

Effects of the selective sphingosine-1-phosphate subtype 1 receptor modulator, TRV045, on cortical excitability using resting-state EEG and transcranial magnetic stimulation

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Introduction

- Anticonvulsant effects of sphingosine-1-phosphate receptor (S1PR) modulators are demonstrated in animal models
- S1PR modulators also alter lymphocyte trafficking and cause immunosuppression, limiting their use as anti-epileptics
- TRV045 is a selective S1PR1 modulator without effects on lymphocyte trafficking, that has shown activity in animal models of epilepsy and chronic neuropathic pain
- TRV045 is an investigational drug and not approved by the FDA or any EU regulatory agency
- Resting-state EEG (pEEG) and Transcranial Magnetic Stimulation - Electromyography (TMS-EMG) can be used to measure effects of antiepileptic drugs (Höller et al. 2018, Ruijs et al. 2022)

Aim

To evaluate whether TRV045 affects cortical excitability in healthy male adults

Methods

- Randomized, double-blind, placebo-controlled, two-way cross-over, multiple dose study in healthy men (age 18-55)
- Subjects received TRV045 250mg or placebo, once daily for 4 days, in randomized order
- pEEG) and TMS-EMG were performed pre-dose and 4 hours post-dose on Day 1 and Day 4
- Main exclusion criteria were increased risk of infection or contra indication for performing TMS
- Endpoints were analyzed with a mixed effects model analysis of covariance

Results

- 25/27 subjects completed the study
- TRV045 was well-tolerated, only headache and fatigue were observed more frequently with TRV045 than with placebo
- Significant increase in alpha power (eyes open), increasing with multiple days of dosing (Figure 1 and 2)
- Significant changes in beta power, gamma power (increases) and delta power (decrease) were also observed on Day 4
- Trend towards decreased single pulse MEP amplitude post-dose on Day 1 only (Figure 3)

Conclusions

- TRV045 is CNS active with evolving effects on pEEG and TMS-EMG over multiple days of dosing
- This data supports further studies to elucidate TRV045's mechanism of action and potential anti-epileptic effects

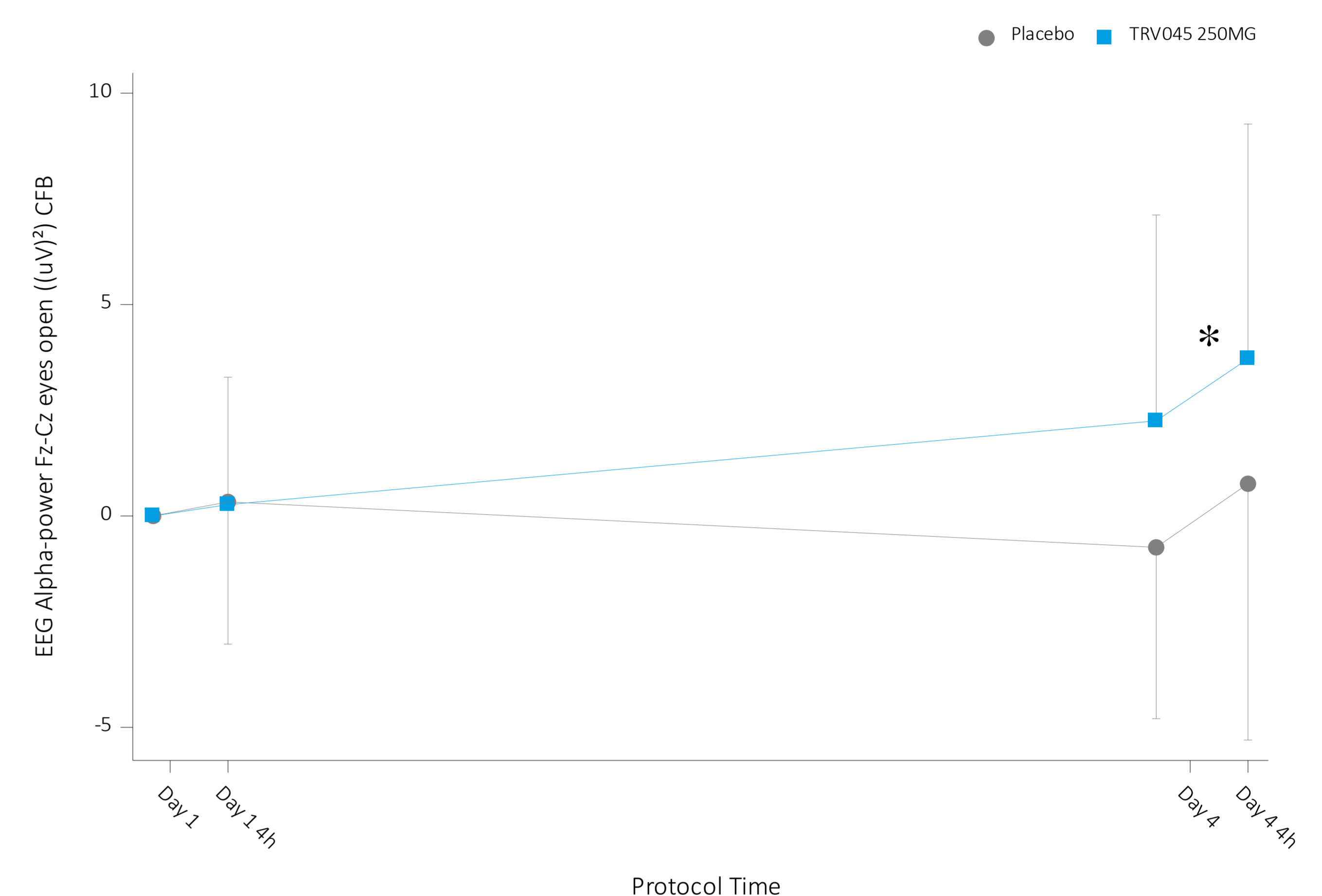


Figure 1: Summary graph EEG Alpha-power Fz-Cz eyes open ((uV)²) – Change from Baseline

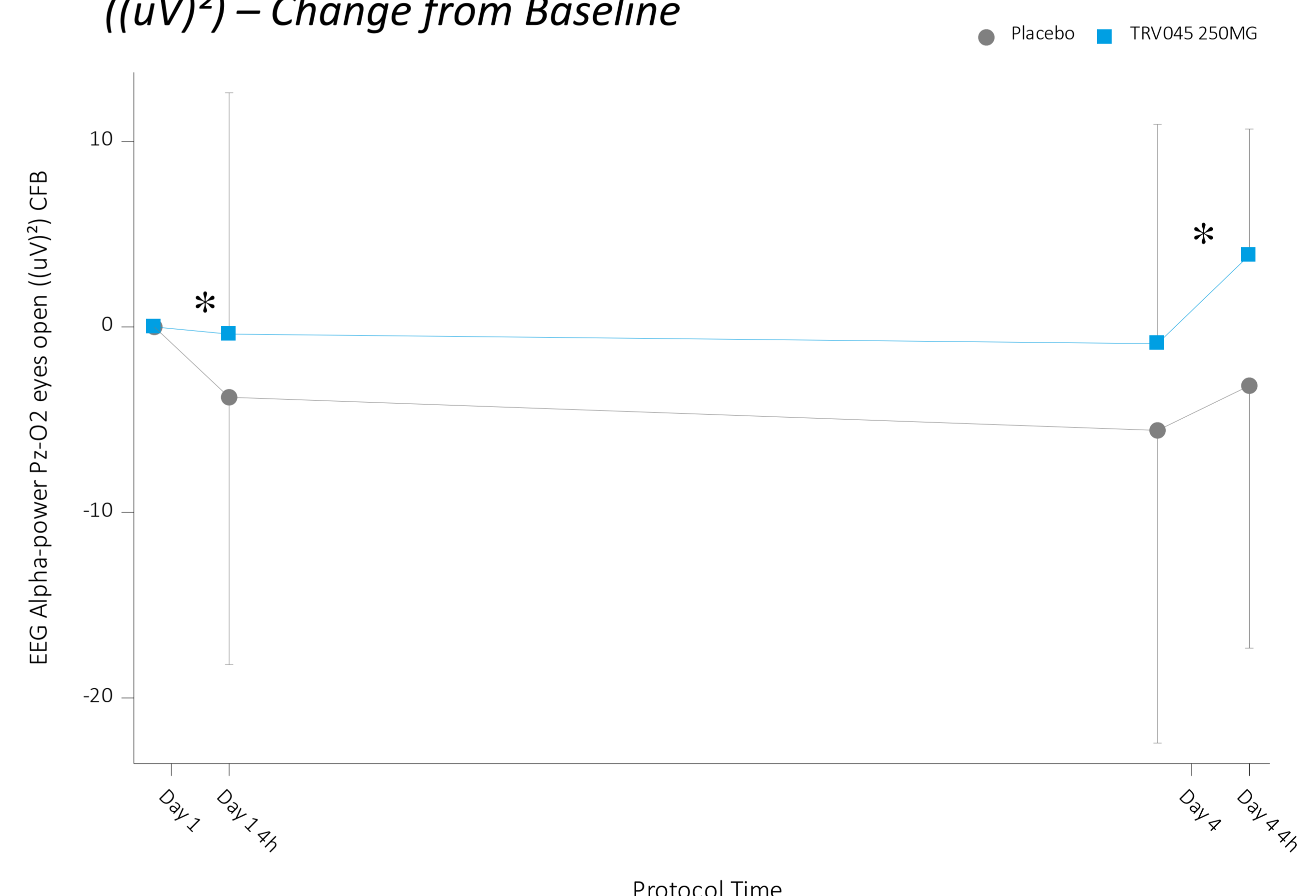


Figure 2: Summary graph EEG Alpha-power Pz-O2 eyes open ((uV)²) – Change from baseline

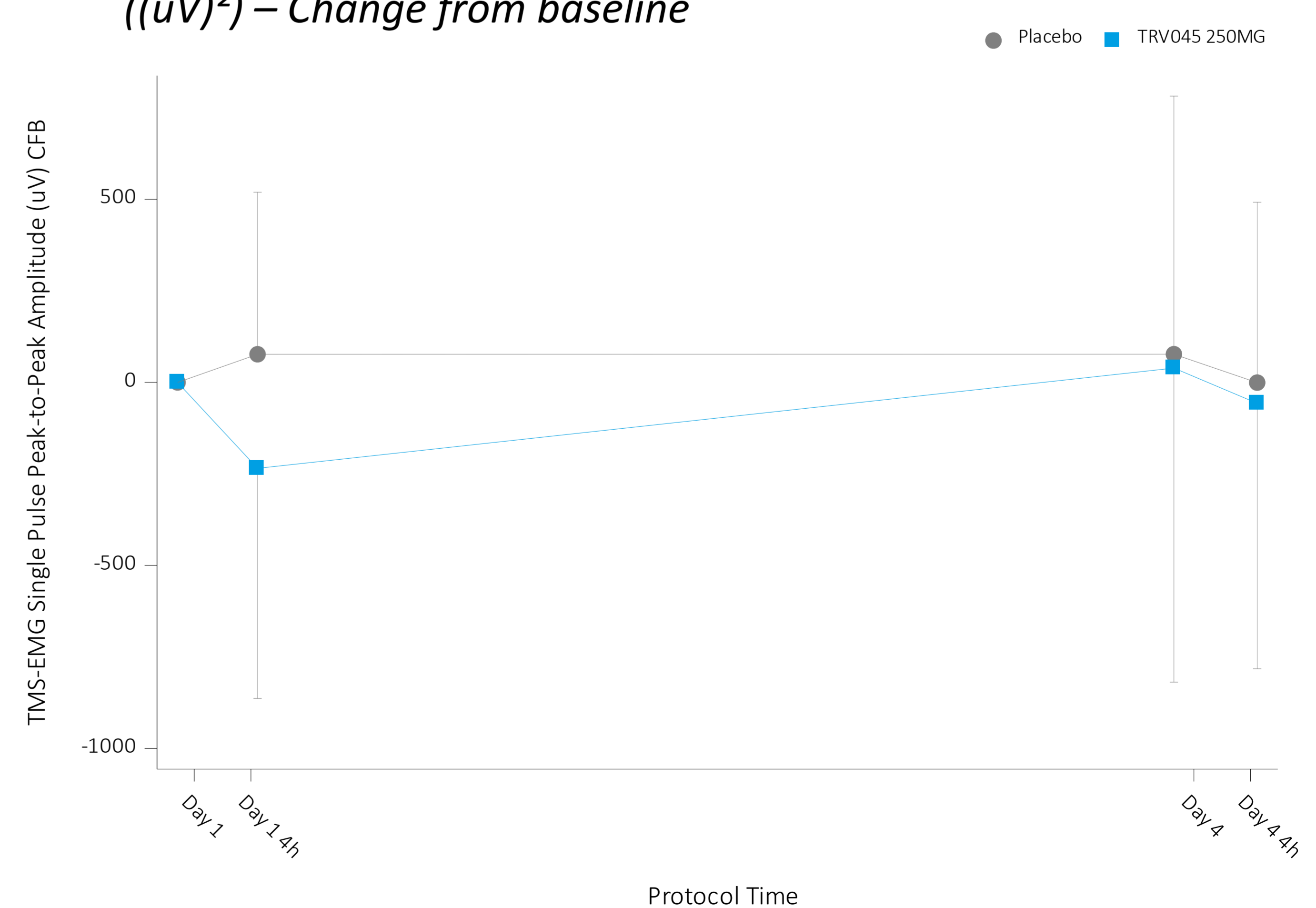
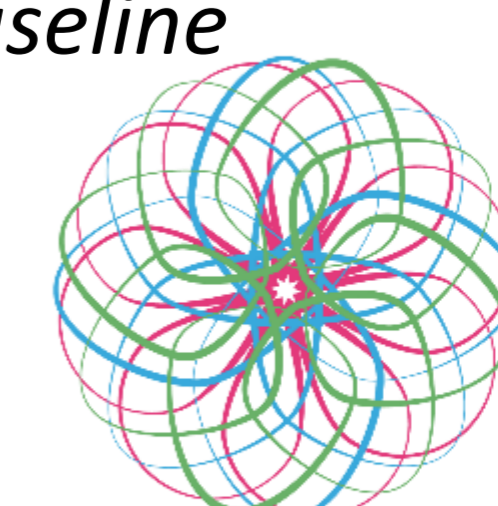


Figure 3: Summary graph TMS-EMG Single Pulse Peak-to-Peak Amplitude (uV) – Change form baseline

* Indicates $p < 0.05$



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