“K\textsubscript{v}7 Modulators in Epilepsy and Depression”

DR. ROBIN SHERRINGTON  
EVP, STRATEGY & INNOVATION | XENON PHARMA CEUTICALS INC.  
FEBRUARY 24, 2021
K<sub>V</sub>7 Potassium Channels Control Neuronal Firing

- K<sub>V</sub>7 channels have important inhibitory control over burst firing maintaining normal neuronal firing in the CNS
- They form hetero or homotetramers
- Modulated by muscarinic receptors, referred to as the M-current
- Loss of the M-current leads to neuronal hyperexcitability
- K<sub>V</sub>7.2/7.3 heterotetramers are the major M-current in the CNS
- Loss of function mutations cause epilepsy

Gunthorpe, Epilepsia 2012; Jentsch, Nature Reviews 2000
Kv7 Openers Proven Mechanism for Control of Seizures

- Ezogabine demonstrated potent seizure reduction in registration trials

**Table 1. KCNQ channels: the primary site for RTG/EZG MoA**

| Pharmacological action | Effect | Level of activity or EC50 or IC50 where determined | Ratio of activity: Free Cmax or Cmin at 1,200 mg/day in patients with epilepsy
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ</td>
<td>Positive allosteric modulator</td>
<td>EC50 = 1.6 μM at KCNQ2/3</td>
<td>~1</td>
</tr>
<tr>
<td>GABA</td>
<td>Positive allosteric modulator at GABA(A) receptors (non-benzodiazepine site)</td>
<td>Significant effects at ≥10 μM in the majority of studies</td>
<td>≥10-fold</td>
</tr>
<tr>
<td>Calcium channels</td>
<td>Weak inhibitor</td>
<td>IC50 &gt; 100 μM at neuronal Ca, channels (29% inhibition at 100 μM)</td>
<td>~20-fold</td>
</tr>
<tr>
<td>Sodium channels</td>
<td>Weak inhibitor</td>
<td>IC50 &gt; 100 μM at neuronal Na, channels (25% at 100 μM)</td>
<td>&gt;100-fold</td>
</tr>
<tr>
<td>Glutamate receptors</td>
<td>No effect at NMDA, AMPA, or kainate receptors</td>
<td>No effect up to 10 μM</td>
<td>&gt;10-fold</td>
</tr>
<tr>
<td>Other: Broad selectivity profile</td>
<td>No additional activities detected</td>
<td>No significant interactions in 62 assays of ion channels, transporters, enzymes, and 2nd-messenger systems at 10 μM</td>
<td>&gt;10-fold</td>
</tr>
</tbody>
</table>

**B. Maintenance phase**

<table>
<thead>
<tr>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo(^a)</th>
<th>RTG/EZG</th>
<th>RTG/EZG</th>
<th>Placebo(^a)</th>
<th>RTG/EZG</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=242</td>
<td>n=241</td>
<td>n=223</td>
<td>n=215</td>
<td>n=187</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>16</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>19</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>29</td>
<td>29</td>
<td>23</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>25</td>
<td>21</td>
<td>15</td>
</tr>
</tbody>
</table>

Gunthorpe, Epilepsia 2012; Porter, Epilepsy Res 2012
$K_v 7$ Therapeutic Target for Seizures and Potentially Depression

Seizures

Depression

Anhedonia

$K_v 7.2/7.3$
Burden of Disease for MDD with Anhedonia

- **WHO ranked major depressive disorder (MDD) as the 3rd cause of burden of disease worldwide**
  - 12 month prevalence ~6%
  - Lifetime prevalence ~15-18%
  - ~30% considered treatment resistant (TRD)

- **Anhedonia is a core symptom of MDD**
  - Associated with poorer treatment outcomes
  - Lengthens time to remission and reduces depression free days in SSRI-TRD with second line therapy
  - Associated with suicidality independent of depressive symptoms in a large cohort of undergraduate students (n = 1,122) and physicians (n = 557)

---

Chronic Social Defeat Stress Model of Depression

- Model of stress related depression
- Discordant behavioural outcomes to CSDS with both susceptible and resilient animals
- Studied to understand the molecular basis of resilience to stressed induced depression
- Tonic firing rather than hyperexcitability of the VTA in the reward system leads to resilient mice
- Gene expression studies showed upregulation of potassium channel including \( K_v7.3 \) (KCNQ3) correlate with resilient phenotype
- \( K_v7.2/7.3 \) heterotetramers effect M-current and blunt VTA hyperexcitability
- Suggests resilience to CSDS is an active molecular process of stress-coping

Krishnan, Cell 2007; Cao, J Neuroscience 2010
Kᵥ7 Channels’ Role in Active Resilience

- Kᵥ7.3 forms heterotetramers with Kᵥ7.2 to effect the M-current and blunt VTA hyperexcitability
- Viral expression of Kᵥ7.3 in VTA reverses the CSDS susceptible phenotype and hyperexcitability and improved anhedonia
- Kᵥ7 opener (ezogabine/retigabine) dosed 8-days (1 mg/kg ip) reversed the susceptibility phenotype mimicking the resilient phenotype
  - Blunted VTA hyperexcitability and normalized social interaction
  - Demonstrated antidepressant activity in the forced swim test of behavioural despair
  - Improved sucrose preference a measure of anhedonia

Friedman, Nature Communications 2016
K_V7 Opener Results in Meaningful Clinical Efficacy in MDD

- Based on the preclinical work, the K_V7 mechanism was evaluated in a proof-of-concept randomized placebo controlled clinical trial (n=45)
  - Ezogabine dosed 300mg TID

Inclusion

- DSM-V MDD or PDD
- Clinically significant anhedonia (SHAPS ≥ 20)
- Illness severity moderate or greater (CGI-S ≥ 4)

Highlighted Demographics

<table>
<thead>
<tr>
<th>Highlighted Demographics</th>
<th>Active</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MADRS</td>
<td>28.4</td>
<td>26.8</td>
</tr>
<tr>
<td>Baseline SHAPS</td>
<td>38.7</td>
<td>33.7</td>
</tr>
</tbody>
</table>

Montgomery–Åsberg Depression Rating Scale

- Estimate=-1.49, SEM=0.37; DF=213, t=-4.04, p<.0001
- Cohen's d = 0.7

Snaith-Hamilton Pleasure Scale

- Estimate=-1.55, SEM=0.37; DF=212, t=-4.1, p<.0001
- Cohen's d = 0.6

Murrough, JW ACNP 2019 Orlando, FL; Costi S, et al., in press
Kv7 and Depression and Anhedonia Review

- Resilience is proposed to be an active coping mechanism to stress induced depression
- Hyperexcitability of the VTA DA neurons underpins susceptibility to CSDS
- Upregulation of voltage gated K⁺ channels including Kv7.3 associated with resilient phenotype
- Kv7.3/7.2 mediated M-current blunts the VTA hyperexcitability and reverses the susceptibility phenotype
- Ezogabine demonstrated beneficial effects in MDD patients including for anhedonia
- A novel molecular mechanism to potentially treat depression through modulation of the reward system

Krishnan, Cell 2007; Feder, Nat Rev Neurosci 2009
### Depression and Anhedonia Present in Animal Models of Epilepsy

<table>
<thead>
<tr>
<th>Epilepsy Model</th>
<th>Forced Swim Test Immobility</th>
<th>Sucrose/Saccharin Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid amygdala kindled TLE rats</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pilocarpine induced status epilepticus rats</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>LiCl-pilocarpine non-convulsive status epilepticus*</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>WAG/Rij genetic absence seizure rats</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hippocampal kindled TLE rats</td>
<td>ND</td>
<td>↓</td>
</tr>
<tr>
<td>Amygdala kindled TLE rats</td>
<td>ND</td>
<td>↓</td>
</tr>
</tbody>
</table>

* *抵抗fluoxetine的抗抑郁障碍和抑郁障碍的后果不依赖于自发性复发性癫痫发作的频率*

Mazarati, Brain 2008; Pineda, Epilepsia 2010; Sankar, Jasper’s Basic Mechanisms of the Epilepsies 2012; Chen, Frontiers in Behavioural Neuroscience 2016; Medel-Matus, Epilepsia 2017; Boldt, Epilepsy & Behavior 2021
Depression Burden in Persons with Epilepsy

- Is a common co-morbidity of epilepsy lifetime prevalence rate reported in the literature ~30-50%
- Greater severity of depression associated with higher seizure frequency
- Is a strong and independent predictor of reduced QOL
  - Depression severity but not seizure frequency predicts QOL in treatment resistant epilepsy
- Lifetime history of depression may predict of resistance to treatment
- Significant cause of non-adherence to anti-seizure medications (ASMs)

Physicians’ Perspectives

- Market research with 20 Epileptologists examined the impact of depression in epilepsy patients with focal onset seizures
- Physicians reported ~35-45% of actively managed focal onset seizure patients suffer from depression
- Physicians highlighted the critical need for ASMs offering a mood benefit for patients that suffer from comorbid depression
  - Current ASMs do not adequately address depression
  - ASM side effect profiles can exacerbate mood-related comorbidities (e.g. levetiracetam)
  - In later lines of treatment, physicians indicated the potential need to choose between improving seizure control at the expense of potentially worsening mood-related comorbidities

Quotes from U.S. KOL Epileptologists

“A great unmet need is improving the treatment of these patients with psychological / psychiatric co-morbidities, due to the disabling effect to patients.”

“If a product can improve both seizures and a comorbidity, I think I could use it to help lessen the treatment burden due to the number of medications a patient is on.”
XEN1101’s Differentiated Profile in Adult Focal Epilepsy

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

<table>
<thead>
<tr>
<th>Ease of Use</th>
<th>Efficacy</th>
<th>Safety / Tolerability</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<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>
</tr>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>✓ No drug allergic reactions observed</td>
<td>✓ Slow elimination could provide coverage for missed doses</td>
<td></td>
</tr>
</tbody>
</table>
XEN1101 in Preclinical Models of Epilepsy and Depression

Maximal electrical shock (MES) is a model of generalized seizures

- XEN1101 demonstrated a significant reduction in seizures

The forced swim test (FST) is a depression model of behavioral despair

- XEN1101 demonstrated a significant reduction in time spent immobile, indicating an anti-depressant effect

The progressive ratio test (PRT) is a model of motivational performance and decisional anhedonia

- XEN1101 significantly increased the total number of lever presses in the test session

Vehicle

<table>
<thead>
<tr>
<th>1 mpk</th>
<th>3 mpk</th>
<th>7.5 mpk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

** (**p<0.01, ***p<0.001)

Vehicle

<table>
<thead>
<tr>
<th>1 mpk</th>
<th>3 mpk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

(*) p<0.05 compared to vehicle
Conclusions

- XEN1101 is a differentiated, next-generation K\textsubscript{V7} potassium channel modulator
- K\textsubscript{V7} channels mediate resilience to chronic stress related depression in animal models through blunting of VTA excitability within the reward system
- Ezogabine a K\textsubscript{V7} opener significantly improved depression and anhedonia in MDD patients
- The results from the two preclinical studies presented at ASENT 2021 support a potential benefit of XEN1101 in mood disorders
- Major depression is a common co-morbidity of persons with epilepsy and significantly impacts their quality of life
- 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
- Anticipate initiating a Phase 2 proof-of-concept clinical trial examining XEN1101 in MDD with anhedonia in 2021

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

Dr. Alison Cutts, “Depression and Anhedonia: Acute Preclinical Efficacy for XEN1101, a Differentiated K\textsubscript{V7} Potassium Channel Modulator”

Dr. Ernesto Aycardi, “Addressing an Unmet Medical Need in Adult Focal Epilepsy with XEN1101, a Novel K\textsubscript{V7} Modulator”

Dr. J.P. Johnson, Jr., “Anticonvulsant Effects of the Differentiated K\textsubscript{V7} Channel Potentiator XEN1101 in Combination with Commonly Used Anti-Seizure Drugs”
Acknowledgements

Xenon Pharmaceuticals Inc.
- Alison Cutts
- Rostam Namdari
- Greg Beatch
- Nina Weishaupt
- Richard Dean
- Jeff Bechard
- JP Johnson
- James Empfield

Intervivo Solutions Inc.
- Guy Higgins
- Leo Silenieks
- Cam MacMillan
- Matt Brown
- Nicole Carroll

Mount Sinai Hospital
- James Murrough