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Quantitative EEG Analysis in Patients with Dravet Syndrome (DS) Treated in the Phase 1/2a MONARCH and ADMIRAL Studies of STK-001, an Antisense Oligonucleotide (ASO)

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BACKGROUND

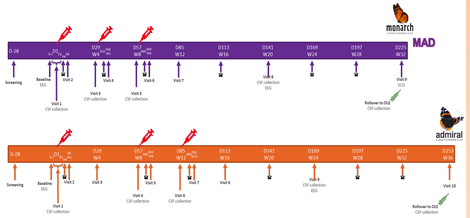
- DS is a severe genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year of life
- In approximately 85% of cases, DS is caused by spontaneous, heterozygous loss of function mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_V1.1$) protein
- Upregulating $Na_V1.1$ protein may restore functioning neurons and prevent seizures and reduce non-seizure related comorbidities in DS
- STK-001 is an investigational proprietary ASO designed to upregulate $Na_V1.1$ protein expression by leveraging the non-mutant (wild type) copy of *SCN1A* to restore physiological $Na_V1.1$ protein levels
- In DS, patients have one functional gene (wild type) copy and one mutated copy, resulting in half as much protein as needed to maintain health
  - *SCN1A* is transcribed into pre-messenger RNA (pre-mRNA) that is spliced to generate productive mRNA (which is translated into $Na_V1.1$ protein) and non-productive mRNA due to the inclusion of an exon that leads to nonsense-mediated mRNA decay (NMD) exon
  - TANGO ASOs bind to specific stretches of *SCN1A* pre-mRNA to prevent the inclusion of the non-productive exon thereby increasing productive mRNA level
  - Increased level of productive mRNA from the functional gene copy increases $Na_V1.1$ protein production restoring it to near normal levels
- Therefore, STK-001 may be the first disease-modifying therapy to address the genetic cause of DS by upregulating $Na_V1.1$ protein levels
- EEG spectral analysis quantifies the amount of rhythmic activity of different frequencies in EEGs
- As EEG spectral patterns may be linked to treatment effect, we initiated a study to assess background spectral features on EEGs recorded as part of the MONARCH and ADMIRAL studies of STK-001

MORE INFORMATION

To find out more: MONARCHstudy.com or Admiralstudy.com. By contacting us, your patient is under no obligation to take part in the study.

METHODS

- MONARCH (NCT04442295) and ADMIRAL (EudraCT Number 2020-006016-24) are ongoing, Phase 1/2a open-label, multi-center studies of STK-001 in patients with DS aged 2-18/<18 years in the US and UK, respectively
- 28 patients were included in this spectral analyses:
  - 20 patients in multiple ascending dose (MAD) cohorts of 20-45 mg per dose in MONARCH
  - 8 patients in MAD cohorts of 30-45 mg per dose in ADMIRAL
  - 2 EEG data points were analyzed: baseline and 3 months after the last dose of STK-001
  - 2 patients were excluded because the 3-month follow-up recording was not available

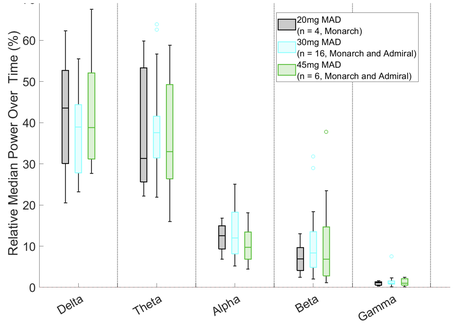


- The EEGs were segmented to the first hour, pre-processed to remove muscle and eye artifacts and subsequently band-pass filtered from 0.1 to 100 Hz with a notch at 50 Hz and 60Hz
- Spectral analyses were performed across the delta, theta, alpha, beta, and gamma bands (0.3 Hz to 100 Hz) to assess peak frequency, median power over time, and relative band power

Waves	Frequency bands (Hz)	Behaviour Trait	Signal Waveform
Delta	0.3 – 4	Deep sleep	
Theta	4 – 8	Deep Meditation	
Alpha	8 – 13	Eyes closed, awake	
Beta	13 – 30	Eyes opened, thinking	
Gamma	30 and above	Unifying consciousness	

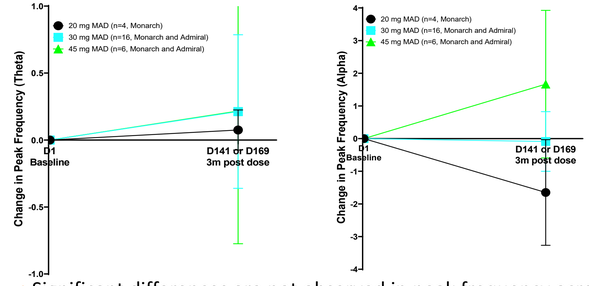
MAD COHORT SPECTRAL ANALYSES RESULTS

Baseline Spectral Analyses



- 1/f correction was applied
- Greater relative band power was observed in the lower frequencies (delta and theta) as compared to higher frequency (alpha, beta, and gamma) bands
- In a healthy control population, we would expect to see higher relative alpha power compared to other bands

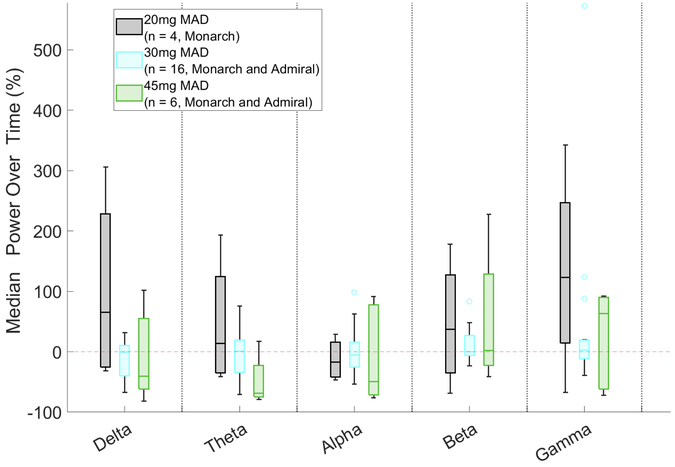
Peak Frequency Baseline to 3 Months Post Last Dose



- Significant differences are not observed in peak frequency across frequency bands (theta and alpha are shown as example)

Comparison of Spectral Power Baseline to 3 Months Post Last Dose

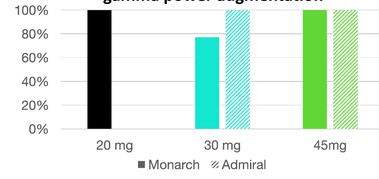
Percentage difference in median power over time 3 months vs baseline



- In the delta and theta band, decreases in median power compared to baseline are observed in the 45 mg MAD cohort
- In the gamma band, increases in median power compared to baseline are observed in the 20 mg and the 45 mg MAD cohort
- A decrease in relative power in the theta band is observed in the 45 mg MAD cohort of ADMIRAL
- Increases in relative gamma power are observed in all dose cohorts
- No differences with respect to sex or age were found

Percentage of patients with relative theta power reduction

Percentage of patients with relative gamma power augmentation



CONCLUSIONS

- Greater delta and theta power compared to alpha power at baseline is consistent with prior data showing increased theta and decreased alpha in children with DS compared with controls (Holmes et al 2012)
- Significant changes are not observed in peak frequency across frequency bands following administration of STK-001
- Initial trends indicate that treatment with STK-001 may modulate theta and gamma power
- Additional data from the ongoing MONARCH and ADMIRAL studies will be analyzed and correlation with clinical assessments will be important for validation

ACKNOWLEDGEMENTS

This study is supported by Stoke Therapeutics. We thank the investigators, health care providers, research staff, patients, and caregivers who participated in this study.