Spectral EEG analysis demonstrates decreased slow-wave activity in patients with Dravet syndrome after treatment with zorevunersen (STK-001), an antisense oligonucleotide

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INTRODUCTION

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy marked by frequent, recurrent seizures and significant cognitive and behavioral impairments[1]
- Approximately 85% of cases are caused by heterozygous, loss-of-function variants of the sodium channel type 1 alpha subunit (*SCN1A*) gene[2], which encodes the $Na_V1.1$ sodium channel alpha subunit[3,4]
- Zorevunersen is an antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression to physiological levels by leveraging the wild-type copy of *SCN1A*
- In children and adolescents, increased slow-wave electroencephalogram (EEG) activity during wakefulness may be associated with developmental impairment and reduced cognitive performance[5,6]
- This study examined EEG data from patients with DS enrolled in the MONARCH and ADMIRAL Phase 1/2a studies and their respective open-label extensions (OLEs) to evaluate potential electrophysiologic markers of treatment effect with zorevunersen

METHODS

- The Phase 1/2a open-label, multicenter MONARCH and ADMIRAL studies and their corresponding OLEs, SWALLOWTAIL and LONGWING, were studies of zorevunersen in patients with DS aged 2–18 years in the US and UK, respectively (Figure 1)
- The EEG analysis included 74 patients with DS (37 females, 37 males) who were treated with single (10–70 mg) or multiple (20–70 mg) ascending doses of zorevunersen in either Phase 1/2a study
- During clinic visits, 234 EEG recordings of 1–2 hours were collected at baseline, at 12 and 24 weeks after the last dose in the Phase 1/2a studies, and an additional 48 weeks after the end of the Phase 1/2a studies (Table 1)
- EEG recordings were pre-processed to remove artifacts and subsequently band-pass filtered from 0.1 to 100 Hz with a notch filter at 50 or 60 Hz to remove powerline noise interference; afterward, the data were segmented into 6-second epochs
- The power spectrum was obtained by applying Welch's method to the epochs; spectral band power was evaluated for the Delta (1–3.5 Hz), Theta (3.5–7.5 Hz), Alpha (7.5–13 Hz), Beta (13–30 Hz), and Gamma (30–100 Hz) bands

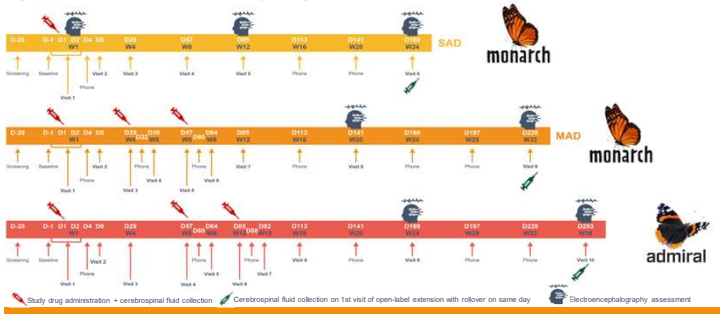
Table 1. EEG recordings per dose group in a sample of 74 patients

Initial zorevunersen dose	Number of patients per dose level	Baseline	Week 12 after last dose of Phase 1/2a	Week 24 after last dose of Phase 1/2a	Week 48 after end of Phase 1/2a
10 mg	5*	4	4	4	0
20 mg	10	9	9	8	0
30 mg	25	24	23	24	11
45 mg	21	19	19	17	6
70 mg	20	18	18	17	0

*One patient received an incorrect dose

METHODS CONTINUED

Figure 1. MONARCH/ADMIRAL Study design



KEY FINDINGS

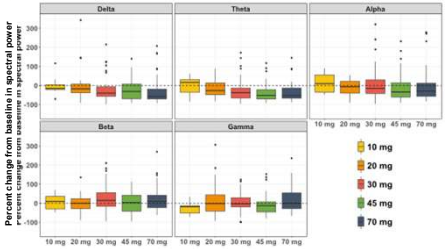
1. Spectral EEG analysis in patients with DS shows a **reduction in slow-wave activity following zorevunersen administration**
2. **Treatment effect on spectral power is most pronounced at the highest zorevunersen doses,** with reduction in slow-wave activity **sustained for months after the last dose**
3. Topographical spectral changes indicate that zorevunersen has a **widespread and durable effect across the brain**
4. Future evaluations may explore the **relationship between changes in spectral power and cognitive improvements** over time and may support the utility of EEG-derived metrics in patients with DS for evaluating treatment effect

RESULTS

Electrophysiological marker of treatment effect

- A decreasing trend in Delta, Theta, and Alpha spectral power was observed post-treatment compared to baseline (Figure 2)
- The decrease in Delta, Theta, and Alpha power was most pronounced at the highest zorevunersen doses
- The same trend was not observed in the Beta and Gamma bands
- These results indicate a dose-dependent treatment effect on spectral power in lower frequency bands

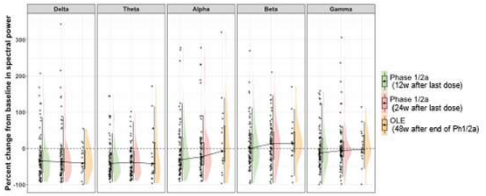
Figure 2. Effect of different zorevunersen dose levels on spectral power in patients with DS



Sustained post-treatment changes over time

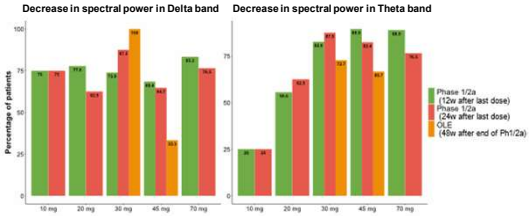
- The decrease in spectral power in the Delta, Theta, and Alpha frequency bands was sustained for up to 24 weeks after the last dose of zorevunersen in the Phase 1/2a studies (Figure 3)
- This effect may potentially extend into the OLE period, but caution is advised as the OLEs are ongoing and their data are incomplete

Figure 3. Change in post-treatment spectral power from Phase 1/2a baseline to follow-up in patients with DS



- When averaged across all doses and timepoints, 74% of patients with DS show a decrease in Delta power, while 68% show a decrease in Theta power (Figure 4)

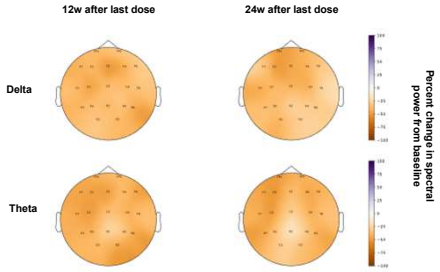
Figure 4. Percentage of patients demonstrating a reduction from Phase 1/2a baseline in Delta and Theta spectral power



Topographical spectral changes

- The decreased spectral power in the lower frequency bands post-treatment compared to baseline in the Phase 1/2a studies is distributed across the scalp, indicating that zorevunersen has a widespread effect across the brain (Figure 5)
- This distributed effect is relatively stable across the follow-up visits at 12 weeks and 24 weeks post-treatment

Figure 5. Topographical changes in Delta and Theta spectral power values from Phase 1/2a baseline in patients with DS



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