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

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ILAE, International League Against Epilepsy.

Speaker Disclosures

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Dravet syndrome: A severe developmental and epileptic encephalopathy[1]

1 out of ~16,000 babies are born with **Dravet syndrome**[2,3]

>90% of Dravet syndrome cases are caused by ***SCN1A*** **gene variants**[4,5]

resulting in **50% reduction in $Na_V1.1$ sodium channel expression**[6]

Currently approved treatments for Dravet syndrome predominantly target seizures, with **no approved treatments for non-seizure symptoms**[3,8–10]

Up to **57%** of patients **fail** to achieve ⩾50% **reduction** in **seizure frequency**[11–13]

Patients experience **prolonged recurrent seizures** and **significant cognitive and behavioral deficits**[2,7]

There is an **urgent need** for **disease-modifying therapies** addressing the underlying channelopathy to **improve both seizure and non-seizure symptoms**

SCN1A, voltage-gated sodium channel alpha subunit 1.

1. Scheffer IE *et al. Epilepsia* 2017; 58 (4): 512–521. 2. Wu YW *et al. Pediatrics* 2015; 136 (5): e1310–e1315. 3. Symonds JD *et al. Brain* 2019; 142 (8): 2303–2318. 4. Gil-Nagel A *et al. Sci Rep* 2023; 13 (1): 3355. 5. Gertler TS *et al. Seizure* 2020; 75: 1–6. 6. Bechi G *et al. Epilepsia* 2012; 53 (1): 87–100. 7. Zuberi SM *et al. Epilepsia* 2022; 63 (6): 1349–1397. 8. Lagae L *et al. Dev Med Child Neurol* 2018; 60 (1): 63–72. 9. Perry *et al. Epilepsia* 2024; 65 (2): 322–337. 10. Isom LL *et al. Neurotherapeutics* 2021; 18 (3): 1524–1534. 11. Devinsky O *et al. N Engl J Med* 2017; 376 (21): 2011–2020. 12. Sullivan J *et al. Epilepsia* 2023; 64 (10): 2653–2666. 13. Guerrini R *et al. Neurol Ther* 2024; 13 (3): 869–884.

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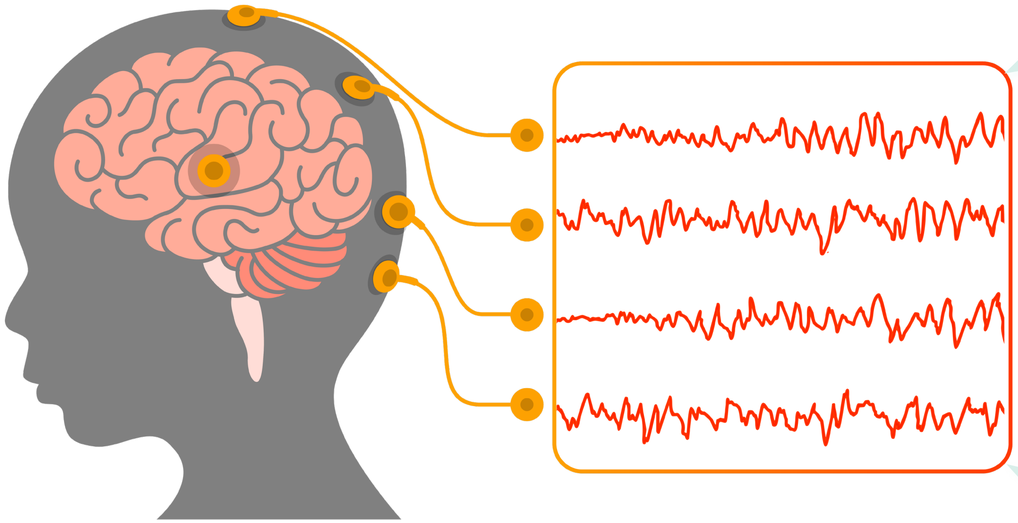
EEG abnormalities in Dravet syndrome



EEG abnormalities have been identified among patients with Dravet syndrome, reflecting underlying network dysfunction caused by *SCN1A*-related impairment of inhibitory interneurons[1,2]

Toddlers with ***SCN1A*-related epilepsy have a significantly lower alpha:delta ratio** compared with age-matched controls[3]

EEG, electroencephalogram; *SCN1A*, voltage-gated sodium channel alpha subunit 1.

1. Capitano F *et al. Proc Natl Acad Sci U S A* 2024; 121(23): e2316364121. 2. Minato E *et al. Seizure* 2021; 91: 108–111. 3. Galer PD *et al. Neurology* 2025; 105 (8): e214148.

Objectives

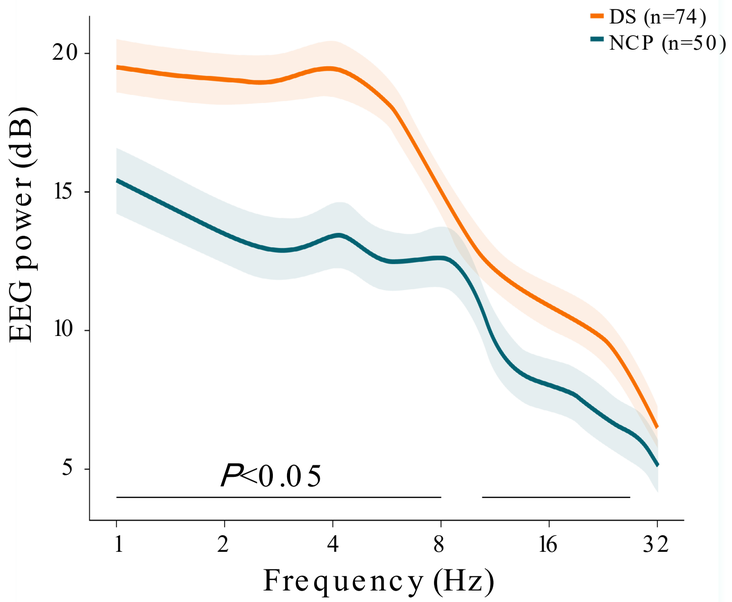
Further understand EEG abnormalities among patients with Dravet syndrome compared with neurotypical controls

Assess EEG findings among patients with Dravet syndrome receiving zorevunersen, an investigational antisense oligonucleotide that increases $Na_V1.1$ protein expression

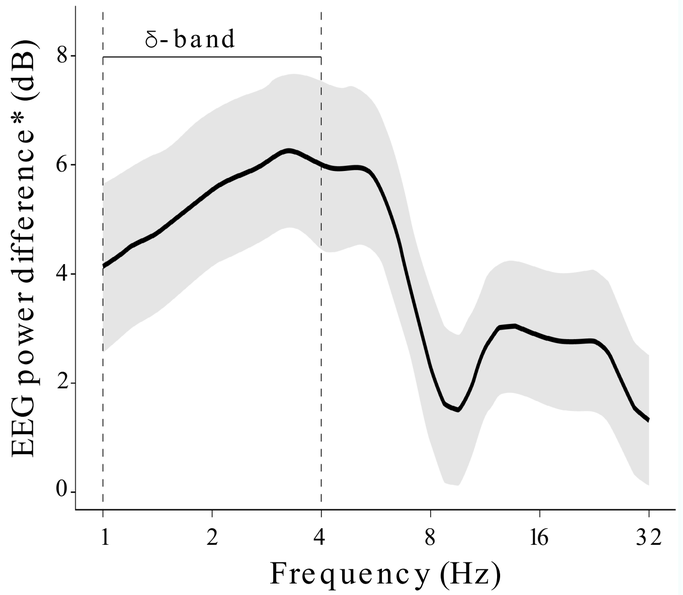
EEG, electroencephalogram.

EEG δ-power is elevated in patients with Dravet syndrome compared with neurotypical control participants (NCPs)

EEG power in patients with Dravet syndrome and NCPs



EEG power difference between patients with Dravet syndrome and NCPs



- Across the 1–32 Hz spectrum, **children with Dravet syndrome showed broadly increased EEG power compared with NCPs** with significant differences at most frequencies ($P<0.05$) except within the α (9–11 Hz) and γ (31–32 Hz) ranges
- The EEG spectral power change was **most pronounced in the δ-band** (1–4 Hz), ranging from 4.13 to 6.00 dB higher in patients with Dravet syndrome than in NCPs ($P<0.05$)

Dravet syndrome data were from the baseline visit of the Phase 1/2a studies (NCT04442295 [USA] and 2020-006016-24 [UK]). NCP data were from epilepsy-unrelated EEGs recorded at Saint-Luc University Hospital (Brussels, Belgium). Absolute power values were averaged across electrodes and log-transformed to dB. Shaded areas represent 95% confidence intervals.

*EEG power difference was calculated by subtracting the EEG power spectra of NCPs from the power spectra of patients with Dravet syndrome.

dB, decibel; DS, Dravet syndrome; EEG, electroencephalogram; Hz, hertz.

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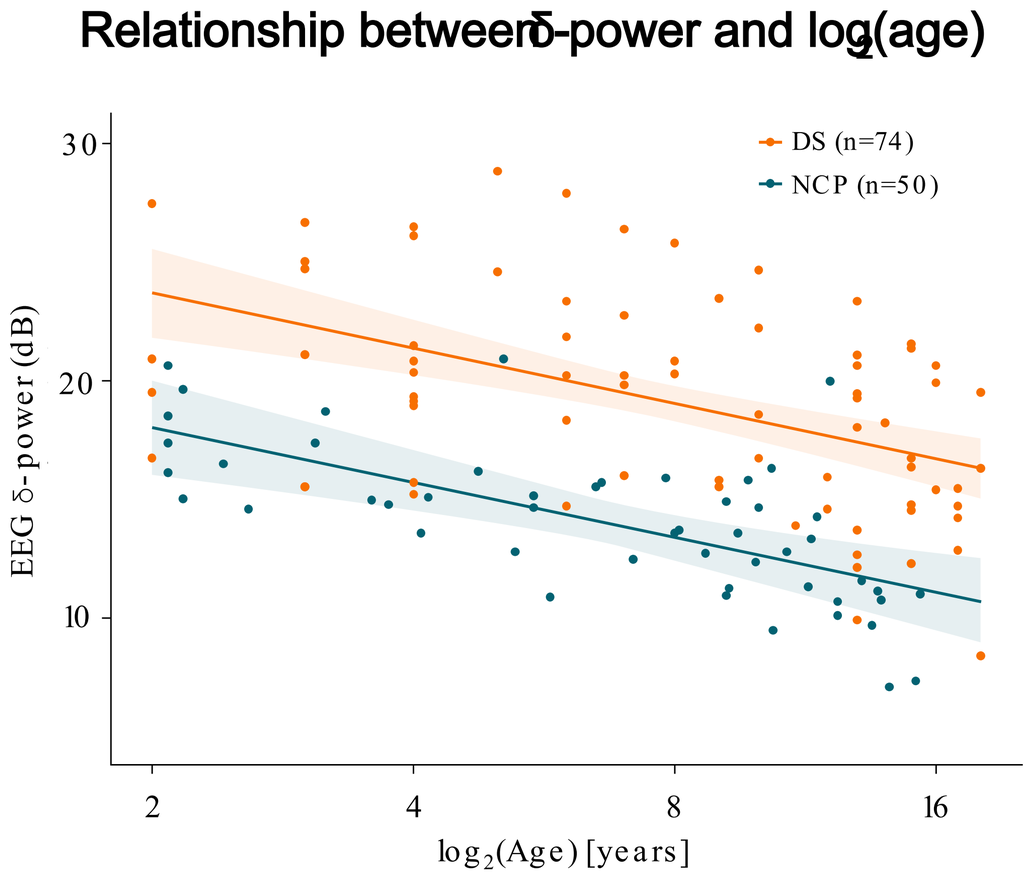
EEG δ-power decreases with age but remains persistently higher in Dravet syndrome



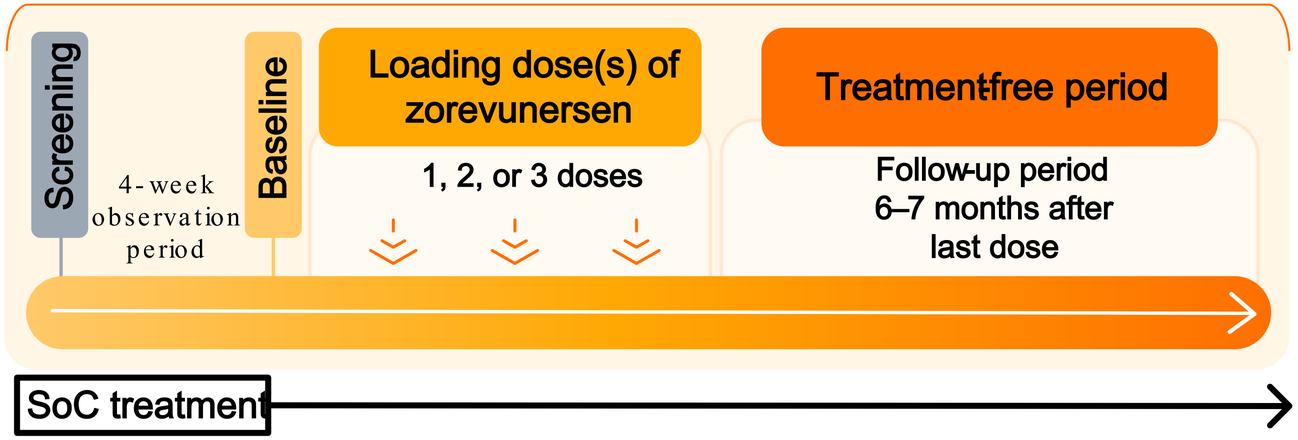
- Analysis of developmental trajectories revealed that δ-power decreased over time as age increased in both groups (Dravet syndrome: −2.34 dB/$\log_2$(age), $P<0.001$; NCP: −2.33 dB/$\log_2$(age), $P<0.001$) without a significant difference in slope (difference: −0.01 dB/$\log_2$(age), $P=0.983$)

- **Despite age-related decline, δ power was consistently elevated in Dravet syndrome compared with NCPs**

Developmental trajectories were derived using a GLM. Shaded areas or error bars represent 95% CIs.
CI, confidence interval; dB, decibel; DS, Dravet syndrome; EEG, electroencephalogram; GLM, general linear model; NCP, neurotypical control participants.

Assessment of EEG δ-power in patients with Dravet syndrome in Phase 1/2a studies with zorevunersen

Zorevunersen is an investigational antisense oligonucleotide that **upregulates $Na_V1.1$ protein expression** by leveraging the wild-type copy of the *SCN1A* gene



Baseline characteristics [1]

- 2–18 years of age with established Dravet syndrome diagnosis
- 81% patients on ⩾3 ASMs; 51% on ⩾4 ASMs
- Most common ASMs: Clobazam (70%), fenfluramine (49%), cannabidiol (44%), and valproate compounds (44%)

Primary endpoints [1]

- Safety profile
- PK and CSF drug exposure

Secondary endpoints [1]

- Change in convulsive seizure frequency, overall clinical status, and QoL

Exploratory endpoints

- Change in 10-20 EEG parameters

Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK).
ASM, antiseizure medication; CSF, cerebrospinal fluid; EEG, electroencephalogram; PK, pharmacokinetics; QoL, quality of life; *SCN1A*, voltage-gated sodium channel alpha subunit 1; SoC, standard of care.
1. Laux L *et al. N Engl J Med* 2026; 394 (10): 969–982.

Assessment of EEG δ-power in patients with Dravet syndrome in Phase 1/2a studies with zorevunersen

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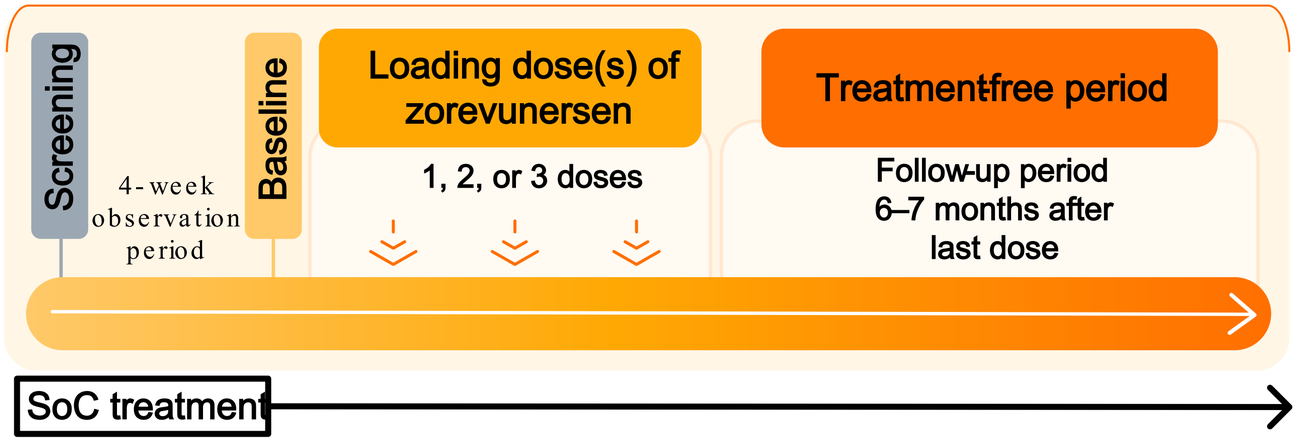


Routine 1- to 2-hour EEGs at baseline and Weeks 12 and 24 after last dose

Analyzed: 15 minutes of preprocessed data (excluding seizure activity)

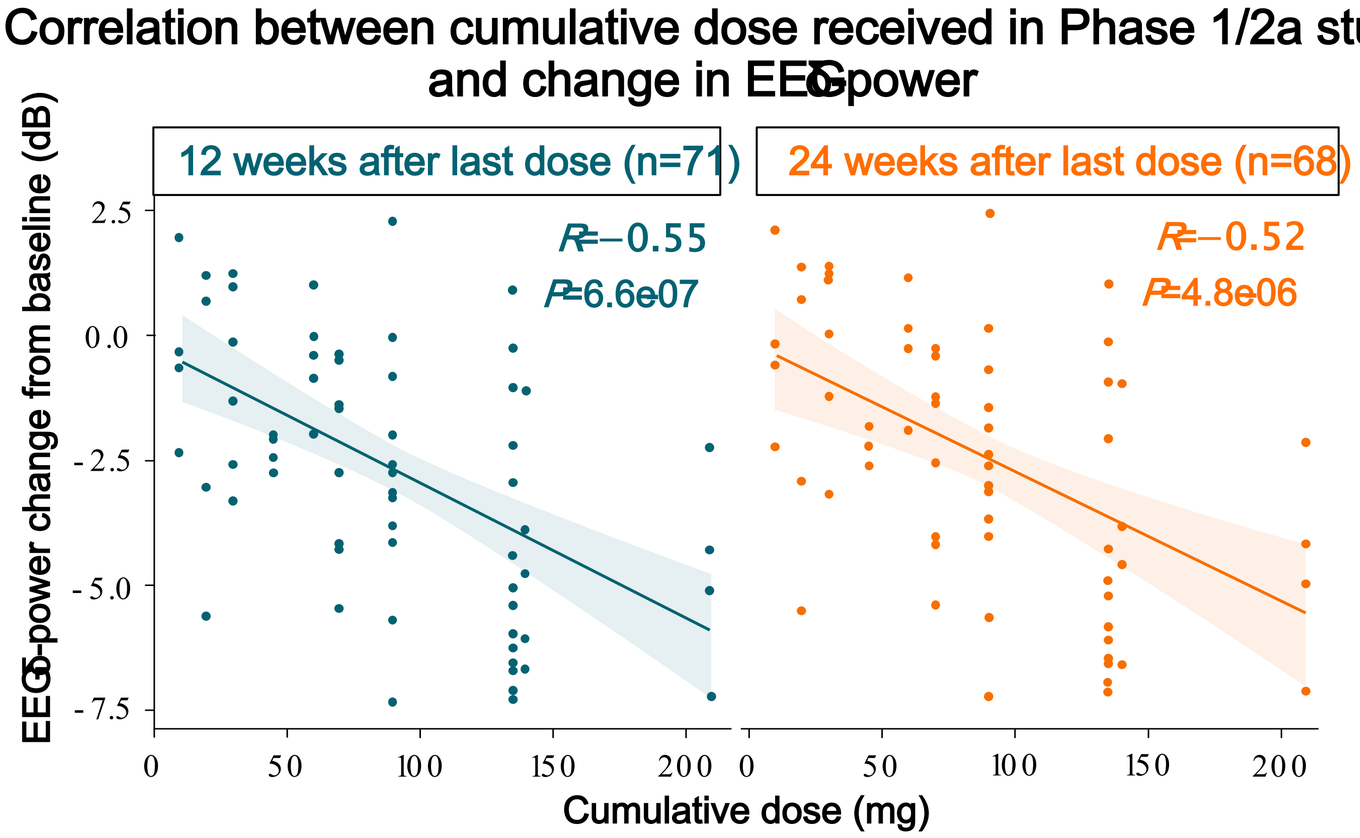
Computed: Power spectra (1–32 Hz, log-scaled) were computed using Morlet wavelet decomposition. EEG δ-power (1–4 Hz) was averaged across electrodes

Baseline characteristics

- EEG analysis included 74 patients with Dravet syndrome with a median age of 9.0 years

Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK).
EEG, electroencephalogram; Hz, hertz; *SCN1A*, voltage-gated sodium channel alpha subunit 1; SoC, standard of care.

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



- The correlation coefficient for cumulative dose was −0.55 at Week 12 and −0.52 at Week 24 ($P<0.05$), suggesting a significant negative association with change in EEG δ-power

*Single dose or sum of all doses for patients receiving multiple doses of zorevunersen. An MMRM was used to predict the correlation between cumulative dose and change in EEG δ-power. EEG segments from two patients were excluded because of 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% CI.

CI, confidence interval; dB, decibel; EEG, electroencephalogram; MMRM, mixed model for repeated measures.

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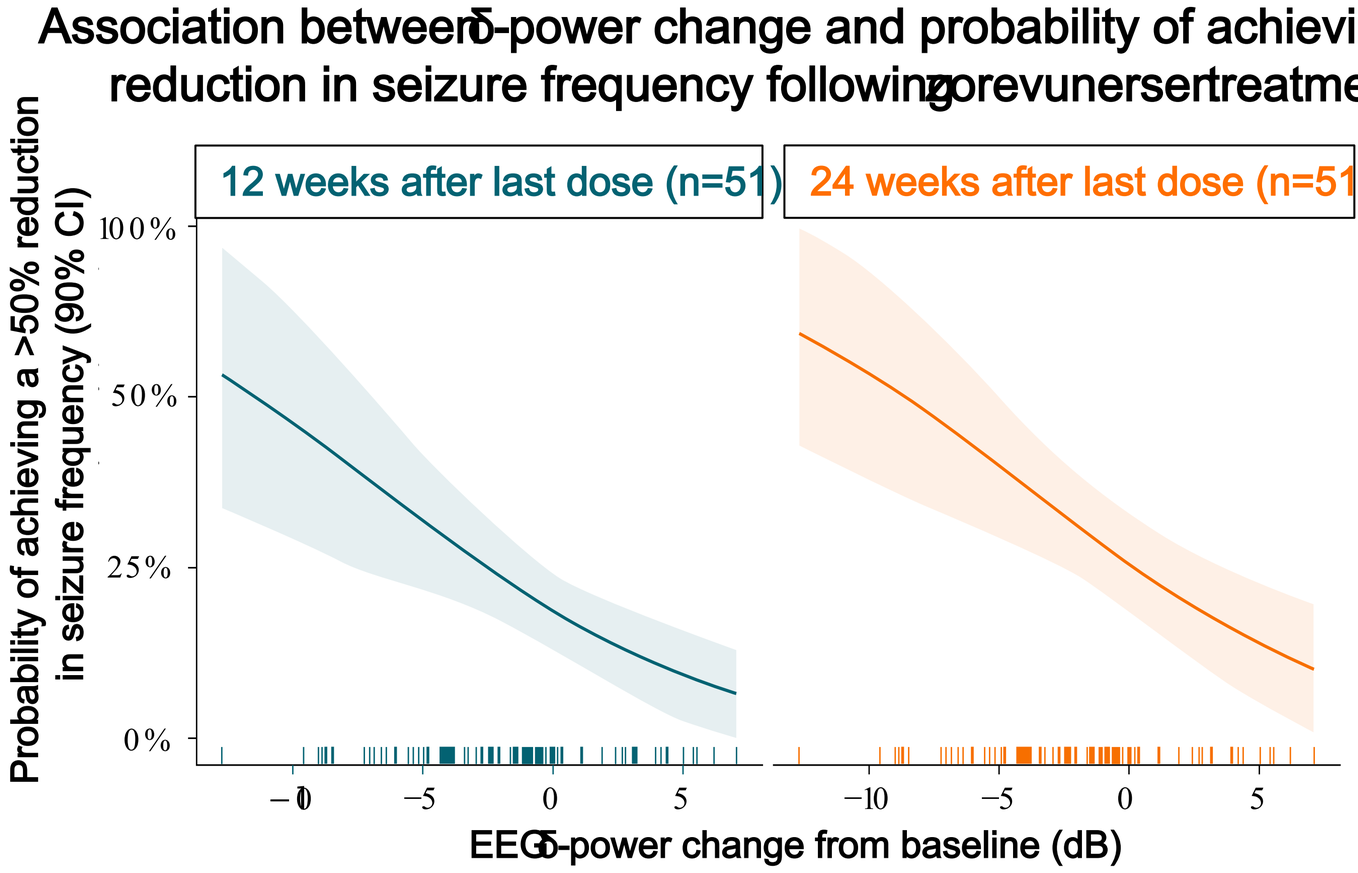
Reduction in δ-power is associated with being a clinical responder to zorevunersen treatment



- Patients with greater reductions in δ-power were more likely to achieve clinical responder status at Weeks 12 and 24
- A clinical responder to zorevunersen treatment was defined as a patient with >50% reduction in seizure frequency

A complete case analysis of patients with non - missing seizure frequency at both visits was performed, and the association between δ-power change and the probability of achieving >50% reduction in seizure frequency (clinical responder status) was evaluated using a logistic regression via generalized estimating equations. Each tick on the x-axis represents a separate patient. The line represents a linear fit and the shaded area represents the 90% CI.

CI, confidence interval; dB, decibel; EEG, electroencephalogram.

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Key takeaways

Dravet syndrome is characterized by EEG abnormalities, particularly in the δ-band (1–4 Hz). **EEG δ-power is elevated in patients with Dravet syndrome** in comparison with neurotypical controls.

Treatment with zorevunersen in patients with Dravet syndrome resulted in **dose-dependent reduction in δ-power at 12 and 24 weeks after last dose**.

Reduction in δ-power is associated with **an increased probability of achieving >50% reduction in major motor seizure frequency**.

Reduction in EEG δ-power after treatment with zorevunersen is an objective measure that suggests **improvement in the underlying epileptic encephalopathy** and **supports the potential of zorevunersen as a disease-modifying therapy in Dravet syndrome**.

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EEG, electroencephalogram; Hz, hertz.

Acknowledgements

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