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A Phase 1 Study Utilizing Transcranial Magnetic Stimulation to Assess the Pharmacodynamic Effects of a Novel Potassium Channel Opener (XEN1101) on Human Cortical Excitability

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BACKGROUND

XEN1101 is a novel voltage-gated potassium ($K_V7.2/3$) channel opener currently in clinical development by Xenon Pharmaceuticals Inc. as a treatment for epilepsy. Transcranial magnetic stimulation (TMS), in combination with electromyography (EMG) and electroencephalography (EEG), allows measurement of resting and active motor threshold (RMT/AMT) and TMS-evoked EEG potentials (TEPs), which may indicate drug effects on corticospinal and cortical excitability, respectively. Several antiepileptic drugs (AEDs) have been shown to significantly increase RMT values and modulate TEPs, indicating a shift towards corticospinal/cortical inhibition.

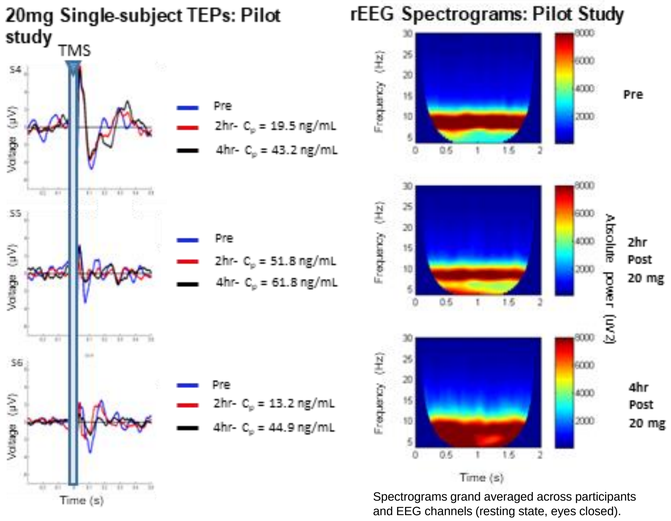
In the pilot study TMS was used to non-invasively determine whether XEN1101 (10, 15 and 20 mg) impacts cortical excitability. The TMS pilot study was designed to inform sample size calculation for a larger randomized, double-blind and placebo-controlled TMS cross-over study (N=20) with XEN1101.

METHODS: PILOT STUDY

Eight healthy, right-handed male subjects (aged 21-35 years, 62.4 - 95.4 kg) from a First-in-Human Phase 1 study (XPF-008-101a) were enrolled in this open-label TMS pilot study. RMT, TEPs and EEGs were recorded prior to XEN1101, 2 and 4 h post dose. Spectral analysis was performed on resting EEGs. Single-subject level analyses were performed via multiple independent sample t-tests to determine effects of XEN1101 on TEP amplitudes. Multiple comparisons were accounted for using cluster-based permutation analysis.

RESULTS: PILOT STUDY

XEN1101, at 4 h post 20 mg (Cplasma = 50 ±10 ng/mL), suppressed TEP amplitudes at late latencies (e.g. the peak at 180ms (P180) after TMS by 1.92 ± 0.03 µV, p<0.01, N=3). The 10 mg (N=2) and 15 mg (N=3) dosages, with mean plasma levels of 23.1 and 36.3 ng/mL XEN1101 at 4 hours, did not show significant and robust TEP modulation. At 4 h post 20 mg, RMT increased 4.3 ± 0.6% from baseline (Poster 3.282) and theta power increased in rEEG. The 20 mg dose of XEN1101 was selected for use in the placebo-controlled, double-blind, TMS cross-over study.

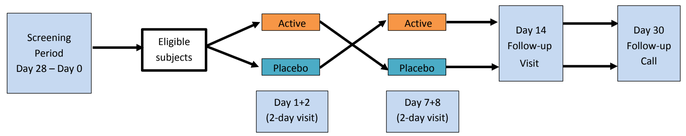


Spectrograms grand averaged across participants and EEG channels (resting state, eyes closed).

METHODS: CROSSOVER STUDY

Twenty healthy, right-handed male subjects (aged 19-40 years, 61.1 - 95.9 kg) were enrolled in a separate randomized, double-blind, placebo-controlled, two-period crossover TMS study. RMT, AMT, TEPs and EEGs were recorded prior to, 2 and 4 h post XEN1101 (20 mg) or placebo. A subset of 16 subjects had TMS/EMG and 8 subjects had TMS/EEG measures recorded at 6 h post dose. Subjects stayed overnight and returned after a 7 day washout between periods to receive the opposite treatment.

Similar TMS-EMG/EEG and rEEG methodologies were used as in the pilot study.



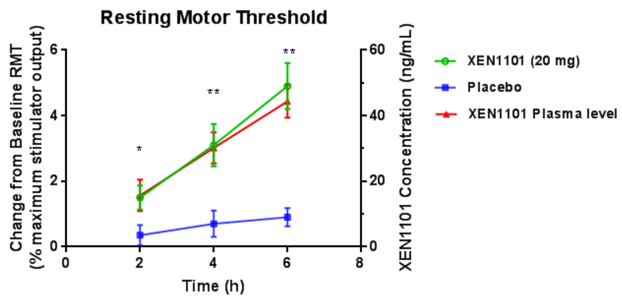
RESULTS: CROSSOVER STUDY

XEN1101 plasma levels were 15.9 ± 21.4 ng/mL at 2h, 30.2 ± 21.1 ng/mL at 4h and 42.1 ± 19.1 ng/mL at 6h. C_{max} was 59.2 ± 13.8 ng/mL and occurred at a median of 7.8 h after dose. The mean ± SD half-life based on 16 subjects with PK samples collected up to 14 days was 127 ± 84.6 h.

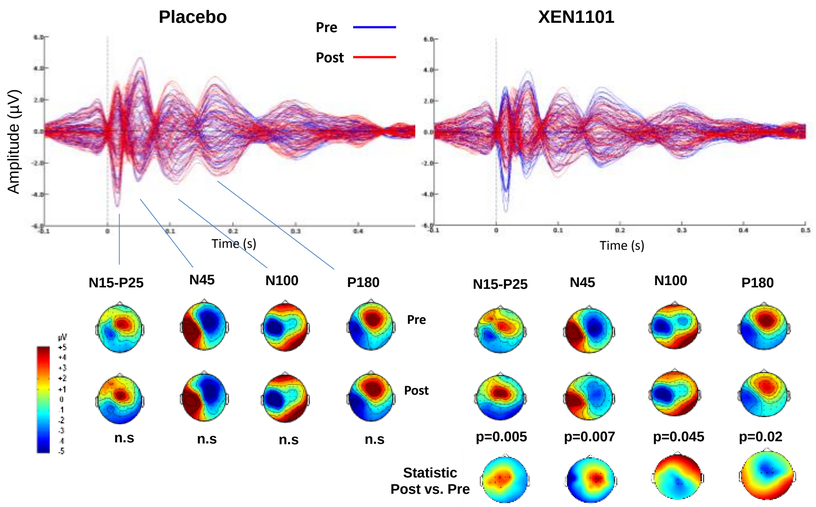
XEN1101-related AEs included dizziness, fatigue, somnolence, headache, disturbance in attention, tension headache, ataxia, diplopia, vision blurred, nausea, and sinus tachycardia. Somnolence was the only placebo-related AE that occurred in more than 1 subject. Moderate AEs during XEN1101 treatment included somnolence (3 subjects), nausea and vomiting (1 subject) and tension headache (1 subject). All other AEs were mild and generally transient. There were no deaths, SAEs, or withdrawals. There were no clinically significant changes in laboratory evaluations, vital signs, or ECG.

RMT increased in proportion to XEN1101 plasma concentration showing a mean ± SEM increase of 4.9 ± 0.7% at 6h (see Figure below). AMT also increased in proportion to plasma concentration with an increase of 2.0 ± 0.4% at 6h. Short Interval Cortical Inhibition (SICI), a measure of GABAergic effects, remained unchanged.

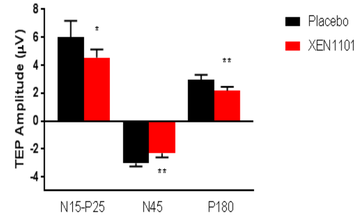
XEN1101 significantly modulated TEPs in a pattern consistent with reductions in cortical excitability. Relative to time-matched placebo, at peak plasma levels, XEN1101 decreased the amplitude of TEPs vs placebo at 25, 45 and 180 ms after the TMS pulse (see Figures). Additional measures of cortical excitability including global mean field power were similarly impacted. XEN1101 also shifted the power spectra of resting state EEGs toward lower frequencies.

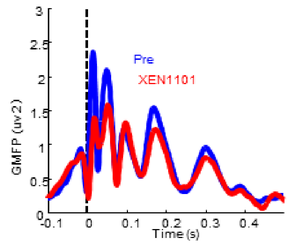


RMT increased in proportion to XEN1101 plasma level. Changes were significant in comparison to time matched placebo treated subjects.



XEN1101, but not time matched placebo, significantly decreased TMS evoked potential amplitudes.





XEN1101 suppressed cortical excitability as evidenced by decreased TMS evoked potential amplitudes and reduction in global mean field power. Effects shown at time of maximum XEN1101 plasma level compared to time matched placebo.

CONCLUSIONS

These TMS studies provided evidence of the CNS effects of a 20 mg dose of XEN1101 as indicated by suppression of cortical and corticospinal excitability.

These results suggest that TMS may be useful in identification of an active dose in healthy volunteers and support continued development of XEN1101 for treatment of patients with epilepsy.