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Poster #2.341

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

Sullivan J,[1] Perry MS,[2] Brunklaus A,[3] Cross JH,[4] Laux L,[5] Schreiber JM,[6] Knupp KG,[7] Brathwaite C,[8] Condon C,[8] Dandurand A,[8] Lynch J,[8] Stutely J,[8] Wang F,[8] Meena,[8] Werneburg B,[8] Parkerson KA,[8] Ticho B[8]

[1]University of California San Francisco, San Francisco, CA, USA; [2]Cook Children's Medical Center, Fort Worth, TX, USA; [3]University of Glasgow, Glasgow, Scotland, UK; [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [5]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [6]Children's National Medical Center, Washington D.C., USA; [7]Children's Hospital Colorado, Aurora, CO, USA; [8]Stoke Therapeutics, Inc., Bedford, MA, USA.

Key Findings

1. 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.
2. At 36 months, **most patients (94.7%) were rated as improved** in overall clinical status by both clinicians and caregivers.
3. 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.
4. Treatment with zorevunersen has been generally **well tolerated, with some patients treated up to 4.5 years.**
5. 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

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Introduction

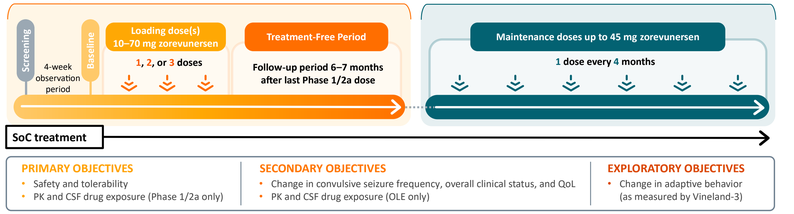
- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy. More than 90% of DS cases are caused by voltage-gated sodium channel α subunit 1 (*SCN1A*) variants that result in 50% $Na_V1.1$ sodium channel expression, causing refractory seizures and significant developmental, cognitive, and behavioral impairments that impact quality of life.[1–6]
- Despite use of standard-of-care (SoC) antiseizure medications (ASMs), natural history study (NHS) results have demonstrated that adaptive functioning and neurodevelopment generally plateau, with developmental gaps widening over time compared with population norms.[7]
- There is an urgent need for disease-modifying therapies that address the underlying channelopathy to improve both seizure and non-seizure symptoms.[8]
- Zorevunersen is an investigational antisense oligonucleotide that upregulates $Na_V1.1$ protein expression by leveraging the wild-type copy of *SCN1A*.[9]
- Here, we present the effects of zorevunersen on seizure burden, cognition, behavior, and overall clinical status, as well as safety, in patients with DS already on standard-of-care ASMs.

Methods

Study design

- The Phase 1/2a open-label, multicenter studies and their corresponding ongoing open-label extensions (OLEs) aim to evaluate the effects of zorevunersen in children and adolescents with highly refractory DS (Figure 1).
- Eligible patients were aged 2–18 years old with an established DS diagnosis and documented *SCN1A* gene variant.

Figure 1. Study design of the Phase 1/2a and OLE studies



Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK). OLE studies: NCT04740476 (USA) and 2021-005626-14 (UK). All patients are currently receiving 45 mg maintenance dosing in the OLE studies.
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.

Results

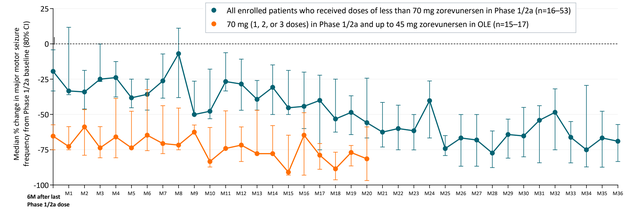
Baseline characteristics

- 81 patients with DS (median [range] age: 10 [2–18] years) received at least one dose of zorevunersen in the Phase 1/2a studies; 75 patients (median [range] age: 11 [2–19] years) rolled over into the OLEs.
- For additional details on the baseline characteristics please scan the QR code.

Continued improvement in seizure and non-seizure outcomes with zorevunersen

- Reductions in major motor frequency were maintained through 36 months of treatment with zorevunersen on top of SoC in the OLE studies (Figure 2). Reductions were greater in patients who received loading doses of 70 mg followed by maintenance doses of <45 mg.

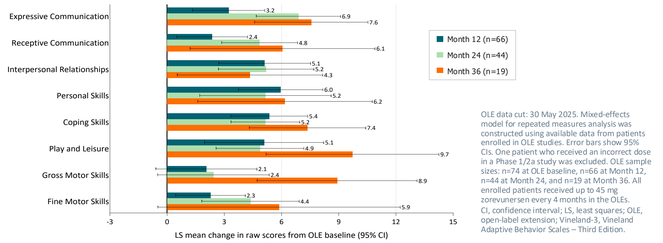
Figure 2. Change in major motor seizure frequency from Phase 1/2a baseline



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.

- Substantial improvements in cognition and behavior were observed through 36 months of treatment with zorevunersen in the OLE studies (Figure 3).
- 94.7% of clinicians and caregivers reported an improvement in overall clinical status at 36 months in the OLEs.

Figure 3. Change in Vineland-3 subdomain raw scores from OLE baseline

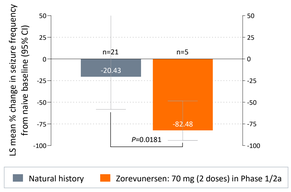


OLE data cut: 30 May 2025. Mixed-effects model for repeated measures analysis was constructed using available data from patients enrolled in OLE studies. Error bars show 95% CIs. One patient who received an incorrect dose in a Phase 1/2a study was excluded. OLE sample sizes: n=74 at OLE baseline, n=66 at Month 12, n=44 at Month 24, and n=19 at Month 36. All enrolled patients received up to 45 mg zorevunersen every 4 months in the OLEs.
CI, confidence interval; LS, least squares; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Comparison of zorevunersen-treated patients to natural history patients

Figure 5. 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

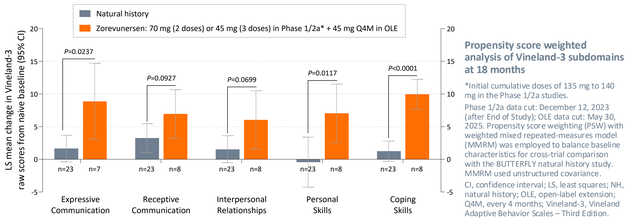


Propensity score weighted analysis of major motor seizure frequency at 6 months

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.

Figure 6. 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)

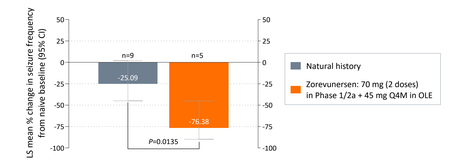


Propensity score weighted analysis of Vineland-3 subdomains at 18 months

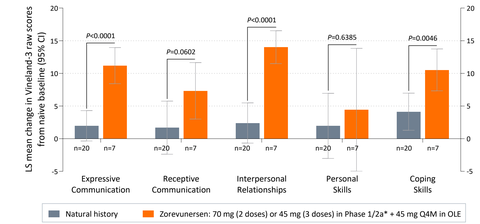
*Initial cumulative doses of 135 mg to 140 mg in the Phase 1/2a studies.
Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025. Propensity score weighting (PSW) with weighted mixed repeated-measures model (MMRM) was employed to balance baseline characteristics for cross-trial 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.

Figure 7. Durable and significant reduction in seizure frequency and improvement in cognition and behavior at 24 months with zorevunersen, compared to natural history

A. Propensity score weighted analysis of major motor seizure frequency at 24 months



B. Propensity score weighted analysis of Vineland-3 subdomains at 24 months



Propensity score weighted analysis of major motor seizure frequency (A) and Vineland-3 subdomains (B) at 24 months.

*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 compound symmetry (seizure frequency) or unstructured (Vineland-3) covariance.
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.

Safety and tolerability*

- Study drug–related treatment-emergent adverse events were reported in 30% of patients (n=24/81) in the Phase 1/2a studies (most common: cerebrospinal fluid [CSF] protein elevations [14%, n=11] and procedural vomiting [5%, n=4]).
- 22% (n=18/81) of patients in the Phase 1/2a studies experienced a treatment-emergent serious adverse event, and all were unrelated to the study drug except for one patient with suspected unexpected serious adverse reactions.
- CSF protein elevation† occurred in 86% of patients and was classified as a TEAE in 45%. No hydrocephalus associated with CSF protein elevation was reported. One patient discontinued treatment because of CSF protein elevation.
- 3 deaths have occurred during the Phase 1/2a and OLE studies (2 due to sudden unexpected death in epilepsy, 1 due to malnutrition); all were unrelated to zorevunersen.
- More than 800 doses of zorevunersen have been administered to date in the Phase 1/2a and OLE studies, for up to 4.5 years (as of November 2025).

*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. TEAE, treatment emergent adverse event.

References: 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. Hartzel I 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. Sullivan J et al. Neurology 2025; 105 (11): e214388. 8. Wirrell EC et al. *Epilepsia* 2022; 63(7): 1761–1777. 9. Lim KH et al. *Nat Commun* 2020; 11(1): 3501.

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