Quantitative Analysis of Continuous EEG in a Phase 1 study of a Novel Potassium Channel Opener (CB03-154) to Assess the Safety and Tolerability

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BACKGROUND

CB03-154 is a novel, highly selective and potent small molecular KCNQ2/3 opener for the treatment of epilepsy. In a first-in-human Phase 1 study, CB03-154 was found to be safe and well tolerated. Many Central Nervous System (CNS) active drugs have effects on the power of different frequency bands in the electroencephalogram (EEG). These EEG changes can be used as a biomarker of CNS penetration, effects on neuronal networks, and to assess potential adverse effects[1] (Jobert et al., 2012). To further explore the impact of the CB03-154 on brain electrical activity, we analyzed changes in EEG power and dominant frequencies across specific bands with Fast Fourier Transform on selected leads. This quantitative electroencephalogram (qEEG) analysis was to detect the drug's effects post dosing and following repeated daily dosing.

METHODS

qEEG analysis was conducted using MATLAB. The single ascending dose (SAD) analysis involved a total of 8 healthy subjects (6 received 30 mg CB03-154 and 2 received placebo as controls). The multiple ascending dose (MAD) analysis included a total of 10 healthy subjects (6 received 20 mg CB03-154 and 4 received placebo, two each from cohort 1 or 2 respectively, once daily for 14 days). EEG data was extracted for pre-treatment (-30min to 0 relative to dosing) and post-treatment (+30 to +60min relative to dosing). In order to assess immediate/acute effects of treatment on qEEG measures, absolute power values in the pre-treatment period were expressed relative to values in the post-treatment period for each recording. In order to assess longer term effects of treatment on qEEG measures, comparison between the pre-treatment values over the different timepoints (Days1, 8 and 14) was performed. For these measures, relative power values were used, which were calculated by dividing power within the frequency band of interest by total power (all spectral power between 1 and 46Hz). Statistical analysis for MAD part was performed using two-way ANOVA in GraphPad Prism 10.1.2. For statistical analysis of SAD part, the unpaired t-test was used.

RESULTS

Statistical analysis of the qEEG results revealed no significant effect of treatment (i.e. CB03-154 vs placebo) for all frequency bands when assessing acute effects for both the MAD cohort (20mg/day) and the SAD cohort (single 30mg dose). In addition, when comparing relative power measures across consecutive sessions (Days 1, 8 and 14) in MAD cohort (20mg/daily) there was no significant effect of treatment for all frequency bands. (Selective results are presented in Figures 1, 2 and 3. Other qEEG results that are not presented in the poster can be found at *https://github.com/bn-li/CB03-154-poster-figures-AES2024.git*)

Figure 1: MAD Analysis of Acute Treatment Effects: Post-Dose 20 mg CB03-154 Relative to Pre-Dose Values

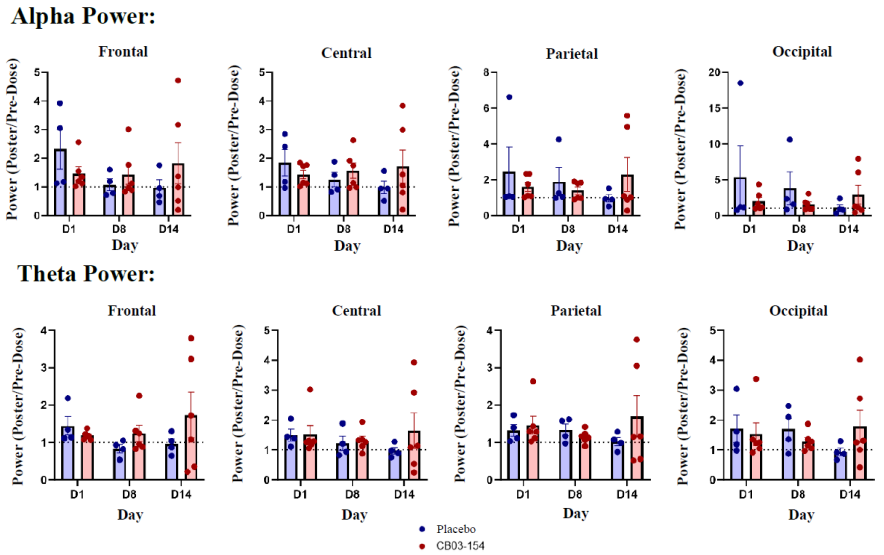


Figure 2: MAD Analysis of Effects Over Time: Pre-Dose Values for All Time Points

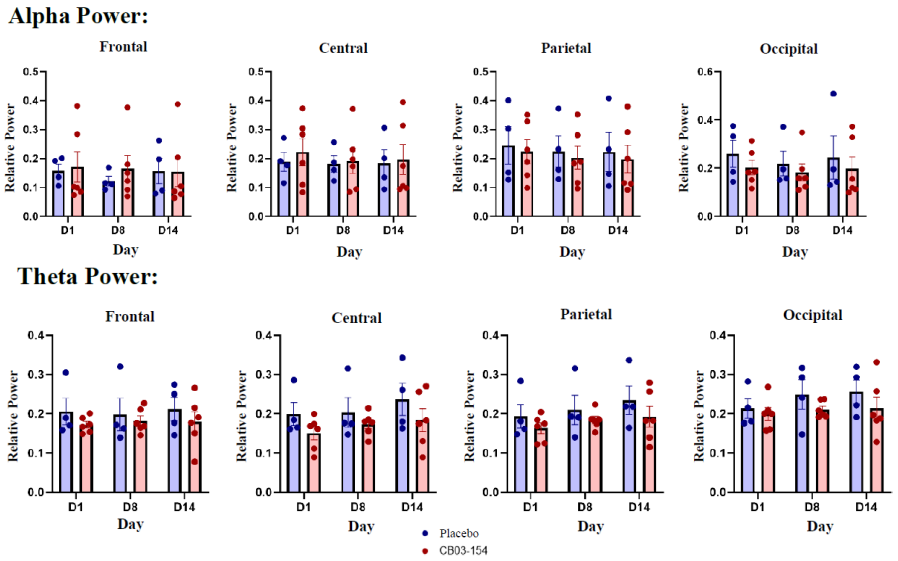
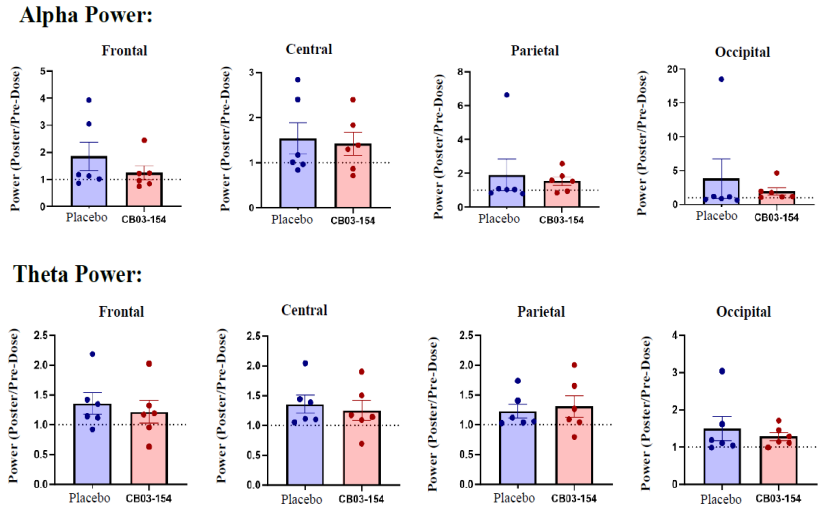


Figure 3: SAD Analysis of Acute Treatment Effects: Post-Dose 30 mg CB03-154 Relative to Pre-Dose Values



CONCLUSIONS

There is no evidence from the qEEG analysis that the study drug (CB03-154) has any adverse brain effects on brain network activity, either when administered acutely or chronically over a two-week period, at the doses tested. Results suggest that CB03-154 should have minimal CNS side-effects at these doses. The lack of frequency spectrum power band effects does not imply a lack of anti-seizure effects at the doses tested, as the changes seen with the older anti-seizure medications relate to their adverse CNS effects not their anti-seizure actions.

REFERENCE

1 . Jobert M, Wilson FJ, Ruigt GS, Brunovsky M, Prichep LS, Drinkenburg WH. The IPEG Pharmaco-EEG Guideline Committee. Guidelines for the Recording and Evaluation of Pharmaco-EEG Data in Man: The International Pharmaco-EEG Society (IPEG). Neuropsychobiology (2012) 66 (4): 201–220.
Acute Treatment Effects