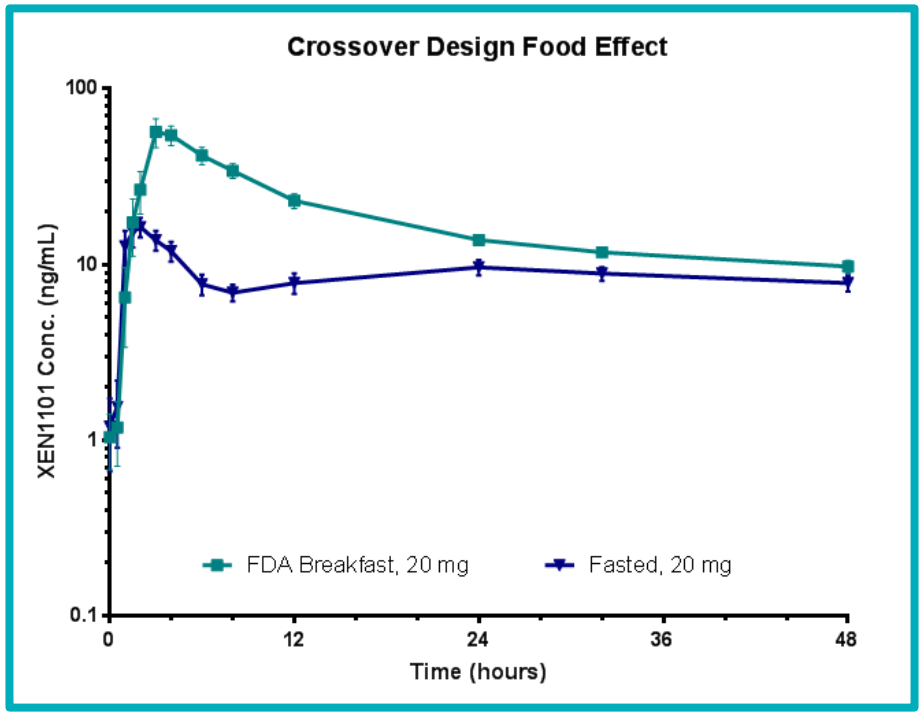
Cohort 3 — 10 mg, n=2

Ph 1b TMS Cross-over



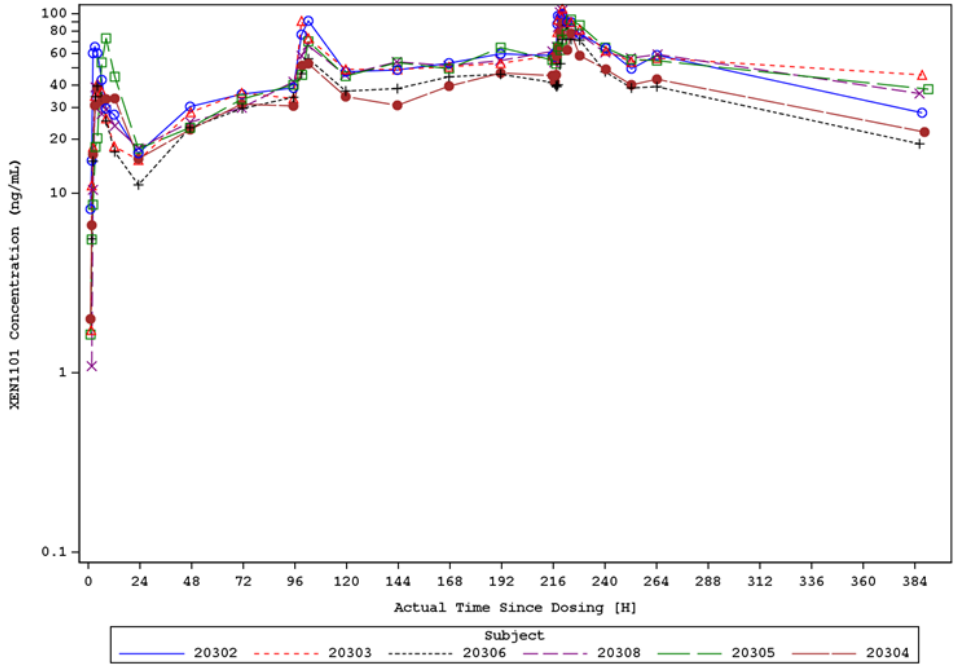
Phase 1: Summary of Single Dose Findings

- Food enhanced absorption and delayed time to C_{max}
- Long terminal elimination half-life
- Minimal renal excretion of unchanged drug
- Generally well tolerated at up to 30 mg
  - Majority of AEs were mild and CNS related
  - Dizziness, headache, somnolence, myalgia, presyncope and blurred vision were the most common related AEs in SAD cohorts
  - No QT prolongation or safety lab signals
  - No SAEs



Phase 1: Summary of Multiple Dose Findings

- XEN1101 has a PK profile consistent with QD
- Near steady-state within 1 week, full steady-state within 3 weeks
- Absorption is enhanced by food
- Exposure increased dose proportionally (15 - 25 mg QD) in fed state
- Low inter-individual PK variability with repeat dose
- AE profile consistent with MOA (e.g., dizziness, sedation, blurred vision)
- No signal of urinary retention
  - Post-void residual volume normal (bladder ultrasound)
- No safety signals in ECG or safety labs; no SAEs

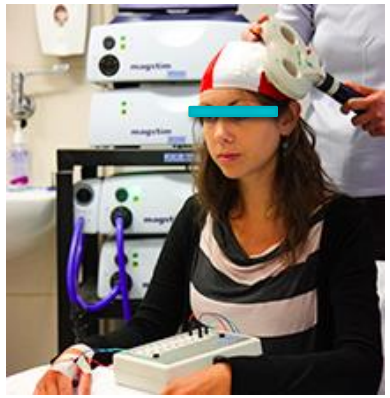


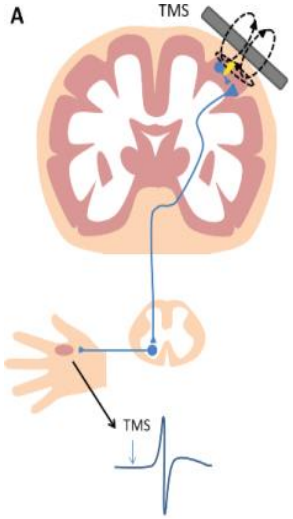
Individual PK profiles for subjects dosed at 25 mg QD XEN1101

Phase 1b: Transcranial Magnetic Stimulation (TMS) PD Study

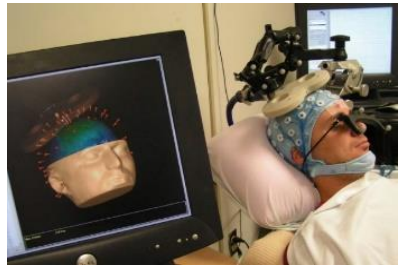
- TMS is a non-invasive tool to study human cortical excitability and target engagement of CNS acting drugs
- Multiple ASMs show effects on TMS at efficacious plasma levels, including ezogabine

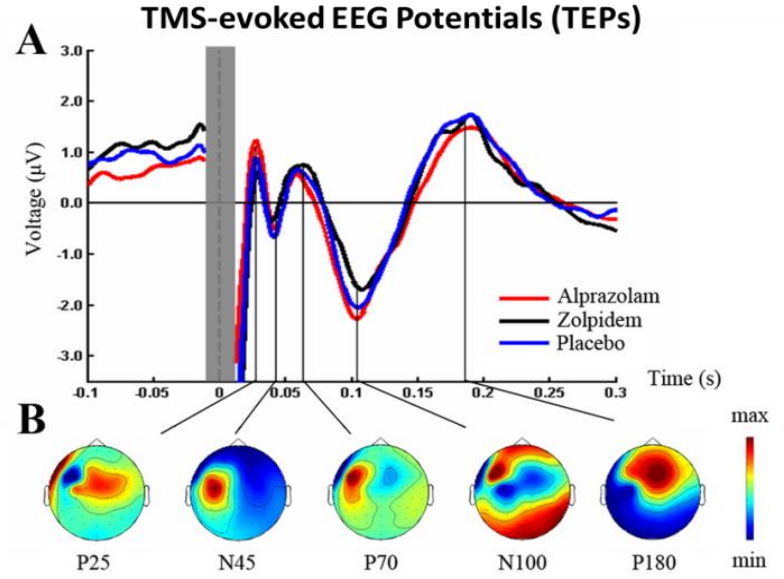
EMG:
Resting Motor Threshold (RMT%) reflects cortico-spinal excitability





EEG:
TMS-evoked EEG potentials (TEPs) allow direct evaluation of cortical excitability in a time-resolved fashion manner

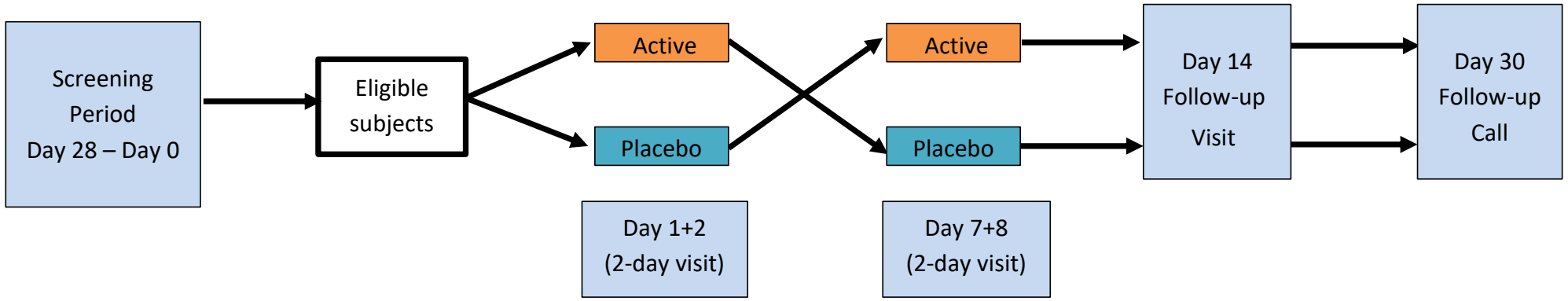




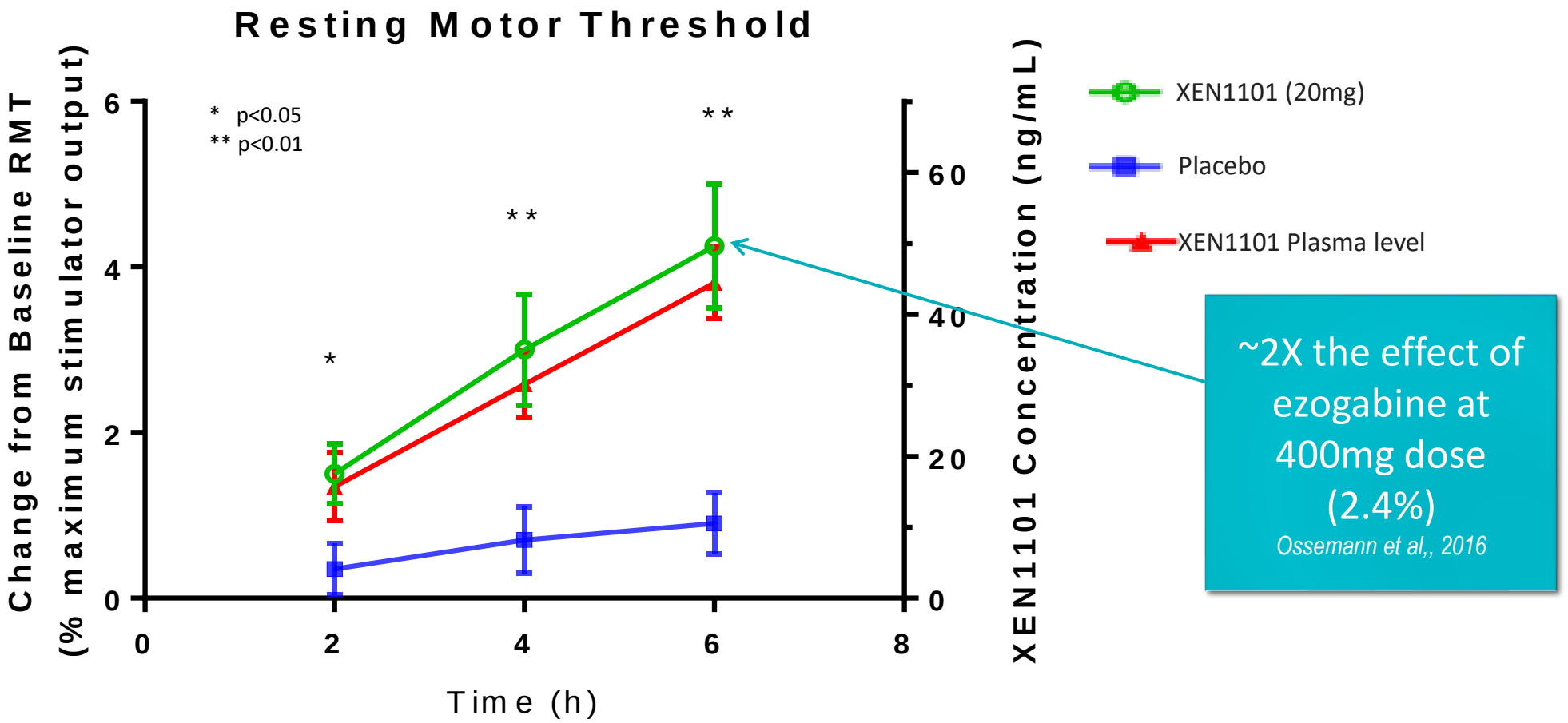
Premoli et al., 2014 *Journal of Neuroscience*

Phase 1b XEN1101 Cross-Over Study

- To evaluate the safety, tolerability, pharmacokinetics and TMS effects of XEN1101 in a double-blind, placebo-controlled, cross-over study
  - London, UK (King's College Hospital)
  - Male healthy volunteers (18-55 years)
  - Single dose, 20 mg
  - N = 20
  - Placebo-controlled, double-blind
  - Cross-over



Phase 1b: XEN1101 Reduced Corticospinal Excitability (TMS-EMG)

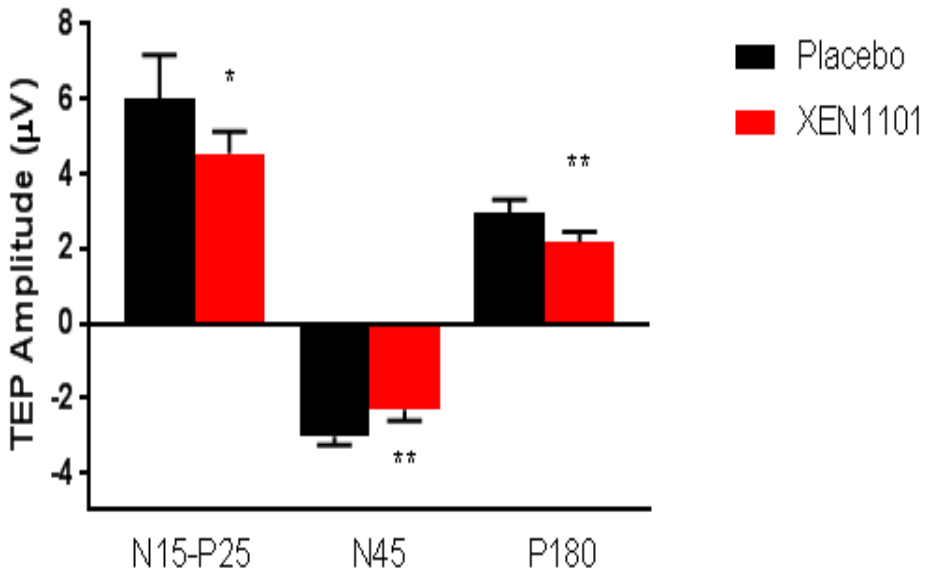


Significant increase in RMT indicates reduced corticospinal excitability; strong PK-PD relationship

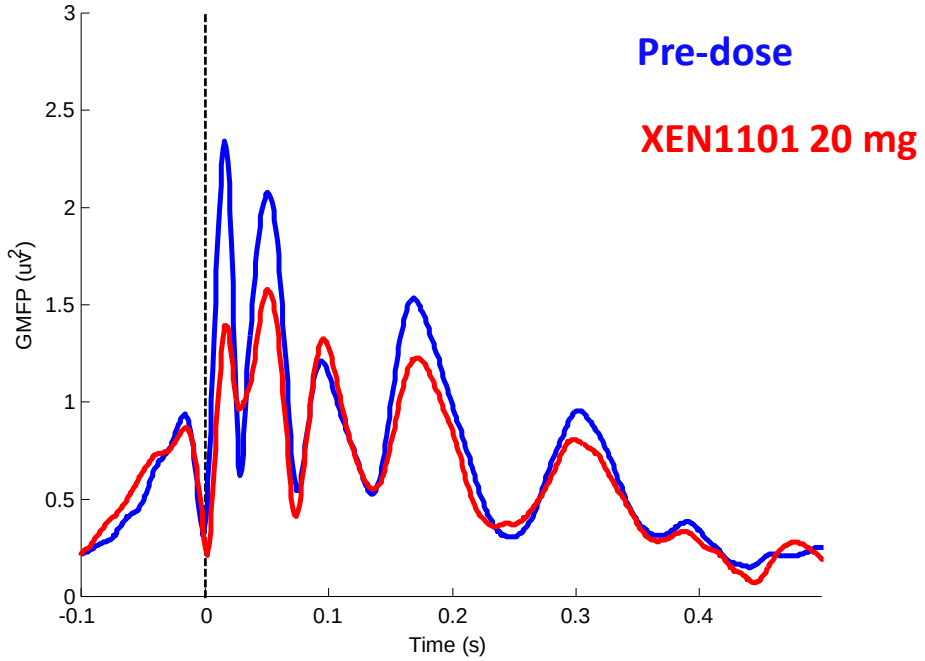
Phase 1b: XEN1101 Reduced Corticospinal Excitability (TMS-EEG)

- XEN1101 reduced the overall amount of electrical activity induced by TMS

TMS evoked potentials (TEPs)



Global Mean Field Power (GMFP)

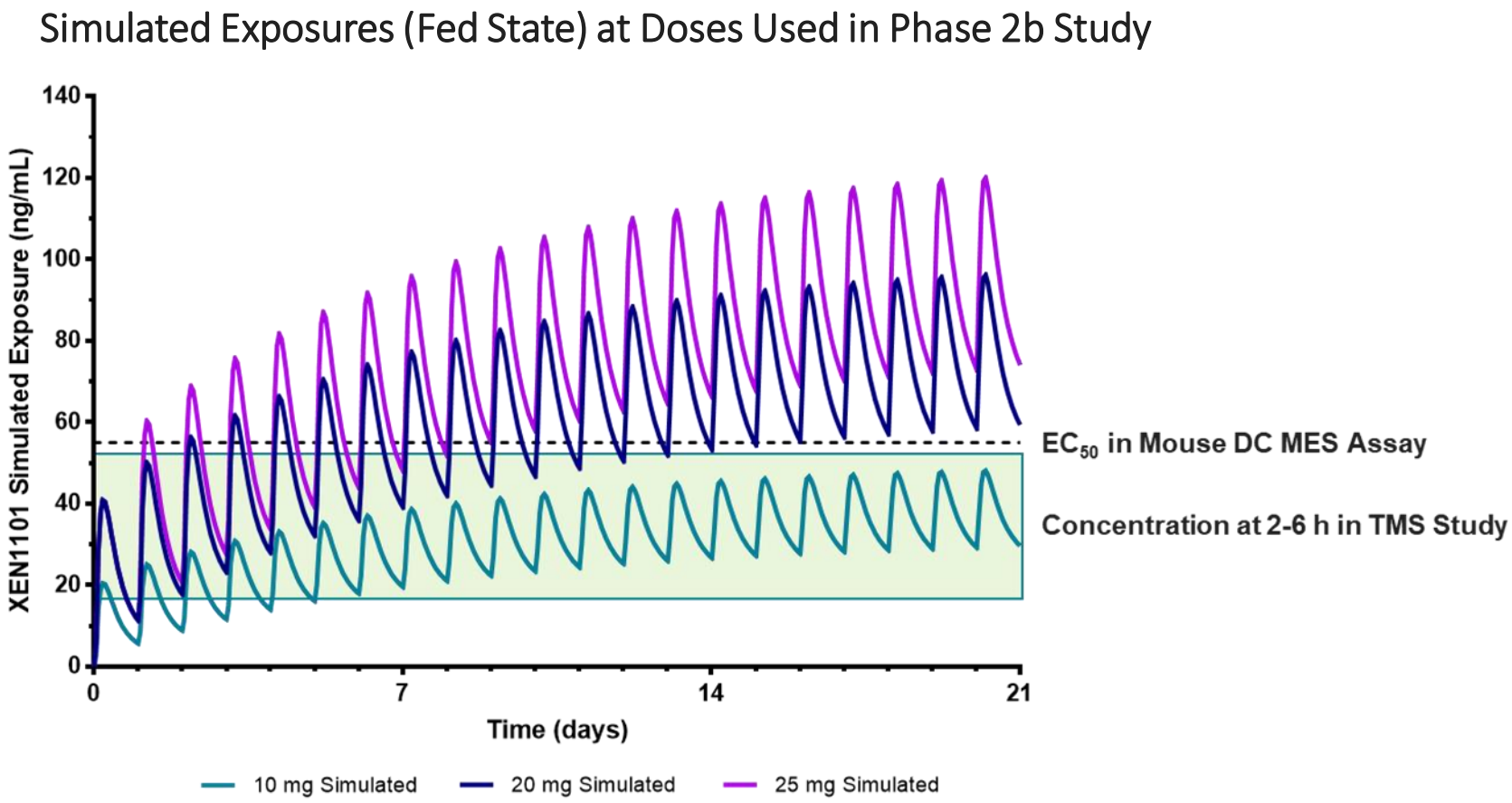


Effects shown at time of maximum XEN1101 plasma level (~45 ng/mL) during assessments compared to time matched placebo.

XEN1101 suppressed cortical excitability as evidenced by decreased TEP amplitudes and reduction in GMFP

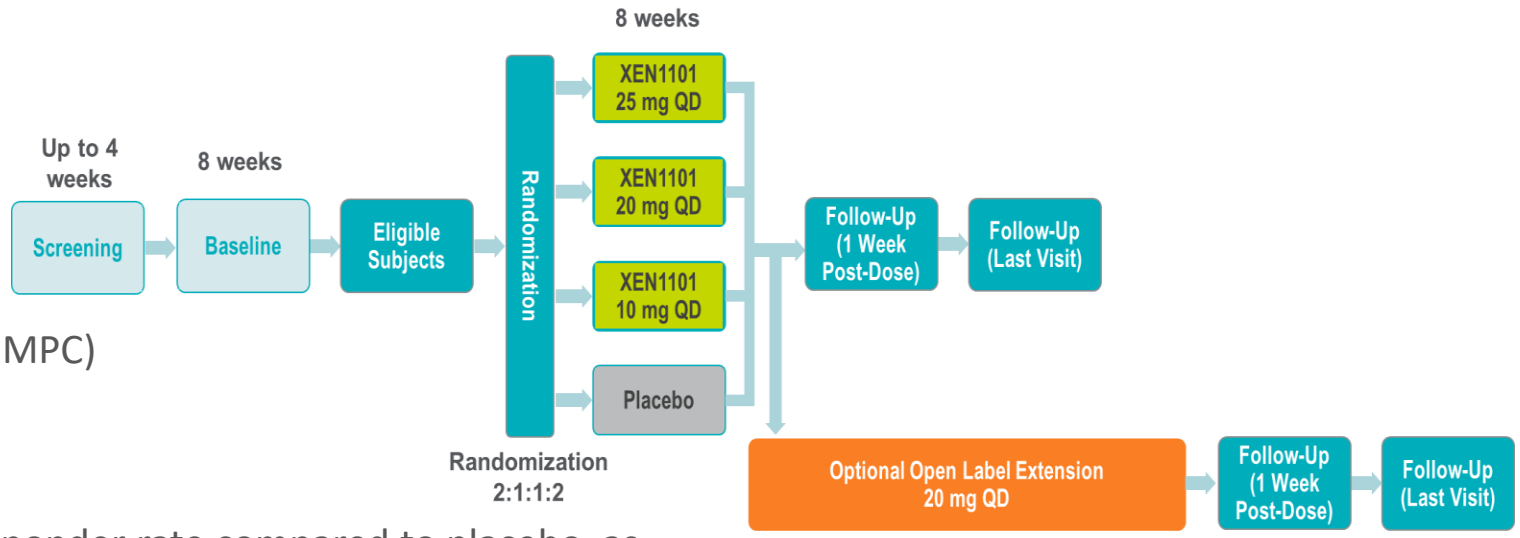
Use of Phase 1 and TMS to Inform Dose Selection in Phase 2b

- Simulations based upon PK parameters in Phase 1
- Dose range chosen in Phase 2 will provide two doses with trough levels above effective level in TMS



X-TOLE Phase 2b Clinical Trial Underway

- **X-TOLE Study**: Randomized, placebo-controlled Phase 2b clinical trial in 300 subjects with focal epilepsy



- Endpoints:
  - The primary endpoint is median percent change (MPC) from baseline in monthly (28 days) focal seizure frequency in the 8-week double-blind treatment period compared to placebo
  - Secondary endpoints include an evaluation of responder rate compared to placebo, as well as evaluation of changes in weekly seizure frequency and quality of life assessments
- Eligibility criteria include:
  - ≥4 countable focal seizures per month during an 8 week baseline period
  - Patients on stable treatment with 1-3 ASMs
- The study is well powered (around 90% power)
  - Designed to detect a monotonic dose response assuming a -20% MPC in placebo and -25%, -30% and -35% MPC at 10, 20 and 25 mg QD XEN1101, respectively
- Electronic diary to capture seizures, allowing subjects to be closely monitored for events and compliance

Conclusions

- XEN1101 is a differentiated, next-generation K_V7 potassium channel modulator
- Adult focal epilepsy is a common form of epilepsy with a high unmet medical need
- Safety, tolerability, and ease of use – in addition to efficacy – are important drug attributes for physicians, patients and caregivers
- With its with unique pharmaceutical properties, XEN1101 may represent a highly differentiated profile in focal epilepsy space:
  - Proven, "only-in-class" anti-seizure mechanism of action
  - Efficacious as monotherapy and in combination with other ASMs in pre-clinical models
  - Well-tolerated in Phase 1 studies and low drop out in blinded Phase 2b
  - Once daily (QD) evening dosing; no titration; low C_{max} to C_{min}
  - No significant DDI predicted; low daily dose
- Topline results from X-TOLE Phase 2b clinical trial are expected in the third quarter of 2021

Please refer to these additional presentations at ASENT 2021 to learn more:

Dr. Robin Sherrington,
"*K_V7 Modulators in Epilepsy and Depression*"

Dr. Alison Cutts,
"*Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated K_V7 Potassium Channel Modulator*"

Dr. J.P. Johnson, Jr.,
"*Anticonvulsant Effects of the Differentiated K_V7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs*"

Acknowledgements

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Clinical development and drug discovery teams at Xenon Pharmaceuticals Inc.