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Zorevunersen continues to demonstrate potential as a disease-modifying therapy in long-term open-label extension studies of patients with Dravet syndrome

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

>90% of DS cases are caused by ***SCN1A* gene variants →**
50% reduction in Na_V1.1 sodium channel expression[2–6]

1 out of ~16,000 babies are born with **DS**[7,8]

Patients experience refractory seizures and **significant cognitive and behavioral deficits**

Current ASMs only target seizures; **up to 57% of patients fail to achieve ≥50% reduction in seizure frequency**[9–11]

No approved treatments for non-seizure symptoms[8,12]

Cognition

Communication

Behavior

Movement

Natural history data show adaptive behavior and neurodevelopment plateau with widening gaps vs. population norms[13]

Urgent need for **disease-modifying therapies addressing the underlying channelopathy** to improve both seizure AND non-seizure symptoms

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

ASM, anti-seizure medication; ASO, antisense oligonucleotide; DS, Dravet syndrome; *SCN1A*, sodium channel protein type 1 alpha subunit.

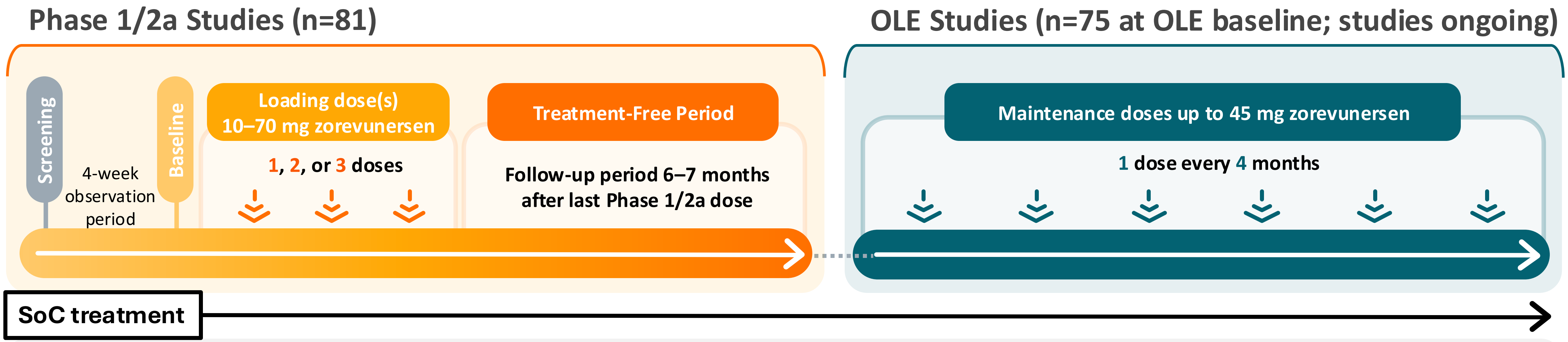
1. Dravet Syndrome Foundation – Voice of the Patient Report. Available at: https://dravetfoundation.org/wp-content/uploads/2022/05/Voice-of-the-Patient-report-5.31.22_compressed.pdf. Accessed November 2025. 2. Hattori J *et al. Epilepsia* 2008; 49 (4): 626–633. 3. Gil-Nagel A *et al. Sci Rep* 2023; 13 (1): 3355. 4. Bechi G *et al. Epilepsia* 2012; 53 (1): 87–100. 5. Li W *et al. Epilepsia* 2021; 62 (9): 2205-2217. 6. Gertler TS *et al. Seizure.* 2020; 75: 1–6. 7. Wu YW *et al. Pediatrics* 2015; 136 (5): e1310–e1315. 8. Symonds JD *et al. Brain* 2019; 142 (8): 2303–2318. 9. Devinsky O *et al. N Engl J Med* 2017; 376 (21): 2011–2020. 10. Sullivan J *et al. Epilepsia* 2023; 64 (10): 2653–2666. 11. Guerrini R *et al. Neurol Ther* 2024; 13 (3): 869–884. 12. Lagae L *et al. Dev Med Child Neurol* 2018; 60 (1): 63–72. 13. Sullivan J *et al. Neurology* 2025; 105 (11): e214388.

Phase 1/2a and OLE studies investigating zorevunersen safety, PK, and effectiveness in children and adolescents with Dravet syndrome

PRIMARY OBJECTIVES
- Safety and tolerability
- PK and CSF drug exposure (Phase 1/2a only)

SECONDARY OBJECTIVES
- Change in convulsive seizure frequency, overall clinical status, and QoL
- PK and CSF drug exposure (OLE only)

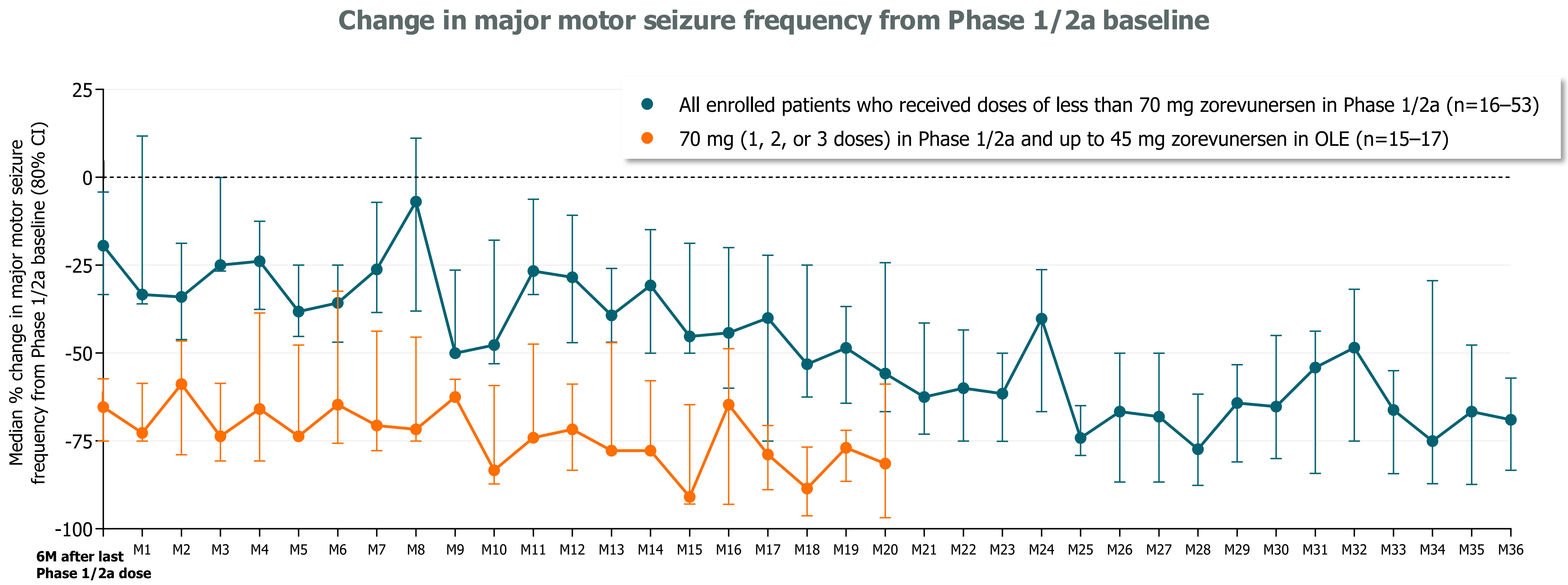
EXPLORATORY OBJECTIVES
- Change in adaptive behavior (as measured by Vineland-3)



Baseline concomitant antiseizure medications (ASMs)
- **81.5% patients on ≥3 ASMs; 50.6% on ≥4 ASMs**
- Most common ASMs: clobazam (70.4%), fenfluramine (49.4%), cannabidiol (44.4%), and valproate compounds (44.4%)

Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK). OLE studies: NCT04740476 (USA) and 2021-005626-14 (UK).
CSF, cerebrospinal fluid; DS, Dravet syndrome; OLE, open-label extension; PK pharmacokinetics; QoL, quality of life; SoC, standard-of-care, Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Reductions in major motor seizure frequency were maintained through 3 years of treatment with zorevunersen on top of SoC in the OLE studies



Reductions were greater in patients who received loading doses of 70 mg followed by maintenance doses of ≤45 mg

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OLE data cut: May 30, 2025. Figure demonstrates an as-treated analysis and major motor seizure frequency was calculated for the 28-day interval preceding each M time point. Error bars show 80% CIs. One patient who received an incorrect dose of zorevunersen in Phase 1/2a, 3 patients who experienced less than the minimum number of convulsive seizures during Phase 1/2a baseline, and 1 patient who transferred into OLE with a delay of approximately 10 months were excluded. Patients were not included in 6M after last Phase 1/2a dose time point if they didn't enter OLE. No exclusions were made for ASM modification. Intervals with <50% diary data were excluded for individual patients. All enrolled patients received up to 45 mg zorevunersen in the OLEs, and OLE study doses were administered once every 4 months.

ASM, anti-seizure medication; CI, confidence interval; M, month; OLE, open-label extension; SoC, standard-of-care.

Propensity Score Weighting (PSW): Balancing treatment and natural history groups to mimic randomization

What is Propensity Score Weighting?

A statistical method to create a pseudo-randomization comparison between treated and untreated (natural history) patient groups when randomization is not possible

Each person in both groups is assigned a **Propensity Score,** the probability of receiving the treatment based on BL characteristics

Weighting is calculated for each person so that the groups have similar BL characteristics, mimicking randomization

Treatment group **Natural History group**

Advantages

Compared to simple propensity score matching, **weighting…**

- Uses all available data (**no patient exclusion**)
- Balances groups based on **multiple covariates simultaneously**
- Results in outcome differences more likely **attributable to the treatment effect** rather than to pre-existing differences in patient populations

Covariates in these analyses

Seizure frequency analysis: Age, baseline 28-day seizure counts, age at first motor seizure, gender, and BMI

Vineland-3 analyses: Age, baseline Vineland-3 sub-domain raw score, baseline 28-day seizure frequency, age at first motor seizure, gender, and BMI

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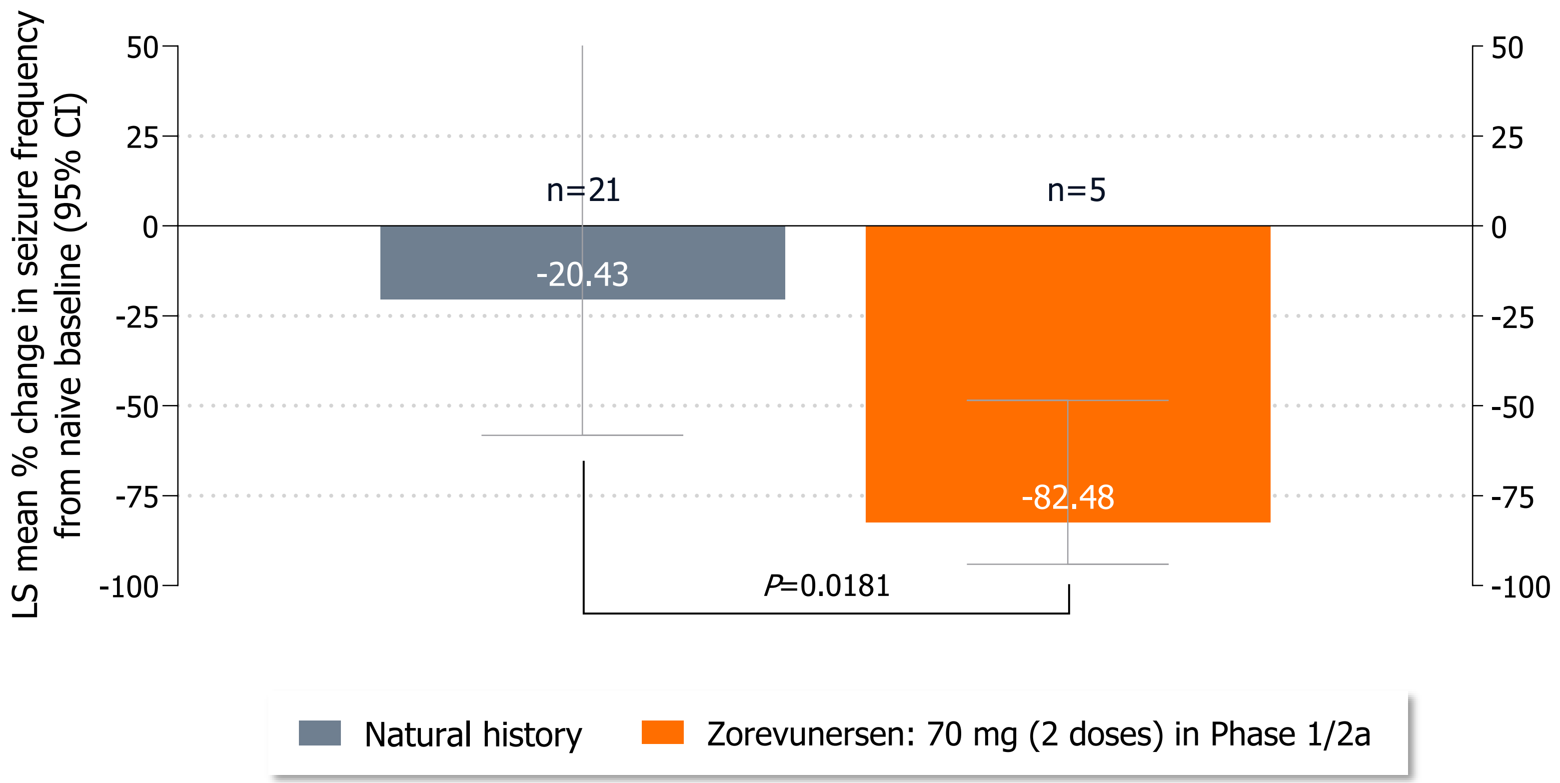
Weighted Mixed Model for Repeated Measures analyses used compound symmetry (CS) covariance for seizure outcomes and unstructured (UN) covariance for Vineland-3 outcomes, with robust standard errors and visit mapping to account for different assessment schedules. BL, baseline; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

1. Austin PC and Stuart EA. *Stat Med* 2015; 34 (28): 3661–3679. 2. Xu S *et al. Value Health* 2010; 13 (2): 273–277.
3. Funk MJ *et al. Am J Epidemiol* 2011; 173 (7): 761–767. 4. Chesnaye NC *et al. Clin Kidney J* 2021;15 (1): 14–20.

Zorevunersen significantly reduced major motor seizure frequency at 6 months

6-month timepoint and dosing are consistent with the Phase 3 study (EMPEROR) primary endpoint

Propensity score weighted analysis of major motor seizure frequency at 6 months

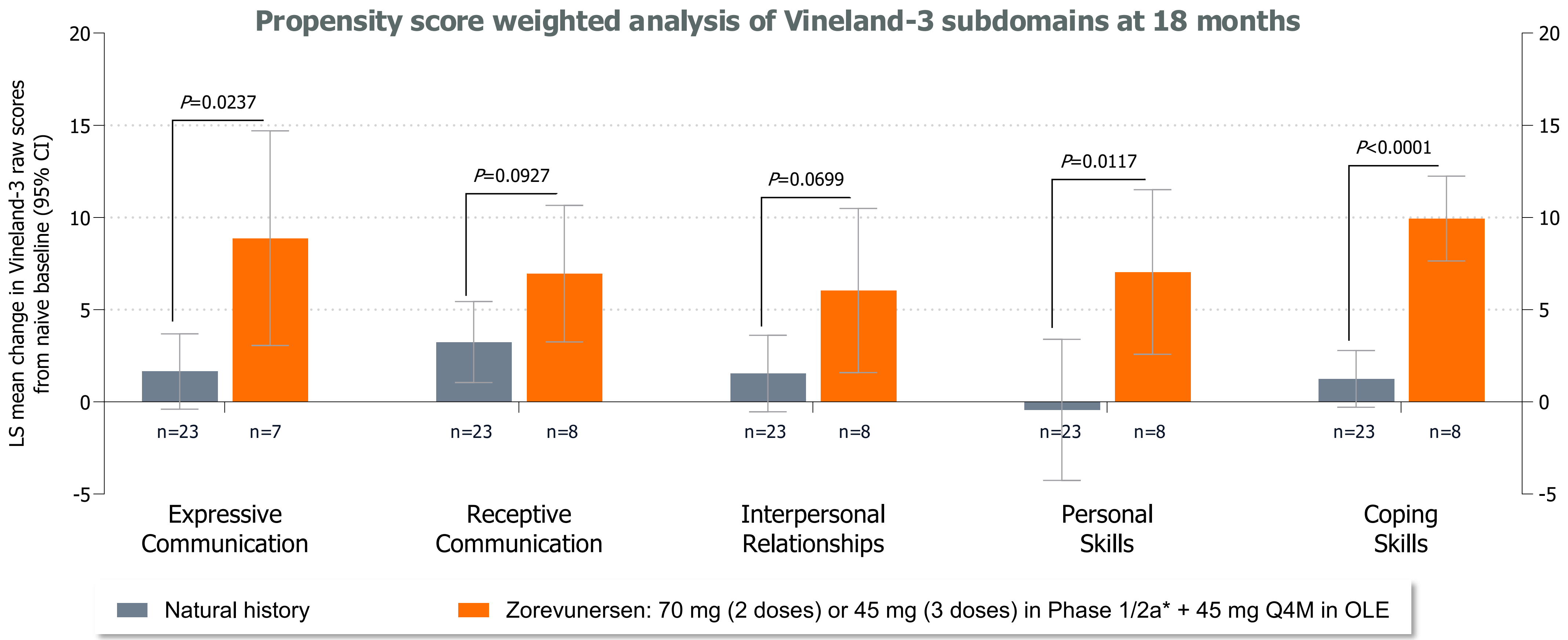


Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025. Propensity score weighting (PSW) with weighted mixed repeated-measures model (MMRM) was employed to balance baseline characteristics for cross-trial comparison with the BUTTERFLY natural history study. MMRM used compound symmetry covariance.

CI, confidence interval; LS, least squares; NH, natural history; OLE, open-label extension; Q4M, every 4 months.

Significant improvements across multiple Vineland-3 subdomains with zorevunersen compared to natural history

At 18 months, cumulative dosing is similar and consistent to that evaluated in the Phase 3 study (EMPEROR)



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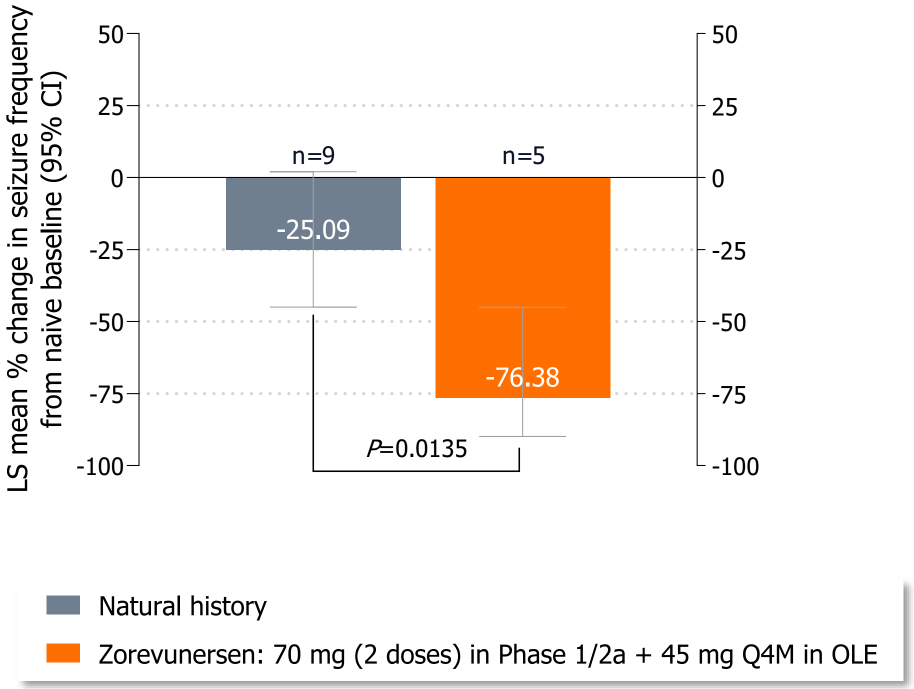
*Initial cumulative doses of 135 mg to 140 mg in the Phase 1/2a studies.

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025. Propensity score weighting (PSW) with weighted mixed repeated-measures model (MMRM) was employed to balance baseline characteristics for cross-trial comparison with the BUTTERFLY natural history study. MMRM used unstructured covariance.

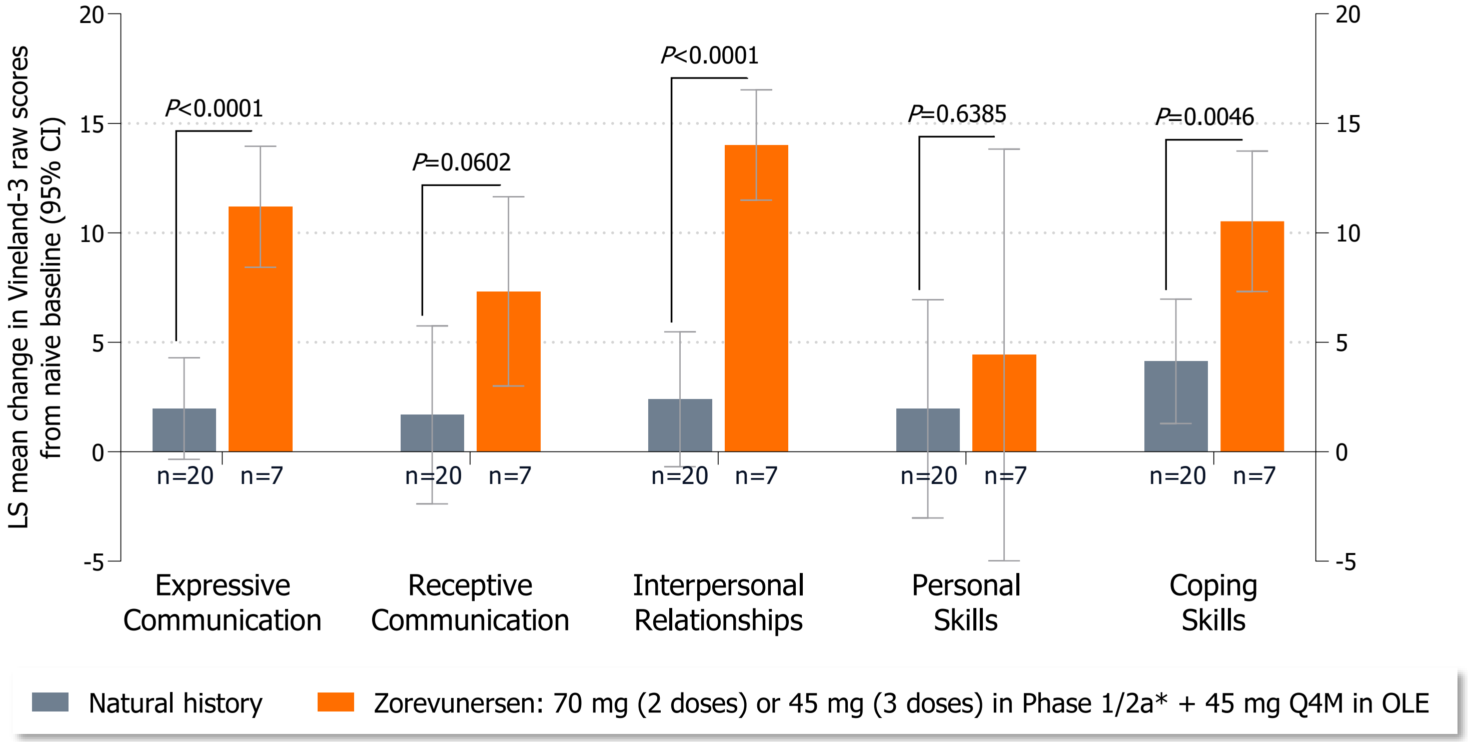
CI, confidence interval; LS, least squares; NH, natural history; OLE, open-label extension; Q4M, every 4 months; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Durable and significant reduction in seizure frequency and improvement in cognition and behavior at 24 months with zorevunersen, compared to natural history

PSW analysis of major motor seizure frequency at 24 months



PSW analysis of Vineland-3 subdomains at 24 months



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CI, confidence interval; LS, least squares; NH, natural history; OLE, open-label extension; PSW, propensity score weighting; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Zorevunersen was generally well tolerated with long-term dosing

Phase 1/2a studies
(n=81)

- **30%** of patients experienced a study drug–related TEAE
  - Most common: CSF protein elevations (14%) and procedural vomiting (5%)
- **22%** of patients experienced a TESAE
  - All were unrelated to the study drug except for one patient with SUSARs
- 1 patient died due to SUDEP, **unrelated to zorevunersen**

OLE studies
(n=75)

- **CSF protein elevation*** occurred in **86%** of patients and was **classified as a TEAE in 45%**
  - No reports of hydrocephalus associated with CSF protein elevation
  - One patient discontinued treatment because of CSF protein elevation
- 1 patient died due to SUDEP and 1 due to malnutrition; both deaths were **unrelated to zorevunersen**

>800 doses†
administered to date in the Phase 1/2a and OLE studies

Patients have received treatment for up to 4.5 years

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025.
*≥1 CSF protein value >50 mg/dL. Percentage based on 72/75 patients who had ≥1 post-baseline CSF protein value in the OLE studies, of whom 62/72 (86.1%) had an elevation.
†Dosing information as of November 2025.
CSF, cerebrospinal fluid; OLE, open-label extension; SUDEP, sudden unexpected death in epilepsy; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

OLE study findings, including comparisons to natural history, support the potential of zorevunersen as a durable, disease-modifying therapy for patients with Dravet syndrome

Patients receiving zorevunersen on top of SoC **experienced substantial and durable reductions in major motor seizure frequency as well as improvements in cognition, behavior, and functioning** that continued to increase over time

At 36 months, **most patients (94.7%) were rated as improved** in overall clinical status by both clinicians and caregivers

Zorevunersen demonstrated **durable statistically significant seizure frequency reduction and improvements in cognition, behavior, and functioning compared to natural history** that support ongoing Phase 3 evaluation

Treatment with zorevunersen has been generally **well tolerated, with some patients treated up to 4.5 years**

Zorevunersen is being investigated in a **global Phase 3 double-blind, randomized, sham-controlled study** to assess the efficacy, safety, and tolerability among children and adolescents with DS

Acknowledgments

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