Implementation of Quantitative and Safety EEG Overlaid on a SAD-MAD Trial: Challenges and Lessons Learned

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What is the Methodological Question Being Addressed? Implementing electroencephalography (EEG) in early phase clinical studies can provide valuable evidence of brain activity of CNS-acting drugs and insight into their safety profiles. However, many methodological considerations exist, and no unifying framework has yet been adopted by the pharmaceutical industry. Thus, there are important challenges for effective and efficient implementation and analysis.

Introduction Quantitative (qEEG) and safety EEG were added during the course of a first-in-human single and multiple ascending dose (SAD-MAD) trial in healthy volunteers. This report aims to highlight operational considerations and limitations encountered and suggest strategies for future studies.

Methods Data collection: EEG data (19 channels, 10/20 system) was collected from 47 healthy normal volunteers participating in one of 5 cohorts (2 SAD, 3 MAD) of a randomized, double-blind, placebo-controlled SAD-MAD trial. Collection times were: screening (1 h with provocation), Day -1 (6.5 h), treatment day 1 (6.5 h), and treatment Day 9 (MAD only, 6.5 h). Each 6.5-h continuous EEG included 11 qEEG time points (5 min each: eyes open, closed). PK samples and standard safety assessments were collected at times corresponding to qEEG timepoints on treatment Days 1 and 10.
Safety review: All EEG records were first visually reviewed by a single epileptologist. Treatment Day 1 records with abnormal findings were escalated for visual review by two additional epileptologists, who also reviewed respective Day -1 records as needed to determine a potential relationship to study drug. For MAD subjects, calls between reviewing epileptologists and the PI enabled determination of whether a subject would be removed prior to dosing on Day 3. Cohort summaries were reviewed to inform dose escalation decisions.
QEEG analysis: Endpoints included oscillatory and fractal component amplitude of standard spectral frequency bands and derived metrics, 2-channel coherence, and exposure-response. In addition to formal time series analysis, qEEG data were analyzed post hoc, centered on each individual subject’s measured Cmax to account for inter-individual variance in observed Tmax.

Results Several operational considerations were identified as potential hurdles to successful implementation. Examples include orchestration of timely initial safety review with escalation for

consensus determination as necessary, and controllability of procedural elements that may contribute to signal noise and variance (e.g., environmental isolation; timing of electrode placement, blood draws). Challenges for study conduct decisions also included the lack of available normative datasets focused on frequency and clinical significance of ‘abnormal’ EEG findings in healthy ‘normal’ adults.

Conclusion Safety and qEEG can be collected simultaneously during the course of traditional SAD-MAD trials, but several practical challenges exist. Drug development efforts would benefit greatly from the construction and implementation of a standardized framework for collecting and reviewing safety EEG data from drug studies in healthy volunteers. Such a framework will facilitate the adoption of EEG in early phase drug trials, which can inform development strategy by providing 2 crucial insights: 1) evidence of potential neurological safety risks (e.g., seizure) identified in preclinical toxicology studies, and 2) evidence of effects on brain activity to support program advancement to phase 1b/2.

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Guidelines I have read and understand the Poster Guidelines

Disclosures DKM served as a safety EEG reviewer as an employee of CortiCare (EEG vendor) and is currently an independent EEG consultant.
LE is a paid consultant of BlackThorn/Neumora and served on the dose escalation committee for the study.
AMH and SRS served as safety EEG reviewers as employees of Duke Comprehensive Epilepsy Center, Duke University School of Medicine.
ALH served as the study principal investigator as an employee of Celerion (CRO).
MEB, KAT, and JT report no conflicts of interest for this work.
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