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Presented at the:
BIOMARIN SCIENTIFIC EXHIBIT
"Genetic Epilepsies – Updates in Science and Diagnosis"

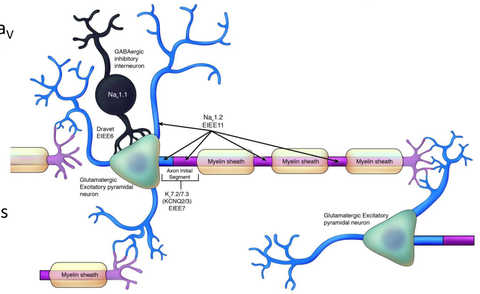
A Phase 1 Study in Healthy Subjects to Assess the Safety, Tolerability and Pharmacokinetics of XEN901, a Novel, Selective $Na_V1.6$ Sodium Channel Inhibitor for the Treatment of SCN8A-Related Epilepsy

Informational Poster Prepared by Xenon Pharmaceuticals Inc.

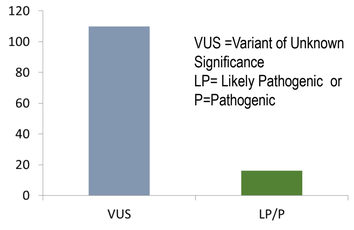
BACKGROUND

XEN901: Novel, selective, small molecule inhibitor of $Na_V1.6$

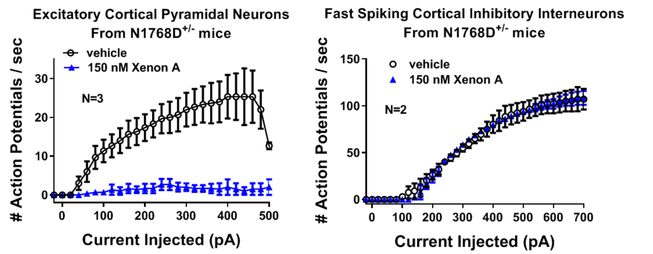
- $Na_V1.6$ is an abundantly expressed Na_V channel in the excitatory pathways in the brain. Current agents lack therapeutic index needed to achieve seizure freedom for many patients.
- High TI of XEN901 could enable improved efficacy with minimal AEs
- Children born with gain-of-function mutations in the *Scn8a* gene (encodes for $Na_V1.6$), can present with SCN8A Developmental and Epileptic Encephalopathy (SCN8A-DEE)



- XEN901, a novel, selective $Na_V1.6$ inhibitor, is being developed for SCN8A-DEE
- SCN8A gain-of-function mutations increase the risk of early mortality
  - 190 children with SCN8A epilepsy were reviewed (Johannesen et al.)[1]:
    - Overall mortality 5.3%
    - Documented SUDEP accounted for 1.6%
- Authors investigated 183 epilepsy-related genes in 9,769 individuals using the Invitae panel (Truty et al.)[2]
  - 126 subjects with SCN8A genotype
  - Majority still being classified as Variant of Unknown Significance (VUS)
  - Functional testing and additional genetic testing likely to identify many more variants as Likely Pathogenic (LP)/Pathogenic (P)
- Separate screen of 70 gene panel identified 30/8565 tests as Pathogenic for *SCN8A* genotype (Lindy et al.)[3]

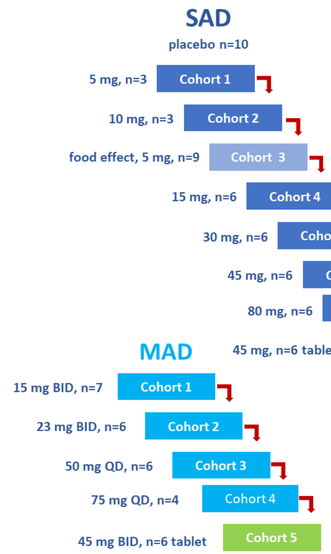


Pre-Clinical Studies Demonstrate Selective $Na_V1.6$ Inhibitor in *N1768D*$^{+/-}$ Mouse Brain Slices Reduces Firing in Excitatory Neurons But Not Inhibitory Interneurons



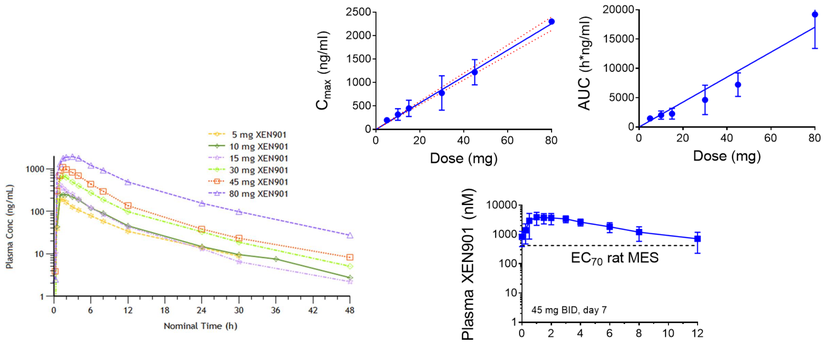
PHASE 1 RESULTS

XEN901 Phase 1 Study Design and Safety Profile



- **Well tolerated following single oral doses up to 80 mg**
  - Plasma levels of up to 2660 ng/mL
  - All TEAEs were mild
  - Restlessness: 1 subject, 45 mg capsule
  - Dizziness and nausea: 1 subject, 80 mg capsule
  - Nausea: 1 subject, 45 mg tablet
- **Well tolerated following multiple doses up to 75 mg QD and 45 mg BID**
  - Plasma levels of up to 2690 ng/mL
  - All TEAEs were mild
  - Fatigue: 1 subject 23 mg BID
  - Nausea, dizziness and headache: 1 subject 50 mg QD
  - Nerve compression: 1 subject 50 mg QD
  - Eye pain: 1 subject 75 mg QD
  - Muscle twitching and insomnia: 1 subject 45 mg BID
  - Muscle twitching: 1 subject 45 mg BID
  - Dizziness: 1 subject 45 mg BID
- **There were no severe TEAEs or serious TEAEs, deaths**
- **No placebo TEAEs**

XEN901's Pharmacokinetic Profile Suitable for at Least BID Dosing

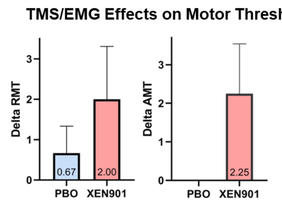


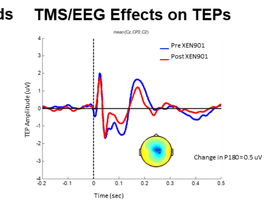
XEN901 SAD Dosing

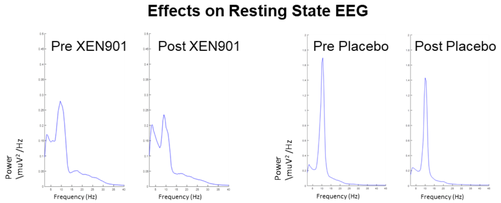
XEN901 MAD Dosing Predicts Adequate Exposure

XEN901 Exploratory TMS Sub-Study

- XEN901's effects on Transcranial Magnetic Stimulation (TMS) measurements and EEG were assessed in 8 subjects with plasma levels >1000 ng/mL from the 50 and 75 mg QD cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on Day 5/6.
- In this pilot study XEN901 showed trends for increases in resting and active motor thresholds (RMT/AMT), decrease in amplitude of TMS evoked potential (TEP) at 180 ms (P180) and an increase in delta power in the resting state EEG.







CONCLUSIONS / NEXT STEPS

- The results to date suggest that XEN901, a novel, first-in-class $Na_V1.6$ inhibitor, is generally safe and well-tolerated at the doses examined
- XEN901 PK is dose proportional in healthy subjects
- The half-life of approximately 8 to 11 hours could potentially support once or twice daily dosing
- Overall safe and well tolerated with C_{max} exposures up to 2700 ng/mL with multiple dosing
- No serious or severe AEs, or AEs leading to subject withdrawal; majority mild and unrelated to XEN901
- Results from pilot TMS study suggest XEN901 has CNS activity, with effects consistent with some other anti-seizure medications

Phase 2 Clinical Planning

- Completed development of a pediatric-specific granule formulation of XEN901
- Completed juvenile toxicology studies to support pediatric development activities
- PK study in healthy adult volunteers with the new pediatric formulation ongoing
- Neurocrine Biosciences obtained an exclusive license to XEN901 and anticipates filing an IND application with the FDA in the middle of 2020 in order to start a proposed clinical trial for XEN901 in SCN8A-DEE patients.

[1]Johannesen *et al*., Epilepsy Research 2018;143:79-81
[2]Truty et al., Epilepsia Open 2019; Jul 1;4(3):397-408
[3]Lindy et al., Epilepsia 2018 May;59(5):1062-1071

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