A First-in-Human Phase I Study to Assess the Pharmacodynamic Profile of a Novel Potassium Channel Opener (XEN1101) on Human Cortical Excitability with TMS-EEG and TMS-EMG

Presented by: Isabella Premoli, PhD | 13th European Congress on Epileptology | August 29, 2018

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Disclosure Declaration

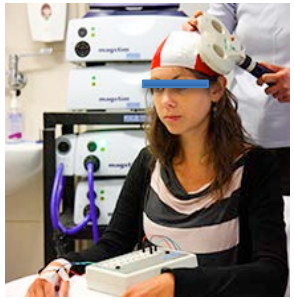
- Xenon Pharmaceuticals Inc. provided financial support for the study of the new antiepileptic drug XEN1101.

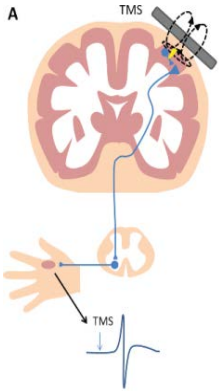
Please note: comparisons of XEN1101 and ezogabine are based on results in published literature, not based on data resulting from head-to-head trials, and are not direct comparisons of safety or efficacy. Different protocol designs, trial designs, patient selection and populations, number of patients, trial endpoints, trial objectives and other parameters that are not the same between the relevant trials may cause any comparisons of results from different trials to be unreliable.

Transcranial Magnetic Stimulation (TMS)

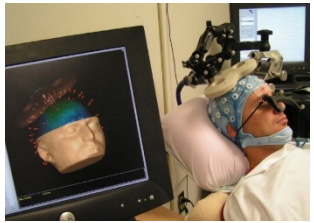
- TMS is a non-invasive tool to study human cortical excitability
- Multiple approved AEDs show effects on TMS at efficacious plasma levels
- Stimulation responses can be measured with:

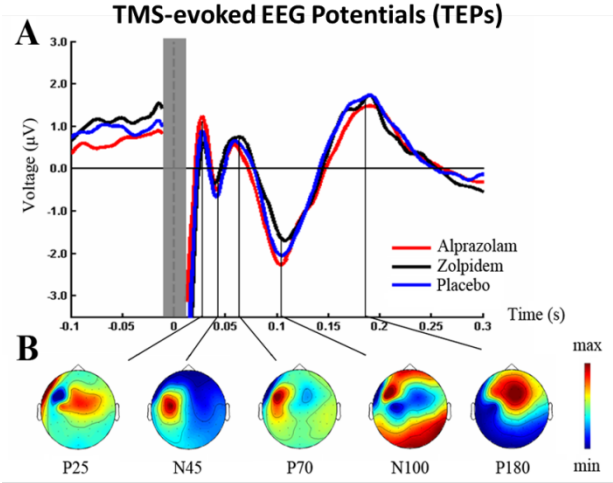
EMG:
Resting Motor Threshold (RMT%) reflects cortico-spinal excitability





EEG:
TMS-evoked EEG potentials (TEPs) allow direct evaluation of cortical excitability in a time-resolved fashion manner





Premoli et al., 2014 *Journal of Neuroscience*

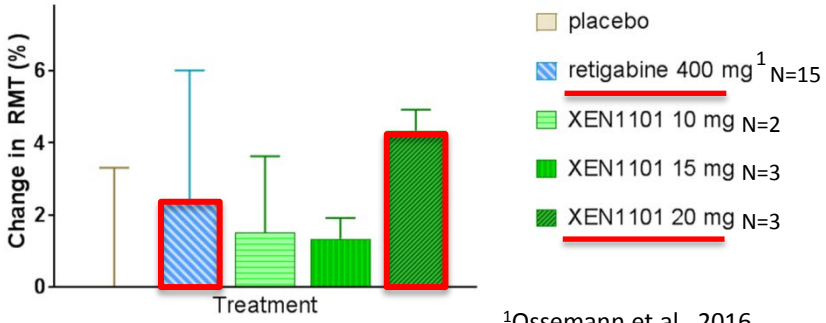
XEN1101: Potential Best-in-Class KCNQ2 Modulator

- Same mechanism of action as retigabine/ezogabine, but with substantial improvements
  - More potent *in vitro* and *in vivo*
  - Improved PK
  - Once daily dosing plus modest selectivity predicts better tolerability
  - No pigmented dimers and no predicted discoloration liability
- Safe and well tolerated in ongoing Phase 1 study
  - 5 SAD cohorts, a food effect cohort, and 3 MAD cohorts of 66 healthy subjects to date
  - TMS Phase 1a pilot study in 8 subjects
  - TMS Phase 1b double-blind, placebo-controlled crossover study in 20 subjects

XEN1101: Pilot TMS-EMG/EEG Study in 8 Subjects

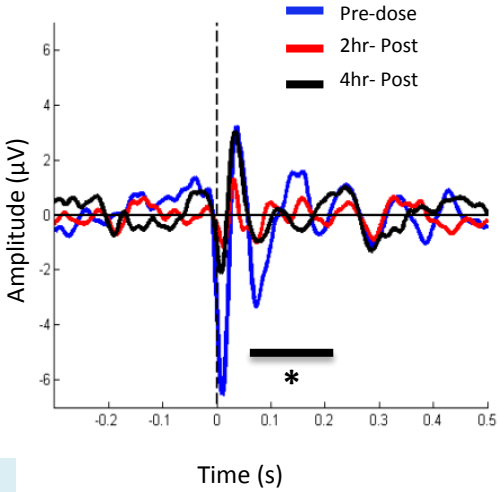
- RMT and TEPs were recorded before, and then 2 and 4 hours post-dose

RMT of XEN1101



[1]Ossemann et al., 2016

TEP of XEN1101 20mg Dose (N=3)



20 mg dose showed:

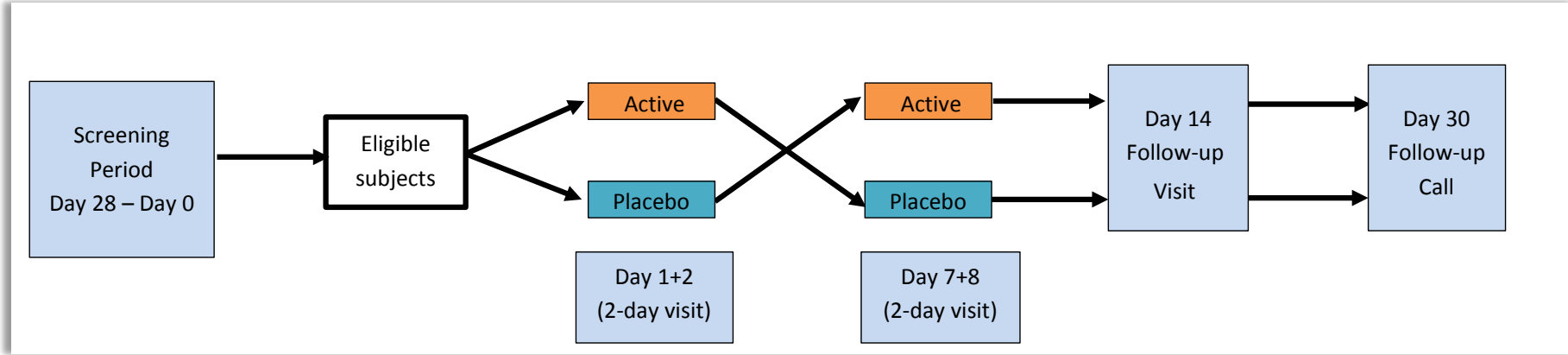
- Strongest significant modulation at 4hrs post-drug
- Pattern of reduced TEP amplitude

RMT is increased at 10 and 15 mg, with robust response at 20 mg

RMT effect of XEN1101 (20 mg) is ~2x retigabine at 1/20th the dose (400 mg)

XEN1101: Double-Blind, Placebo-Controlled, Crossover TMS Study

- XEN1101, 20 mg dose
- RMT and TEPs were recorded at baseline, 2, and 4 hours (N=20)
- Measurements at 6 hours added based on PK:
  - RMT (N=16)
  - TEPs (N=8)



TMS Crossover Study: Demographics, Safety, and Tolerability

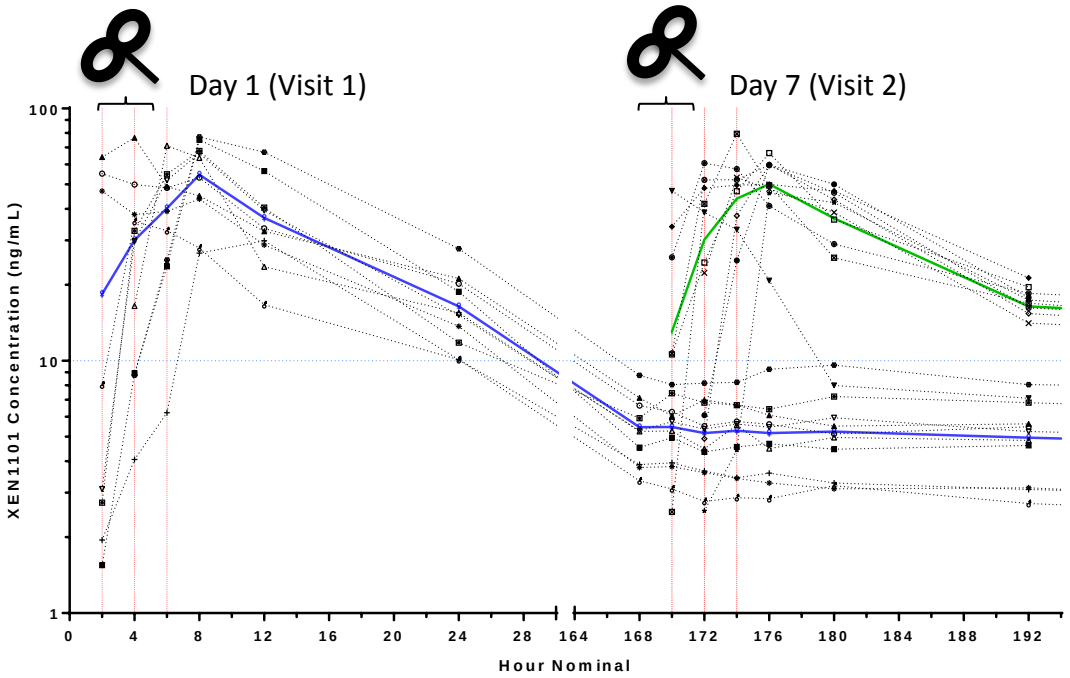
20 Healthy male volunteers were enrolled in the crossover study

- All subjects completed both periods
- Age range (19-40 years)
- Weight range (61.1-95.9 kg)

XEN1101 was safe and well tolerated

- All adverse events (AEs) were transient and mild or moderate
  - Dizziness, somnolence, fatigue, headache, attention disturbance were the most common AEs
- AEs were consistent with other anti-epileptic drugs
- There were no clinically significant changes in vital signs, ECG or safety labs
- There were no withdrawals, SAEs, or deaths

TMS Measurements at Time Points During Rising Plasma Levels



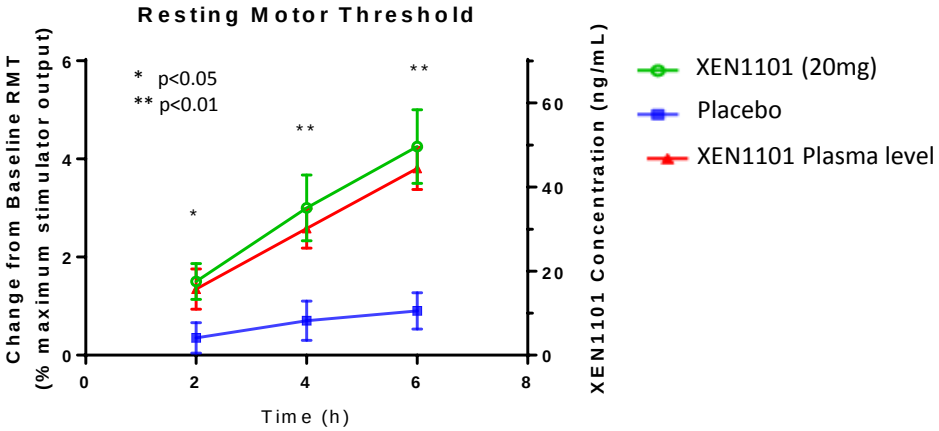
- Prolonged absorption
- Long elimination half-life
- TMS assessments were made during the rising phase of XEN1101 plasma levels:
  - 2h: 15.7 ± 21.5 ng/mL
  - 4h: 30.2 ± 21.1 ng/mL
  - 6h: 44.4 ± 20.2 ng/mL
  - C_{max} = 59.2 ± 13.8 ng/mL
  - T_{max} range = 2-12 hours

4- and 6-hour Measurements May Be 'Under-Estimates' of Effect Based on T_{max} Range

Time and Concentration Effects of XEN1101 using TMS-EMG Measure

Time effect

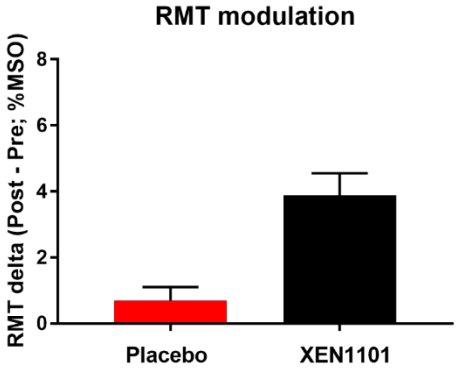
(2, 4, and 6 hours post dose)



~4% effect at t=6 hours vs placebo

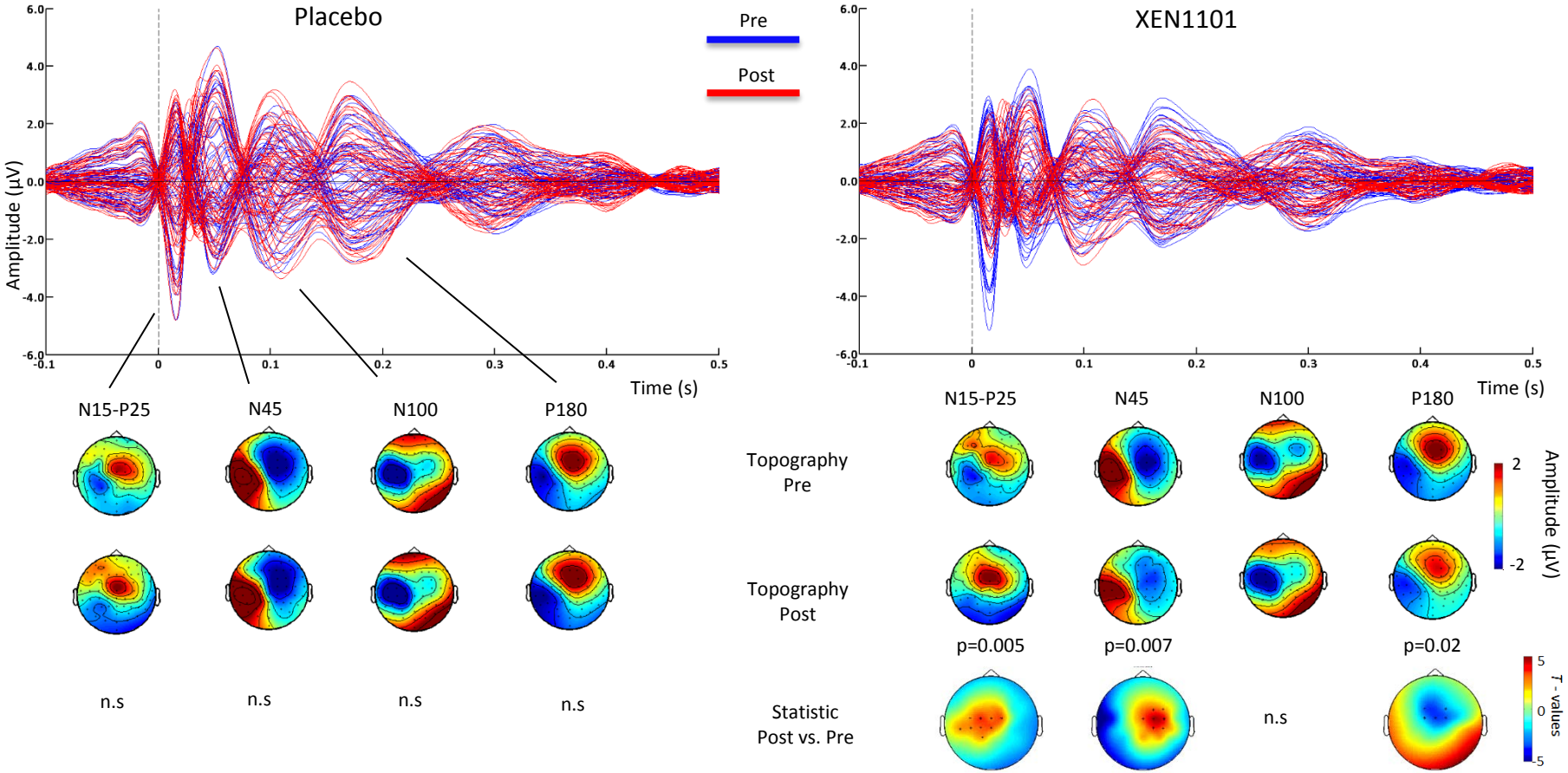
Concentration effect

(Average of the high concentration of XEN1101 = 45 ng/mL)



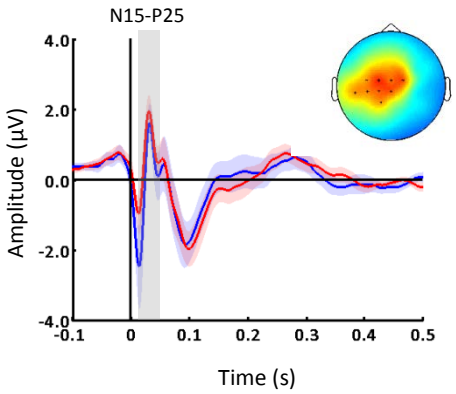
Significant Increase in RMT Indicates Reduced Corticospinal Excitability; Strong PK-PD Relationship

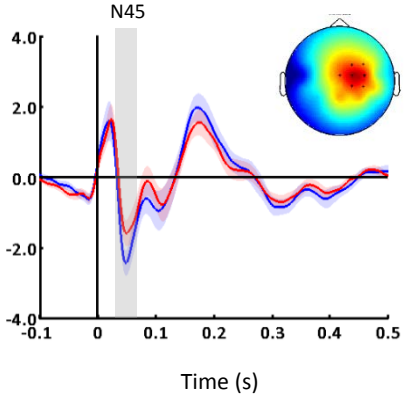
TMS-EEG: XEN1101's Effect on TEPs During High Plasma Exposure

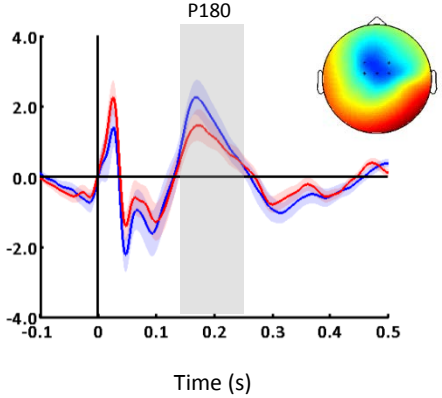


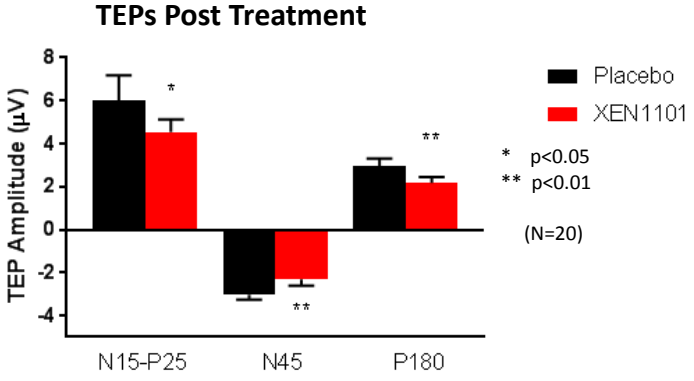
XEN1101 Yielded Significant Modulation of Early TEPs and N45 and P180

TMS-EEG: Effect of XEN1101 on TEPs







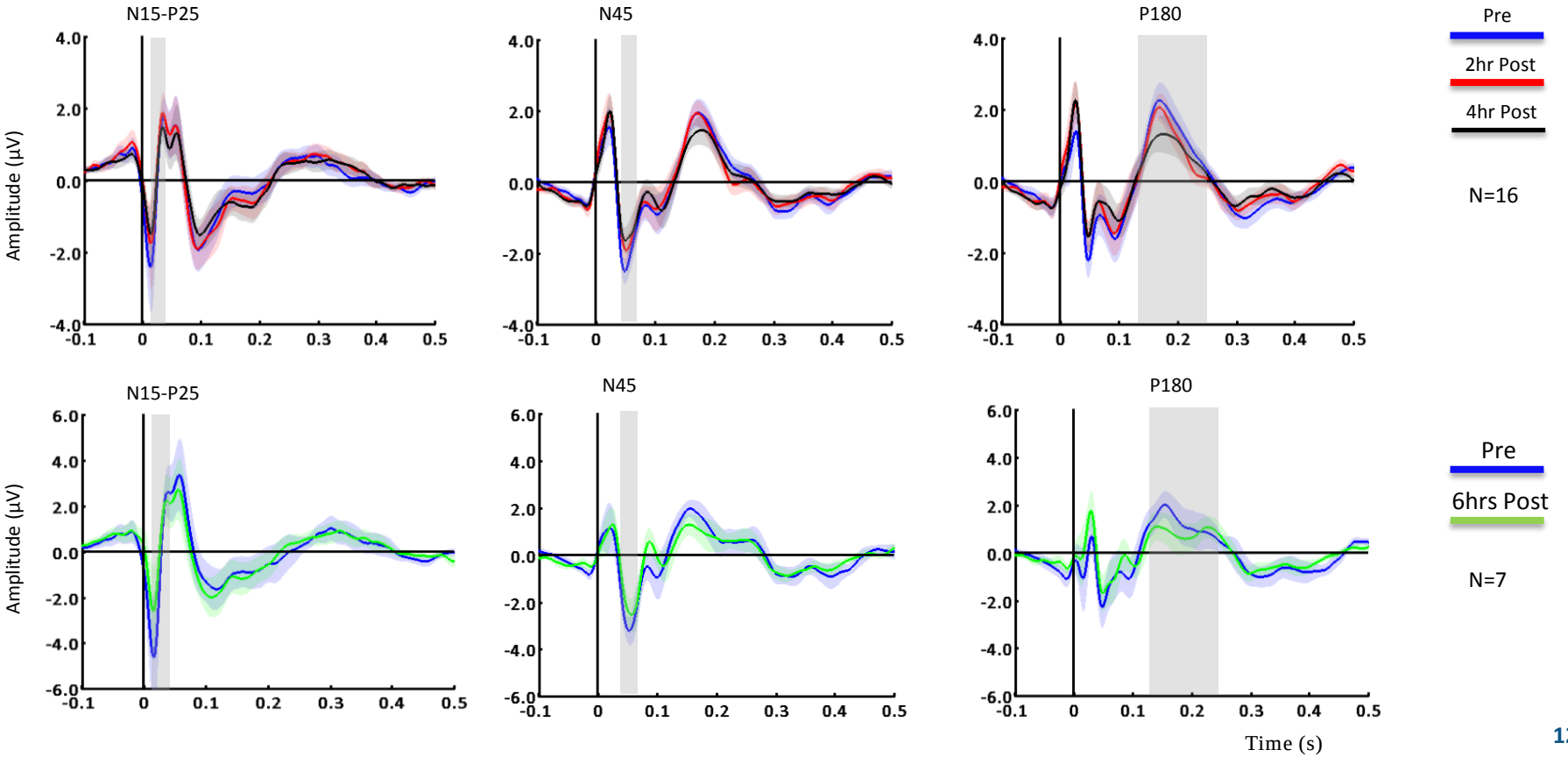


XEN1101 Fingerprints on TEPs:

- ↓N15-P25 complex
- ↓N45
- ↓P180

XEN1101 Significantly Modulates TEPs and Decreases Cortical Excitability

TMS-EEG: Effect of XEN1101 on TEPs at 2, 4, and 6 hours

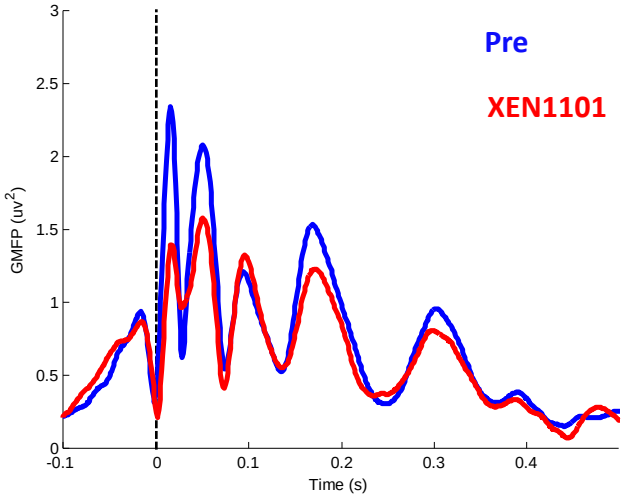


TMS-EEG: XEN1101 Causes Reduction of Cortical Excitability

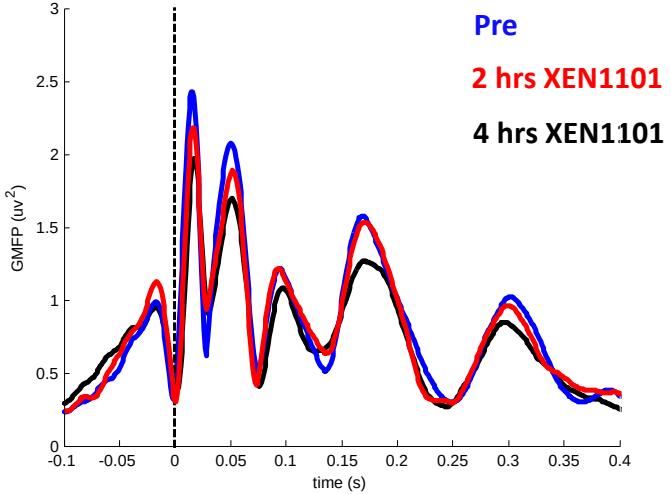
- TEPs: complex spatio-temporal profile
- Global Mean Field Power (GMFP) shows the overall amount of electrical activity induced by TMS

Concentration effect

(Average of the high concentration of XEN1101 = 45 ng/mL)



Time effect



XEN1101 Reduces Cortical Excitability Over Time with Prolonged Absorption

Conclusions

TMS was used to evaluate the corticospinal and cortical activity profile of XEN1101 compared to placebo in healthy male volunteers

- XEN1101 was safe and well tolerated, with typical AEs for this mechanism of action
- XEN1101 showed significant plasma concentration dependent reduction of corticospinal (RMT) and cortical (TEP) excitability
  - Effects on RMT were consistent with the pilot study and were more potent and of higher magnitude than retigabine/ezogabine (Ossemann et al., 2016)
  - Effects on TEPs showed a unique fingerprint of activity
  - TMS data consistent with observations of other AEDs at effective plasma levels
  - Results support the further development of XEN1101 in patients with epilepsy

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