“Anticonvulsant Effects of the Differentiated $K_v7$ Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs”

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Rationale for Testing XEN1101 in Combination with Other ASMs

- XEN1101 is a differentiated “next generation” Kv7 potassium channel modulator being developed for the treatment of epilepsy and potentially other neurological disorders.

- Kv7 channels are important modulators of neuronal resting membrane potential and XEN1101 potentiation of Kv7 is predicted to provide robust activity in epilepsy.

- Rational polypharmacy is common in clinical practice.

- XEN1101 mediated inhibition of neural activity was predicted to accentuate the efficacy of anti-seizure medications (ASMs) acting by other mechanisms.
XEN1101 is a Potent Inhibitor of Seizures in Rodent Models

- XEN1101 inhibits seizures in rodent seizure models* at low plasma concentrations
- Low plasma levels reduce the likelihood of off-target activity

* Mouse Alternating Current Maximal Electroshock (MES) Assay and 6Hz Psychomotor Seizure Assay (34 mA)
Potency Differentiates XEN1101 from Established ASMs

- XEN1101 is more potent* than many current ASMs in preclinical models of epilepsy

![](image)

<table>
<thead>
<tr>
<th></th>
<th>XEN1101</th>
<th>ezogabine</th>
<th>lacosamide</th>
<th>phenytoin</th>
<th>cenobamate</th>
<th>valproic acid</th>
<th>levetiracetam</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC$_{50}$</td>
<td>0.3</td>
<td>3.5</td>
<td>22</td>
<td>27</td>
<td>70</td>
<td>1,400</td>
<td>2,900</td>
</tr>
<tr>
<td>Fold XEN1101</td>
<td>-</td>
<td>12</td>
<td>73</td>
<td>90</td>
<td>230</td>
<td>4,700</td>
<td>10,000</td>
</tr>
</tbody>
</table>

* Potency measures from Xenon data in mouse MES or 6Hz 34 mA assays
Combining XEN1101 with Common ASMs Provides Robust Seizure Protection

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

![Graphs showing the fraction of seizures for different treatments and combination doses.](image-url)
Combining XEN1101 with Cenobamate Provides Robust Seizure Protection

- Combining ineffective or weakly active plasma levels of XEN1101 and cenobamate provides robust seizure protection in the mouse MES assay.

- Improved efficacy is not explained by increased plasma concentration of either agent - not a DDI effect.

- Combination doses were well tolerated.
Conclusions

- XEN1101 is a differentiated, next-generation Kv7 potassium channel modulator
- Combining sub-efficacious doses of XEN1101 and other ASMs provides robust efficacy
- Improved efficacy is not an apparent DDI effect
  - Not explained by increased plasma levels of XEN1101 or other ASMs
- Combination dosing was well tolerated in the dose ranges explored
- This work suggests that XEN1101 can be used as monotherapy or applied in rational polypharmacy to treat seizures
- The Phase 2b “X-Tole” clinical trial is underway to evaluate the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in approximately 300 adult patients with focal epilepsy
  - Topline results 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. Ernesto Aycardi, “Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel Kv7 Modulator”

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