“Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel Kv7 Modulator”

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**Xenon’s Ion Channel, Neurology-Focused Pipeline**

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<th>Therapeutic Program</th>
<th>Indication</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
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<td>XEN496 (Potassium Channel Modulator)</td>
<td>Orphan Pediatric Epilepsy</td>
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<td>XEN007* (Calcium Channel Inhibitor)</td>
<td>Childhood Absence Epilepsy</td>
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<td>Ion Channel Modulators</td>
<td>Orphan Channelopathies</td>
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<tr>
<td>NBI-921352 (XEN901) and Na\textsubscript{v}1.6/1.2 Sodium Channel Inhibitors</td>
<td>Epilepsy (Orphan Pediatric and Adult Focal)</td>
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<td>FX301</td>
<td>Post-operative Pain</td>
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<td>Na\textsubscript{v}1.7 Inhibitors</td>
<td>Pain</td>
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*NXN007* is in a physician-led, Phase 2 proof-of-concept study 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

[Diagram showing neuronal firing and potassium channel activity]
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)**

- GABA
- Glutamate Receptors
- Sodium Channels
- SV2A & Other Mechanisms

**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**:

<table>
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<tr>
<th>Ease of Use</th>
<th>Efficacy</th>
<th>Safety / Tolerability</th>
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<tr>
<td>✅ Once daily (QD) dosing</td>
<td>✅ Proven anti-seizure mechanism of action</td>
<td>✅ Favorable safety profile and well-tolerated in Phase 1</td>
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<tr>
<td>✅ No titration; at efficacious doses immediately</td>
<td>✅ Broad efficacy in multiple pre-clinical seizure models as monotherapy or in combination with other ASMs</td>
<td>✅ Evening QD dosing with $C_{\text{max}}$ (and related CNS AEs) during sleeping hours</td>
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<td>✅ No significant DDI predicted</td>
<td>✅ Greater effect on TMS target engagement</td>
<td>✅ Low $C_{\text{max}}$ to $C_{\text{min}}$ provides better tolerability</td>
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<tr>
<td>✅ Low daily dose</td>
<td>✅ Phase 2b trial modeled for median monthly seizure reduction in the range of currently used ASMs</td>
<td>✅ To date, low drop out rates and high conversion rates to OLE in ongoing blinded Phase 2b trial</td>
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<td>✅ No drug allergic reactions observed</td>
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<td>✅ Slow elimination could provide coverage for missed doses</td>
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**Safety / Tolerability**

- Favorable safety profile and well-tolerated in Phase 1
- Evening QD dosing with $C_{\text{max}}$ (and related CNS AEs) during sleeping hours
- Low $C_{\text{max}}$ to $C_{\text{min}}$ 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

Ezogabine IC\textsubscript{50} = 3.5 uM

XEN1101 IC\textsubscript{50} = 0.22 uM

Mouse ED\textsubscript{50} or TD\textsubscript{50} (Mean: 95% CI)
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
XEN1101 Phase 1 Adaptive Integrated Design

SAD
- placebo n=8
  - 5 mg, n=3
  - 15 mg, n=3
  - 20 mg, n=6
  - 30 mg, n=6
  - food effect, 20 mg, n=10
  - Fed 25 mg, n=6
  - Optional

MAD
- placebo n=6
  - Cohort 1
  - fasted, 15 mg, n=6
  - fed, 15 mg, n=6
  - 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
- Drug
- Placebo
- X
- Placebo
- Drug
- 20 mg, n=20
Phase 1: Summary of Single Dose Findings

- Food enhanced absorption and delayed time to $C_{\text{max}}$
- 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
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)

**Resting Motor Threshold**

- **XEN1101 (20mg)**
- **Placebo**
- **XEN1101 Plasma level**

- * $p < 0.05$
- ** $p < 0.01$

- Change from Baseline RMT (% maximum stimulator output)
- Time (h)

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

~2X the effect of ezogabine at 400mg dose (2.4%)

Ossemmann et al., 2016
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)**

![Graphs showing TEP Amplitude and GMFP](image)

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 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 Kv7 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 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 Cmax to Cmin
  - 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, “Kv7 Modulators in Epilepsy and Depression”

Dr. Alison Cutts, “Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated Kv7 Potassium Channel Modulator”

Dr. J.P. Johnson, Jr., “Anticonvulsant Effects of the Differentiated Kv7 Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs”
Acknowledgements

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