XEN1101: A Novel, Next-Generation KCNQ2 Modulator for the Treatment of Epilepsy

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NOTE: Comparisons of XEN1101 and ezogabine are based on results in published literature, not based on data resulting from head-to-head trials, and are not direct comparisons of safety or efficacy. Different protocol designs, trial designs, patient selection and populations, number of patients, trial endpoints, trial objectives and other parameters that are not the same between the relevant trials may cause any comparisons of results from different trials to be unreliable.
XEN1101: Best-in-Class 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 predict better tolerability
  • No predicted pigmentation liability
    • Does not form pigmented dimers
• Modulating cortical activity in healthy volunteers (TMS)
  • Within predicted efficacious exposures
• Safe and well tolerated in ongoing Phase 1 study
Presentation Overview

• Background on Kv7.2 and XEN1101
• Phase 1 Trial Design and Results
  • PK, Safety
  • TMS Pilot Study
• Ongoing Studies and Future Development Plans
• Summary
KCNQ2 is a Highly Genetically Validated Target

M-Current Gradient Correlates with Disease Severity
XEN1101 Based on Proven Mechanism of Action

\[ K_{\nu}7.2 \text{ Attenuates Neuronal Hyper-Excitability} \]
## Multiple Predicted Benefits of XEN1101 over Ezogabine

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Key Difference to Ezogabine / Predicted Impact</th>
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</table>
| Chemistry                 | • No dimerization or oxidative color changes  
• Predict no skin and retinal pigmentation                                                                    |
| Potency                   | • 10-50X greater *in vitro* potency on Kv7.2/3                                                               |
| Pharmacokinetic (PK)      | • Once daily dosing vs TID  
• Predict better CNS tolerability                                                                          |
| Pre-clinical Efficacy & TMS Signal | • Broadly effective at lower doses in multiple preclinical epilepsy models  
• Superior TMS signal of cortical activity in humans at a significantly lower dose |
Increased Potency of XEN1101

![Graph showing the dose-response relationship between XEN1101 concentration (µM) and GV0.5 Vmax (mV). The EC50 is 27 nM.]

<table>
<thead>
<tr>
<th>Assay</th>
<th>EC50</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Kv7.2/Kv7.3</td>
<td>27 nM</td>
<td>CNS</td>
</tr>
<tr>
<td>Kv7.3/Kv7.5</td>
<td>94 nM</td>
<td>CNS</td>
</tr>
<tr>
<td>Kv7.4</td>
<td>113 nM</td>
<td>Bladder</td>
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</table>
Improved Therapeutic Index of XEN1101

Mouse ED$_{50}$ or TD$_{50}$ (Mean: 95% CI)

XEN1101

Ezogabine

mg/kg
Metabolism Suggests Minimal Risk for Drug-Drug Interactions

- Metabolism
  - Highly stable in liver microsomes and hepatocytes
  - No risk of DDI through inhibition of CYP450 enzymes
    - No inhibition of CYP1A2, 2C9, 2C19, 2D6 & 3A4 tested at 3µM
    - No significant time-dependent inhibition of CYP1A2, 2C9, 2C19, 2D6 & 3A4
  - Very low risk of susceptibility to DDI from other CYP inducers
    - Not metabolized by CYP1A2, 2B6, 2C8, 2C9, 2C19 & 2D6
    - Minor role of CYP3A4 in metabolism
  - Not a CYP450 inducer
    - No significant induction of PXR at 1µM
Clinical Overview of XEN1101

• Phase 1 protocol: Adaptive integrated design
  • SAD/MAD/Food Effect (FE) study
  • Pilot TMS study (Phase 1a)
  • TMS Cross-over study (Phase 1b)

• Planning Phase 2 clinical trial in Adult Focal Epilepsy

• Pediatric development options currently being evaluated
  • Focal seizure population
  • Explore precision medicine in KCNQ2 population
XEN1101 Phase 1 Trial Design

SAD
placebo n=6
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
Cohort 6
Cohort 7

MAD
placebo n=2
Cohort 1 fasted, 15 mg, n=6
Cohort 2
Cohort 3
Cohort 4

TMS Pilot
Cohort 1 10 mg, n=2
Cohort 2 15 mg, n=3
Cohort 3 20 mg, n=3

TMS Cross-over
Drug
Placebo
X
Drug
Placebo
20 mg, n=15-20
Optional
XEN1101 Single Ascending Dose

Long Half-Life Consistent with Once Daily Dosing
XEN1101 Repeat Dosing for 7 Days

Achieve Steady State Plasma Levels at Approximately 7 days
Food Enhances XEN1101 Exposure

Cross-Over Design Food Effect
Chronic Low Daily Dosing Achieves Exposures Required for TMS and Pre-Clinical Efficacy
No Signal of Urinary Retention in Clinic to Date

- Single doses of XEN1101: 5-30 mg
  - No urinary retention or hesitation AEs noted in 28 volunteers
  - $C_{\text{max}}$ range up to 104 ng/mL
- Multiple doses of XEN1101: 15 mg QD for 7 days
  - No urinary retention or hesitation AEs noted in 6 volunteers
  - $C_{\text{max}}$ range up to 57.7 ng/mL
  - Post-void residual volume bladder ultrasound normal

### Post Void Residual Volume Evaluation in MAD

<table>
<thead>
<tr>
<th>Study Day</th>
<th>XEN1101 (N = 6)</th>
<th>Placebo (N = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dose</td>
<td>37.0 ± 27.8 mL</td>
<td>28.0 ± 15.6 mL</td>
</tr>
<tr>
<td>Day 7</td>
<td>13.2 ± 5.6 mL</td>
<td>8.5 ± 0.7 mL</td>
</tr>
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Interim Preliminary Safety Summary

• Ongoing study, evaluated SAD: 5, 15, 20, 30 mg, MAD: 15 mg
• No SAEs or deaths
• No clinically significant ECG or Laboratory findings
• Majority of AEs were mild and resolved spontaneously
  • Most common AEs were headache, dizziness, and drowsiness
  • One severe AE: vasovagal reaction following a blood draw and standing
• Post void residual volume (MAD) not increased; no chromaturia
• Overall safe and well tolerated
Transcranial Magnetic Stimulation (TMS)

• TMS uses a magnetic pulse to stimulate human motor cortex
  • Response can be measured with
    • EMG (motor threshold for finger twitch)
    • EEG (characteristic response pattern)
• TMS is used to assess cortical excitability in response to AEDs in both volunteers and patients
• Provides an opportunity for an early indicator of pharmacological effects consistent with anti-epileptic activity in human volunteers
TMS EMG

TMS-evoked Motor Potentials (MEPs)

Rogasch et al., 2013 Schiz Bull

TMS EEG

TMS-evoked EEG Potentials (TEPs)

Premoli et al., 2014 Journal of Neuroscience
Prior TMS-EMG Cross-Over Study Using Ezogabine

- Double-blind, placebo-controlled cross-over study
- 15 healthy subjects
- Single 400 mg dose of ezogabine
- TMS-EMG performed at $C_{\text{max}}$ of 2 hours
  - No TMS-EEG performed
- Resting Motor Threshold (RMT) increased
  - $2.4 \pm 3.6\%$

Ossemann et al, Epilepsy Res, 126, 78, 2016
TMS Strategy for XEN1101

Goal:
• Seeking a marker of early target engagement in humans

Objectives:
• Compare magnitude of effects of XEN1101 vs ezogabine
• Provide preliminary evidence for CNS target engagement
• Determine dose and sample size for robust double-blind, placebo-controlled, TMS-EMG/EEG cross-over study
XEN1101 Open-Label Pilot TMS Study

- 8 male subjects
- Entered pilot TMS study after completing SAD cohort
- Three dose levels (10, 15, 20 mg) evaluated, open label
- TMS-EMG and TMS-EEG evaluations compared to baseline
XEN1101: Substantial RMT Response at Low Dose

TMS-EMG Effect of XEN1101 Observed at 20 mg vs Ezogabine at 400 mg

Retigabine data from Osseman et al., Epilepsy Research 2016; 126:78-82

XEN1101 TMS-pilot study data recorded at 4 hours after dose
TMS-EEG: Provides Biomarkers of Physiological Processes

Premoli et al., 2014 Journal of Neuroscience
XEN1101 Shows Robust Response & Emerging EEG Signature

TMS-EEG of XEN1101 20 mg Dose

Pattern of Reduced N100 and P180 Amplitudes

<table>
<thead>
<tr>
<th>20 mg</th>
<th>Pre</th>
<th>Post 2h</th>
<th>Post 4h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N100</td>
<td>P180</td>
<td>N100</td>
</tr>
<tr>
<td>mean</td>
<td>-3.87</td>
<td>1.61</td>
<td>-2.23</td>
</tr>
<tr>
<td>SD</td>
<td>0.77</td>
<td>0.73</td>
<td>1.43</td>
</tr>
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Topographical Map 180 ms

Statistically Significant XEN1101 Suppression at 4 hours (p<0.01)
Summary of Pilot TMS Results

• EMG
  • Signal at 10 and 15 mg, with robust response at 20 mg
  • TMS-EMG effect of XEN1101 observed at 20 mg vs ezogabine at 400 mg

• EEG
  • 20 mg dose shows statistically significant modulating activity, with reproducible and specific pattern of response
    • Reduced amplitudes of N100 and P180 peaks
    • Effects on evoked potentials similar in magnitude to lamotrigine and levetiracetam

• Well-powered, placebo-controlled cross-over nearing completion
  • N=15-20
  • 20 mg
Summary of XEN1101 Interim Phase 1 / Pilot TMS Results

• XEN1101 has a PK profile consistent with once a day dosing
• Mild transient AE profile consistent with MOA (e.g., dizziness, sedation)
• Majority of AEs mild except a vasovagal reaction during standing orthostatic BP test immediately after blood draw
• No safety signals in ECG or Safety Labs; no SAEs
• Exposure enhanced by food
• Steady state plasma levels reached at ~ 7 days
• Low inter-individual exposure with repeat dose
• Robust TMS response detected at 20 mg
• TMS cross-over study ongoing at 20 mg
XEN1101 Phase 1b TMS 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 = 15-20
  - Placebo-controlled, double-blind
  - Cross-over
XEN1101 Phase 2 Clinical Planning

- Proposed plans include a Phase 2 clinical trial (H2:18 start) in adult patients with focal seizures
- Pediatric development options currently being evaluated
  - Focal seizure population
  - Precision medicine in KCNQ2 population
XEN1101 Summary

• Best-in-class K\textsubscript{v}7.2 modulator
• Highly clinically, pharmacologically and genetically validated mechanism
• Substantial improvement over ezogabine
  • Pigmentation issue appears resolved
  • More potent and predicted improved TI
  • Predict lower CNS-related AEs due to QD dosing with low peak to trough ratio
• Phase 1 clinical trial and TMS placebo-controlled cross-over study ongoing
  • Interim data suggests XEN1101 is safe and well tolerated
  • Exposure within predicted efficacy range at low doses
  • Oral PK supports QD dosing
  • Robust TMS signal with increased RMT and a distinct N100 and P180 pattern at 20 mg
• AED polypharmacy, without predicted DDI liability
• Phase 2 start expected in second half of this year
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