A Phase 1 Study in Healthy Subjects to Assess the Safety, Tolerability and Pharmacokinetics of XEN901, a Novel, Selective Na$_{v}$1.6 Sodium Channel Inhibitor for the Treatment of SCN8A-Related Epilepsy

**BACKGROUND**

XEN901: Novel, selective, small molecule inhibitor of Na$_{v}$1.6

- Na$_{v}$1.6 is an abundantly expressed Na$_{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 have a shorter life span of 8 to 11 years.

**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: 1 subject 45 mg BID
- 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
  - Plasma levels >1000 ng/mL from the 50 and 75 mg QD cohort compared to 3 placebo subjects. TMS measures were recorded on baseline and on Day 5/6.
- There were no severe TEAEs or serious TEAEs, deaths
- No placebo TEAEs

**XEN901 In SNCA-Related Disorders**

**Pre-Clinical Studies Demonstrate Selective Na$_{v}$1.6 Inhibitor in N1768D Mouse Brain Slices Reduces Firing in Excitatory Neurons But Not Inhibitory Interneurons**

**XEN901’s Pharmacokinetic Profile Suitable for at Least BID Dosing**

**XEN901 Exploratory TMS Sub-Study**

- XEN901’s effects on Transcranial Magnetic Stimulation (TMS) measurements and EEG were assessed in 8 subjects with plasma levels >3000 ng/mL from the 50 and 75 mg QD cohort compared to 3 placebo subjects. TMS measures were recorded on 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 40 ms power in the resting state EEG.

**CONCLUSIONS / NEXT STEPS**

- The results to date suggest that XEN901, a novel, first-in-class Na$_{v}$1.6 inhibitor, is generally safe and well tolerated at the doses examined.
- XEN901 PK is dose proportional in healthy subjects.
- The half-life of approximately 8 to 11 hours could potentially support once or twice daily dosing.
- Overall safe and well tolerated with C$_{max}$ exposures up to 2700 ng/mL with multiple 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 SCNB-DEE patients.

**Neurocrine Biosciences, Inc.**

*Updated June 6, 2019, by the authors.*