XEN1101, a Novel Modulator of Kv7.2/3 for the Treatment of Epilepsy

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**XEN1101: Improved 2\textsuperscript{nd} Generation K\textsubscript{V}7.2 Opener**

- **Human genetic validation of KCNQ2 target**
  - *De novo* dominant negative missense mutations cause EIEE7

- **Good pharmacological validation** as ezogabine was approved in 2011 for treatment resistant epilepsy

- **Potential for best-in-class K\textsubscript{V}7.2 opener**
  - XEN1101 has improved pharmacokinetics, selectivity and pharmacology over ezogabine
    - Removed from the market in mid-2017 for commercial reasons

- **Clear clinical and regulatory pathway**

- **FIH study initiated October 2017**

- **Anticipate early PD readout via TMS study currently underway as part of Phase 1 trial**
XEN1101: Improved 2nd Generation Kv7.2 Opener

- No potential to form colored dimers
- ~20-fold more potent for Kv7.2/7.3 heterotetramers over ezogabine
- ~2-3-fold more selective over Kv7.4 and Kv7.5
- No activity on Kv7.1, hERG, GABA
- Greater potency than ezogabine and other AEDs in multiple animal models
- Higher therapeutic index based on rat rotarod and mouse TD50 compared to ezogabine
- Improved PK predicts once daily dosing in humans leading to reduced frequency of Cmax related CNS AEs
**XEN1101: Potent Efficacy in Animal Models**

- More potent than ezogabine and other AEDs in animal models

<table>
<thead>
<tr>
<th></th>
<th>Mice IP MES $ED_{50}$ (mg/kg)</th>
<th>Mice IP Metrazol $ED_{50}$ (mg/kg)</th>
<th>Mice IP Picrotoxin $ED_{50}$ (mg/kg)</th>
<th>Mice IP Bicuculline $ED_{50}$ (mg/kg)</th>
<th>Mice IP 6 Hz, 32 mA $ED_{50}$ (mg/kg)</th>
<th>Mice IP 6 Hz, 44 mA $ED_{50}$ (mg/kg)</th>
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<tbody>
<tr>
<td>Ezogabine</td>
<td>29.51</td>
<td>&gt;50</td>
<td>33</td>
<td>&gt;50</td>
<td>12.1</td>
<td>20.25</td>
</tr>
<tr>
<td><strong>XEN1101</strong></td>
<td><strong>6.1 (2.2)</strong></td>
<td><strong>3.9</strong></td>
<td><strong>9.86</strong></td>
<td><strong>2.59</strong></td>
<td><strong>3.7</strong></td>
<td><strong>5.0</strong></td>
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<td>Carbamazepine</td>
<td>7.81</td>
<td>&gt;50</td>
<td>&gt;18.2</td>
<td>&gt;50</td>
<td>75% @ 40 mg/kg</td>
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<tr>
<td>Gabapentin</td>
<td>78.1</td>
<td>47.5</td>
<td>&gt;500</td>
<td>&gt;500</td>
<td>No activity</td>
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<tr>
<td>Lamotrigine</td>
<td>7.47</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>50% @ 20 mg/kg</td>
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<tr>
<td>Levetiracetam</td>
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<td>&gt;500</td>
<td>&gt;500</td>
<td>4.7</td>
<td>19.4</td>
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<tr>
<td>Topiramate</td>
<td>33</td>
<td>&gt;800</td>
<td>&gt;500</td>
<td>&gt;500</td>
<td>&gt;300</td>
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Electrically induced seizures: MES and 6 Hz  
GABA$_A$ antagonists: Bicuculline and Picrotoxin  
Chemical convulsant: Metrazol
XEN1101 Improved Therapeutic Index Versus Ezogabine

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

Tested 1h Post Dose

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<tr>
<th></th>
<th>scPTZ</th>
<th>scPicrotoxin</th>
<th>scBicuculline</th>
<th>MES</th>
<th>6Hz 32mA</th>
<th>6Hz 44mA</th>
<th>Rotarod</th>
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<tr>
<td>Ezogabine</td>
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mg/kg
PK in NHP predicts once daily dosing in humans.

- Mean plasma concentrations in NHP after repeat oral dosing
- Low peak to trough ratio
- Supports QD dosing
XEN1101 Development Overview

- **Phase 1**: Adaptive integrated design underway, readout expected mid 2018
- **SAD/MAD study with pilot TMS** (transcranial magnetic stimulation)
- **TMS cross-over study**
  - Dosing following selection of dose from SAD/MAD/pilot TMS
- **Chronic GLP toxicology studies in rat and NHP in progress**
- **Phase 2** to follow ezogabine precedent in refractory focal seizures
- **Exploring treating early onset epileptic encephalopathies including KCNQ2-encephalopathy (EIEE7)**
XEN1101 Summary

- Best/only-in-class $K_{\text{V}}7.2/3$ modulator
- Highly genetically and clinically validated mechanism
- Highly efficacious in a broad range of epilepsy animal models
- Excellent oral PK in animal models predicts once daily dosing
- Expect lower $C_{\text{max}}$ related CNS AEs compared to ezogabine
- No potential for pigmentation as seen with ezogabine
- Human PK, safety and PD studies ongoing
- Phase 2 planned to initiate H2:2018 in focal adult-onset seizures
- Parallel evaluation of precision medicine strategy to treat KCNQ2-encephalopathy
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