XEN901: A Novel, Highly Selective Na\textsubscript{V}1.6 Inhibitor for the Treatment of Epilepsy

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Eilat XIV Meeting | May 15, 2018 | Madrid, Spain
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XEN901: A Highly Selective Na\textsubscript{v}1.6 Inhibitor

- Potent and highly selective Na\textsubscript{v}1.6 inhibitor
  - Avoid inhibition of Na\textsubscript{v}1.1 and Na\textsubscript{v}1.5 to improve safety profile
  - Novel sodium channel binding site and mechanism of action
- Precision medicine to selectively address the etiology of Early Infantile Epileptic Encephalopathy type 13 (EIEE13)
  - Gain-of-function mutation in SCN8A causes EIEE13
  - Excellent efficacy in transgenic mouse model for EIEE13
- Treatment for focal seizures that achieves higher levels of seizure freedom with an improved side effect profile
  - Excellent efficacy in Maximal Electroshock Seizure (MES) models with high therapeutic index
- Favorable PK and safety profile in ongoing Phase 1
  - Expect regulatory filing for Phase 2 by year-end

*Potential Best in Class Sodium Channel Inhibitor*
Rationale for Selective $Na_V 1.6$ Inhibitors

- Low TI of currently used $Na_V$ inhibitors is generally dose limiting
  - Non-selective among $Na_V$’s in CNS (1.1, 1.2 and 1.6) and CV (1.5)
    - Block of $Na_V 1.1$ proconvulsant: highly expressed in GABAergic interneurons
      - Dravet Syndrome usually loss of function mutation in $Na_V 1.1$
    - No benefit to block of $Na_V 1.5$ and introduces risk of CV adverse effect
  - Low potency – requires high dose/exposure
  - Adverse effects preclude achieving seizure freedom

- Precision medicine for treating etiology of EIEE13 (SCN8A epilepsy)
- Modest suppression of $Na_V 1.6$ activity needed for seizure control
Highly Selective Inhibitors Targeting Voltage Sensor Domain IV

- Therapeutically used Na$_v$ inhibitors bind in pore domain
  - Promiscuous, low affinity binding site
- High affinity and selectivity achieved by binding VSD4 in an extracellular site

Xenon’s Approach: Target VSD4 in Na$_v$1.6 to Achieve High Selectivity
**XEN901 is a Potent and Selective Inhibitor of Na\(_V\)1.6**

- >100-fold selective vs. other Na\(_V\)'s
  - Inhibition of Na\(_V\)1.1 is pro-convulsant
  - Inhibition of Na\(_V\)1.5 poses CV risk

- >100-fold more potent than non-selective AEDs
XEN901 is Potent Across EIEE13 Mutations

- Mutations known to cause EIEE13 were incorporated into Na\textsubscript{v}1.6 and potency of block by XEN901 was evaluated
- 7 of 8 mutants are blocked with similar potency as WT channel
  - R1617Q in the binding site; although block is weaker, still more potent than currently available Na\textsubscript{v} inhibitors
Early Infantile Epileptic Encephalopathy Type 13

- Precision medicine to treat the etiology of a severe childhood epilepsy
  - Caused by SCN8A GOF mutations
  - Early genetic testing support estimates of ~15-20% of Dravet patient numbers
  - ≈50 births/year in U.S.

- SCN8A mouse model of EIEE13
  - Use for target engagement and screening assay
  - Phenotype similar in mice and humans
Seizure Control/Freedom in SCN8A Tg Mouse Model of EIEE13

- XEN901 completely suppresses seizures in modified 6 Hz assay
  - Elicit tonic-clonic seizure in Tg mice, no seizures in wild type mice (dotted line)
  - Suppress to wild type at EC$_{70}$
- >100-fold greater potency compared to current treatments for EIEE13

**Graph:**
- Average cumulative Racine score
- Brain$_{Total}$ Concentration (μM)

**Legend:**
- XEN901
- Phenytoin
- Carbamazepine
- Lacosamide

**Modified Cumulative Racine Score**
- 0 = no response
- 1 = Shaking/ Jerking / Facial Tremor, Freezing, Blinking
- 2 = Forelimb clonus or Straub tail
- 3 = Loss of balance, Rearing and falling
- 4 = Clonic Seizure
- 5 = Tonic-Clonic seizure with extension of hind limbs
XEN901 is Potent and Efficacious in MES

- Therapeutically used Na\textsubscript{v} antagonists active in MES assay – good translational model
- Concentration-dependent increase in efficacy
- Doses of 3-200 mg/kg
- Chronic dosing leads to ~10x increase in potency
- High safety margin
- Similar observations in rat MES assay

![Graph showing concentration vs. fraction of animals with tonic seizure](image)
Potency in the MES Model Driven by $\text{Na}_V1.6$

- Potency in both assays highly correlated with potency against $\text{Na}_V1.6$ and brain concentration
- Good correlation between SCN8A Tg mouse and MES assays
- Independent of potency at $\text{Na}_V1.2$ or other sodium channels
Striving for Seizure Freedom with XEN901

- Current Na$_v$ channel AEDs require 1-5 times the mouse MES EC$_{50}$ for clinical efficacy.
- Current agents lack therapeutic index needed to achieve seizure freedom for many patients.
- High TI of XEN901 could enable high level of efficacy with minimal adverse events.

Mouse MES Assay

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fraction of animals with tonic seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>XEN901</td>
<td>[Plasma] (µM)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td></td>
</tr>
</tbody>
</table>

Shaded areas correspond to published clinical plasma concentrations.
## Improved Therapeutic Index Over Other Na\textsubscript{V} Inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC\textsubscript{70} Plasma (\textmu M)</th>
<th>Toxic Plasma Levels (\textmu M)</th>
<th>Safety Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>XEN901 (acute)</td>
<td>0.264</td>
<td>45</td>
<td>170</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>20</td>
<td>54</td>
<td>1.7</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>60</td>
<td>233</td>
<td>3.8</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>12</td>
<td>63</td>
<td>5.3</td>
</tr>
</tbody>
</table>

- EC\textsubscript{70} = plasma concentration where 70% of mice are protected from tonic seizure induction in MES assay
- Toxic = minimum plasma concentration where severe adverse behavioral effects were observed
XEN901: Favorable Motor Impairment Safety Margin

- Rotarod assay to assess possible motor impairment
- Data expressed as function of dose (for comparison with literature values)
  - Safety margin based on dose in mouse
    - MES for XEN901: >25
  - Other literature comparisons:
    - Carbamazepine (po): 7.7
    - Phenytoin (po): 10.3
    - Lacosamide (ip): 6.0

Potential Best in Class Safety Margin for XEN901
XEN901 Phase 1 Trial Design

SAD
placebo n=8
5 mg, n=3  Cohort 1
10 mg, n=3  Cohort 2
food effect, 5 mg, n=9  Cohort 3
15 mg, n=6  Cohort 4
30 mg, n=6  Cohort 5
45 mg, n=6  Cohort 6
Cohort 7

MAD
Cohort 1
Cohort 2
Cohort 3
Cohort 4
Optional

Anticipate Complete Phase 1 Results in H2, 2018
PK in Phase 1 SAD Study with XEN901

- XEN901 shows dose proportional exposure with single doses of 5-45 mg
- PK displays low inter-individual variability
- PK profile suitable for at least BID dosing ($t_{1/2} = 8-11$ hours)
Interim Preliminary Safety Summary

- Ongoing placebo-controlled, randomized (3:1), double-blind study
  - Single doses completed at 5, 10, 15, 30, and 45 mg
- No SAEs or deaths
- No clinically significant ECG, or Laboratory findings
- All reported AEs to date are mild or moderate
  - Related AEs were mild and resolved spontaneously
  - Most common AE was headache
- Overall safe and well tolerated with $C_{\text{max}}$ up to 1600 ng/mL in SAD

*Interim Results Show Good Safety and Tolerability of XEN901*
Safe Exposure in Phase 1 at or Above EC_{90}

Shaded area corresponds to range between highest C_{max} and C_{12hrs} at 45 mg dose.
XEN901 Proposed Phase 2 Clinical Planning

• Anticipate completing ongoing Phase 1 SAD and MAD in H2, 2018
• Expect regulatory filing for Phase 2 clinical trial in adult focal seizures by year-end
• Pediatric development options currently being evaluated
  • Focal seizure population
  • Explore precision medicine in SCN8A population
**XEN901 Summary**

- XEN901 inhibits Na\textsubscript{v}1.6 with high potency and selectivity
  - Novel binding site and mechanism of inhibition
  - Isoform selectivity enables high therapeutic index

- Best in class safety margin
  - Demonstrated seizure freedom in rodent models
  - Excellent PK, safety, tolerability to date in Phase 1 at predicted therapeutic plasma concentration

- Promising for treatment of both focal seizures in adults and as a precision medicine for treating infants with EIEE13 or other childhood epilepsies

*“Best-in-Class” Potential of XEN901*
Acknowledgements / Contributors

Chemistry
Kristen Burford
Sultan Chowdhury
Shannon Decker
Christoph Dehnhardt
Jim Empfield
**Thilo Focken**
Wei Gong
Mike Grimwood
Abid Hassan
Qi Jia
Verner Lofstrand
Shaoyi Sun
Steve Wesolowski
Michael Wilson
Alla Zenova

Biology
Elaine Chang
Alison Cutts
Richard Dean
Celine Dube
Mandy Feng
Sam Goodchild
**JP Johnson Jr.**
Kuldip Khakh
Jenny Li
Sophia Lin
Janette Mezeyova
Karen Nelkenbrecher
Noah Shuart
Parisa Karimi Tari
Matthew Waldbrook
Diana Weeratunge
Ray Winquist
Clark Xie
Clint Young

Pharmacokinetics
Gina de Boer
Navjot Chahal
Rainbow Kwan
Andrea Lindgren
**Luis Sojo**

Clinical
**Greg Beatch**
Ernesto Aycardi
Jay Cadieux
Y. Paul Goldberg
Heather Kato
Lena Legkaia
Rostam Namdari
Robin Sherrington

University of Michigan (mouse model)
Miriam Meisler
Jacy Wagnon