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Poster 3.489

Electrophysiological improvements in patients with Dravet syndrome following treatment with zorevunersen, an investigational antisense oligonucleotide

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Key Findings

1. Treatment with zorevunersen in patients with Dravet syndrome resulted in dose-dependent reduction in δ-power at 12 and 24 weeks after last dose.
2. Reduction in δ-power is associated with an increased probability of achieving >50% reduction in major motor seizure frequency.
3. Reduction in EEG δ-power after treatment with zorevunersen suggests improvement in the underlying encephalopathy and supports the potential of zorevunersen as a disease modifying therapy in DS.

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Introduction

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy. More than 90% of DS cases are caused by voltage-gated sodium channel α subunit 1 (*SCN1A*) variants that result in 50% $Na_V1.1$ sodium channel expression, causing refractory seizures and significant developmental, cognitive, and behavioral impairments that impact quality of life.[1–7]
- Zorevunersen is an antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression by leveraging the wild-type copy of *SCN1A*.
- In children and adolescents, increased electroencephalogram (EEG) δ-power activity during wakefulness may be associated with developmental impairment and reduced cognitive performance.[8,9]
- δ-power decreases with age but remains persistently higher in patients with DS compared with neurotypical controls.[10]
- This study examined EEG data from patients with DS treated with zorevunersen in Phase 1/2a studies.

Methods

- EEG data were obtained from patients with DS aged 2–18 years receiving single or multiple doses of ≤70 mg zorevunersen enrolled in the MONARCH and ADMIRAL Phase 1/2a studies and their respective OLEs.
- Routine 1–2-hour EEGs at baseline and Weeks 12 and 24 after last dose were assessed.
- Fifteen minutes of preprocessed data were used to compute power spectra using Morlet wavelet decomposition; mean δ-power (1–4 Hz) averaged across electrodes was the primary EEG endpoint.
- A mixed repeated-measures model (MMRM) evaluated the effects of cumulative dose in Phase 1/2a studies on longitudinal δ-power changes, including fixed effects for cumulative dose and visit, and using baseline δ-power and $\log_2$(age) as covariates; an unstructured covariance matrix modeled the covariance in repeated observations within patients.
- Exploratory analyses examined correlations between δ-power change and clinical outcomes.
- Associations with responder status (>50% reduction in seizure frequency) were examined using logistic regression via generalized estimating equations, adjusting for baseline δ-power and age.
- Please scan the QR code for number of patients as per dose level and time point.

Results

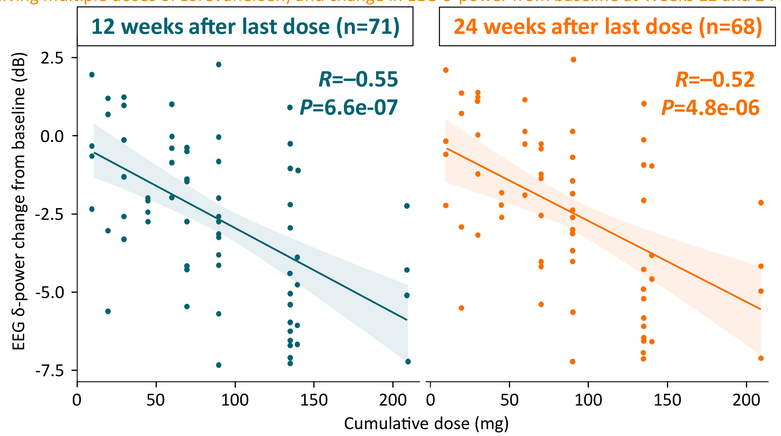
Baseline characteristics

- These analyses included 74 patients with DS with a median age of 9.0 years.

Dose-dependent decrease in δ-power after treatment with zorevunersen

- The correlation coefficient for cumulative dose in Phase 1/2a studies in the MMRM was –0.55 at Week 12 and –0.52 at Week 24 with p-values < 0.05 suggesting a significant negative association with change in EEG δ-power (**Figure 1**).

Figure 1. MRMM-predicted correlation between cumulative dose received in Phase 1/2a studies (i.e., single dose or sum of all doses for patients receiving multiple doses of zorevunersen) and change in EEG δ-power from baseline at Weeks 12 and 24 after last dose.

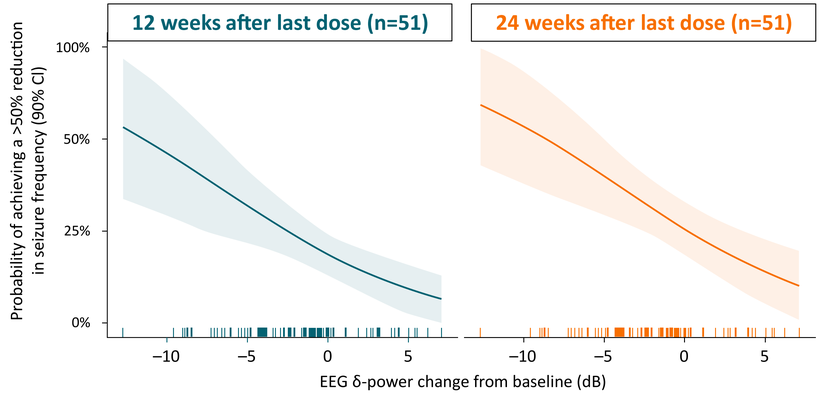


EEG segments from two patients were excluded due to poor data quality. One patient lacked the EEG recording at the 12-week visit, and four patients lacked EEG recordings at the 24-week visit. The line represents a linear fit and the shaded area represents the 95% confidence interval. dB, decibel; EEG, electroencephalogram.

Reduction in δ-power is associated with clinical responder status

- Logistic regression via generalized estimating equations demonstrated that patients with greater reductions in δ-power were more likely to achieve clinical responder status at Weeks 12 and 24 (**Figure 2**).
- A clinical responder was defined as a patient with >50% reduction in seizure frequency.

Figure 2. Association between δ-power change and probability of achieving >50% reduction in seizure frequency using logistic regression via generalized estimating equations.



A complete case analysis of patients with non-missing seizure frequency at both visits was performed. A clinical responder was defined as a patient with >50% reduction in seizure frequency. The line represents a linear fit and the shaded area represents the 90% CI. CI, confidence interval; dB, decibel; EEG, electroencephalogram.

- Exploratory analyses between δ-power and Vineland-3 raw scores are ongoing.

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