2026

CHILD NEUROLOGY SOCIETY

55th ANNUAL MEETING

October 14-17, 2026 • Montreal, QC

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Zorevunersen demonstrates potential as a disease-modifying therapy in patients with Dravet syndrome: A matching-adjusted indirect comparison between natural history and patients receiving zorevunersen

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Disclosures

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- Consulting fees: Aucta, Elemental Medicines, Encoded Therapeutics, Jazz Pharmaceuticals, Longboard, Marinus, Neurocrine, Stoke Therapeutics, Takeda, UCB Pharma, Xenon, Zenas, Zogenix
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Dravet syndrome: A severe genetic developmental and epileptic encephalopathy

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55th ANNUAL MEETING
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>90% of DS cases are caused by ***SCN1A* gene variants → reduced functional $Na_V1.1$ expression**[1–4]

1 out of ~16,000 babies are born with DS[5]

Patients experience refractory seizures, including GTC and focal-to-BTC seizures, and **significant cognitive and behavioral deficits**[6]

Current ASMs only target seizures; **up to 57% of patients fail to achieve ≥50% reduction in seizure frequency**[7–13]

No approved treatments for non-seizure symptoms[10–13]

Cognition **Communication** **Behavior** **Movement**

Natural history data show widening gaps in adaptive functioning and neurodevelopment vs. population norms[6]

Urgent need for **disease-modifying therapies addressing the underlying genetic cause of DS** to improve both seizure AND non-seizure symptoms[10]

Zorevunersen is an investigational ASO that is designed to **upregulate $Na_V1.1$ protein expression** via the wild-type copy of the *SCN1A* gene[14,15]

ASM, antiseizure medication; ASO, antisense oligonucleotide; BTC, bilateral tonic-clonic; DS, Dravet syndrome; GTC, generalized tonic-clonic; *SCN1A*, voltage-gated sodium channel alpha subunit 1.

1. Balestrini S *et al. CNS Drugs* 2026; 40 (4): 535–548. 2. Li W *et al. Epilepsia* 2021; 62 (9): 2205–2217. 3. Gertler TS *et al. Seizure* 2020; 75: 1–6. 4. Bechi G *et al. Epilepsia* 2012; 53 (1): 87–100. 5. Wu YW *et al. Pediatrics* 2015; 136 (5): e1310–e1315. 6. Sullivan J *et al. Neurology* 2025; 105 (11): e214388. 7. Devinsky O *et al. N Engl J Med* 2017; 376 (21): 2011–2020. 8. Sullivan J *et al. Epilepsia* 2023; 64 (10): 2653–2666. 9. Guerrini R *et al. Neurol Ther* 2024; 13 (3): 869–884. 10. Wirrell EC *et al. Epilepsia* 2022; 63 (7): 1761–1777. 11. Biocodex, Inc. DIACOMIT – prescribing information; 2026. 12. UCB, Inc. FINTEPLA – prescribing information; 2025. 13. Jazz Pharmaceuticals plc. EPIDIOLEX – prescribing information; 2026. 14. Isom LL *et al. Neurotherapeutics* 2021; 18 (3): 1524–1534. 15. Lim KH *et al. Nat Commun* 2020; 11 (1): 3501.

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

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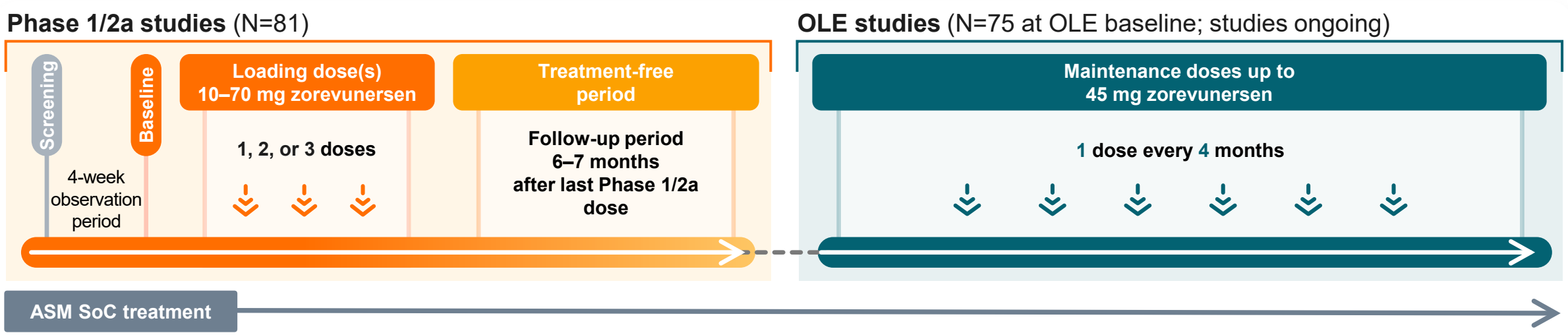

PRIMARY ENDPOINTS	SECONDARY ENDPOINTS	EXPLORATORY ENDPOINTS
• Safety profile • PK and CSF drug exposure (Phase 1/2a only)	• Change in convulsive seizure frequency, overall clinical status, and QoL • PK and CSF drug exposure (OLE only)	• Change in adaptive behavior (as measured by Vineland™-3)

Baseline concomitant ASMs[1]

- **81% patients on ≥3 ASMs; 51% on ≥4 ASMs**
- Most common ASMs: Clobazam (70%), fenfluramine (49%), cannabidiol (44%), and valproate compounds (44%)

Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK). OLE studies: NCT04740476 (USA) and 2021-005626-14 (UK). Vineland™ is a trademark of NCS Pearson, Inc. This presentation was prepared by Stoke Therapeutics. Stoke Therapeutics is not affiliated with, sponsored by, or endorsed by Pearson, and Pearson has not reviewed or approved this presentation.
ASM, antiseizure medication; CSF, cerebrospinal fluid; OLE, open-label extension; PK, pharmacokinetics; QoL, quality of life; SoC, standard of care; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.
1. Laux L *et al. N Engl J Med* 2026; 394 (10): 969–982.

Patients treated with zorevunersen experienced reductions in major motor seizure frequency on top of SoC

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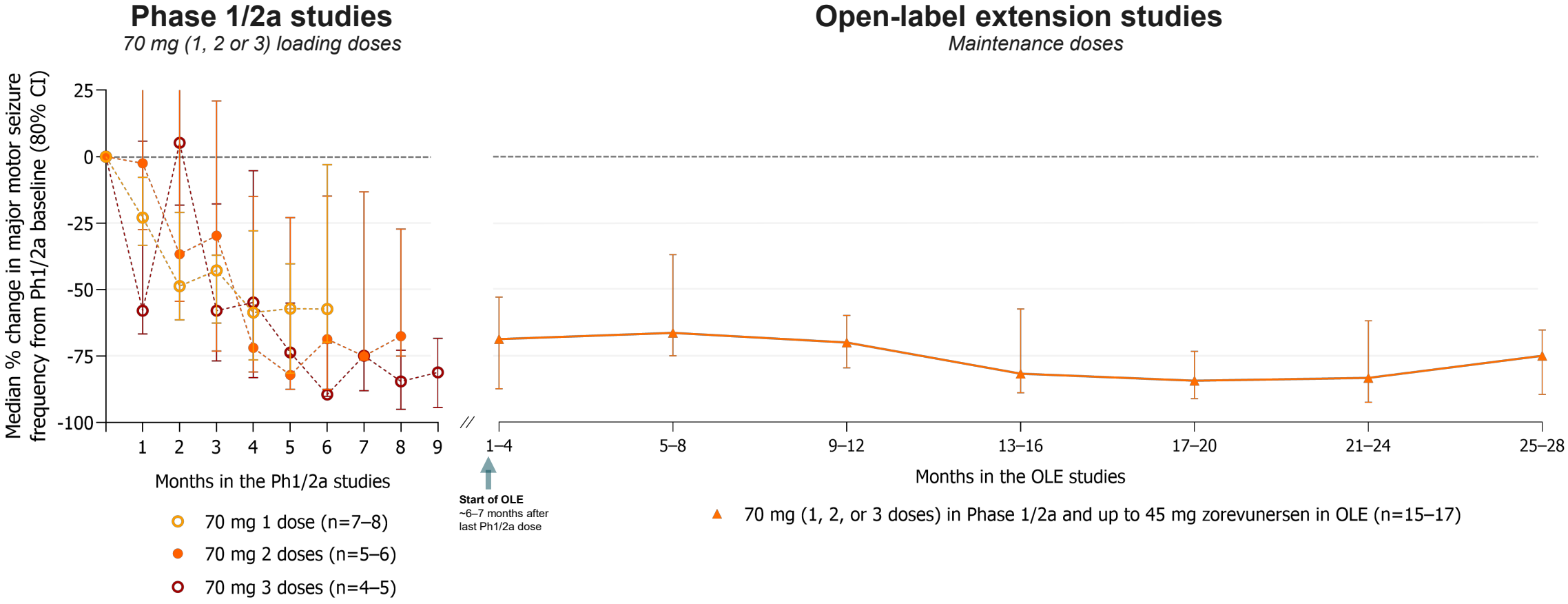
55th ANNUAL MEETING
October 14-17, 2026 • Montreal, QC



66%–84% reductions in major motor seizure frequency in the OLE studies through Month 28

Phase 1/2a data cut: 12 December 2023 (after End of Study).[1] OLE data cut: 19 February 2026. n=15 to 17 patients in the 70 mg (1, 2, or 3 doses) group had evaluable percent change-from-baseline data across visits. 1 month = 4 weeks. Major motor seizures are defined as hemiclonic, focal with motor signs, focal-to-bilateral tonic-clonic, generalized tonic-clonic, tonic, tonic/atonic (drop attacks), and clonic. Reported data show changes in major motor seizure frequency per 28 days from Phase 1/2a baseline. CI, confidence interval; OLE, open-label extension; Ph, Phase; SoC, standard of care.

1. Laux L *et al. N Engl J Med* 2026; 394 (10): 969–982.

Frequency of GTC and focal-to-BTC seizures was reduced following treatment with zorevunersen in the OLE studies

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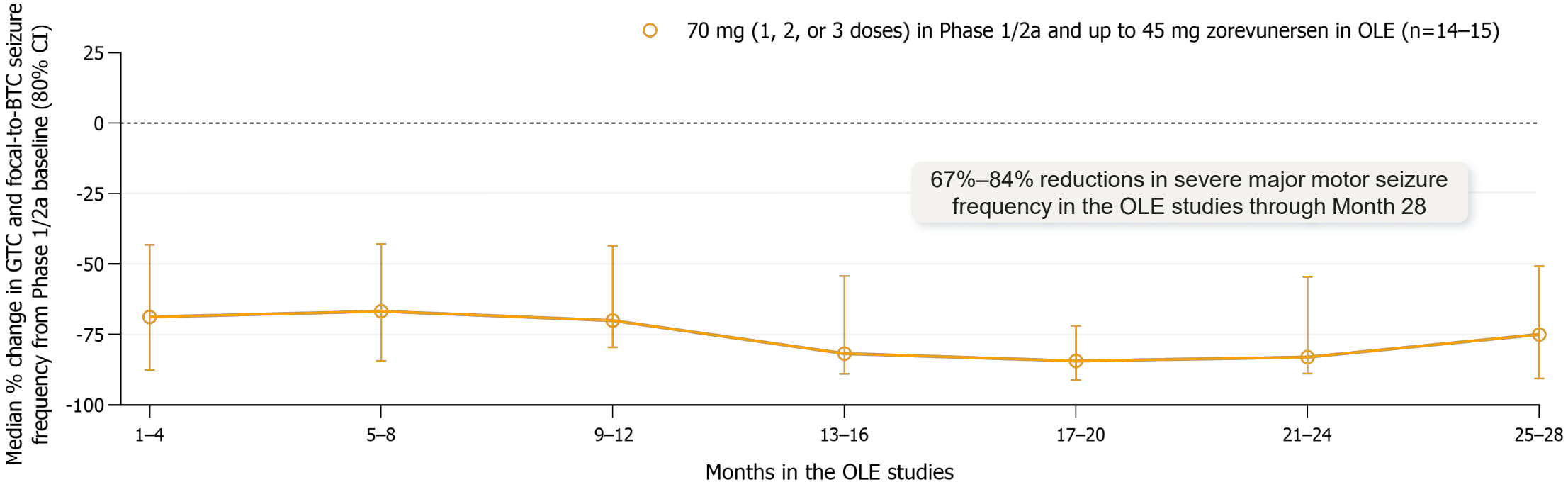
October 14-17, 2026 • Montreal, QC

Change in GTC and focal-to-BTC seizure frequency from Phase 1/2a baseline



These severe seizure types are the leading risk factor for SUDEP (≥3 GTC seizures per year OR: 15.46)[1–3]

Data cut date: 19 February 2026. n=14 to 15 patients in the 70 mg (1, 2, or 3 doses) group had evaluable percent change-from-baseline data across visits. 1 month = 4 weeks. Reported data show changes in GTC and focal-to-BTC seizure frequency per 28 days from Phase 1/2a baseline.

BTC, bilateral tonic-clonic; CI, confidence interval; GTC, generalized tonic-clonic; OLE, open-label extension; OR, odds ratio; SUDEP, sudden unexpected death in epilepsy.

1. Harden C *et al. Neurology* 2017; 88 (17): 1674–1680. 2. Devinsky O *et al. Lancet Neurol* 2016; 15 (10): 1075–1088. 3. Hesdorffer DC *et al. Epilepsia* 2011; 52 (6): 1150–1159.

Patients receiving zorevunersen experienced improvements in cognition, behavior, and functioning, contrasted with the natural history of patients with DS

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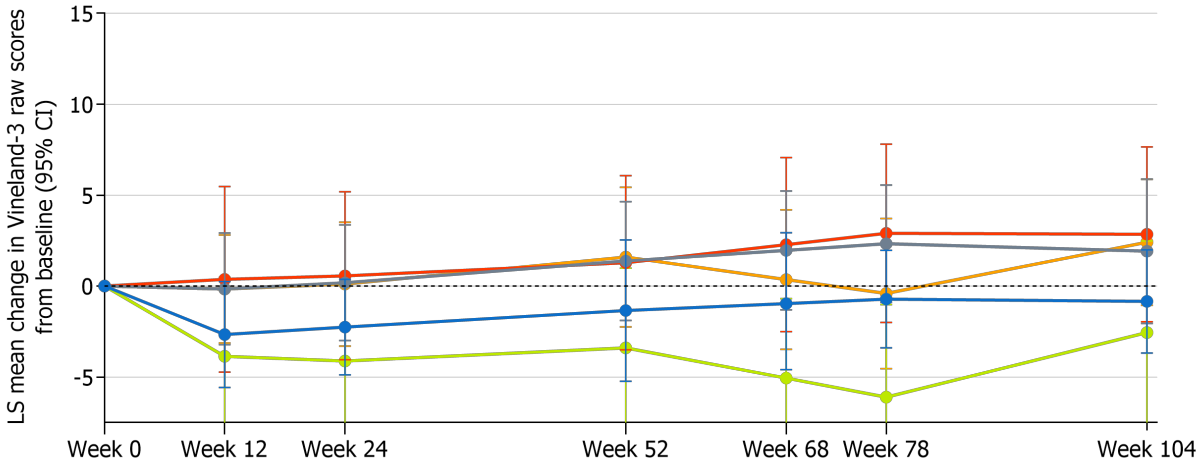
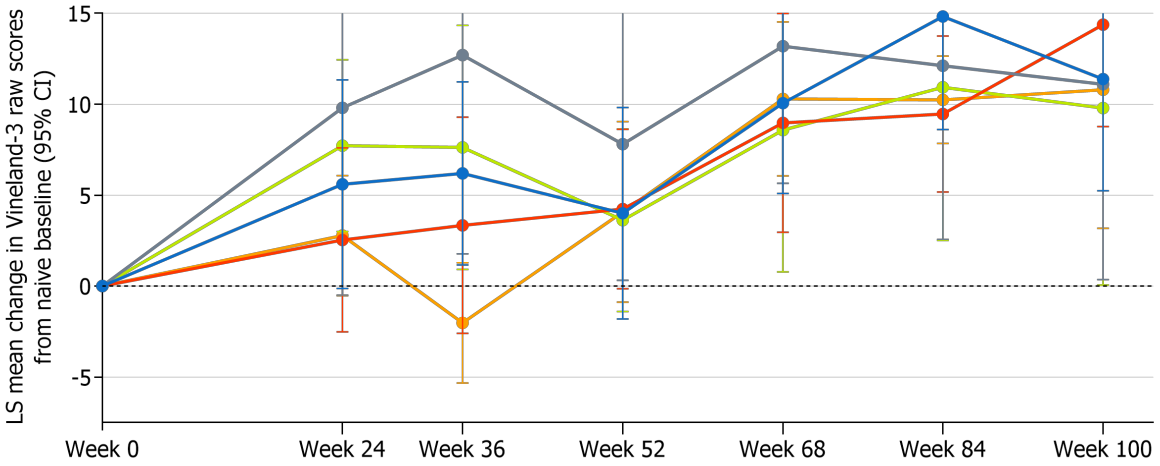
October 14-17, 2026 • Montreal, QC

Natural history patients



Expressive Communication
Receptive Communication
Interpersonal Relationships
Personal Skills
Coping Skills

Patients receiving a Phase 3–like regimen of zorevunersen, from Phase 1/2a baseline



Loading dose*
6–7-month treatment-free period
Maintenance dose of 45 mg zorevunersen every 4 months

Phase 1/2a
Open-label extension

Patients receiving a Phase 3–like regimen of zorevunersen experienced substantial and durable improvements in cognition, behavior, and functioning

OLE data cut: 30 May 2025. A matching-adjusted indirect comparison (MAIC) was conducted to compare BUTTERFLY natural history patients with zorevunersen-treated patients from the UK Phase 1/2a ADMIRAL study and its open-label extension (OLE), LONGWING. Baseline characteristics were balanced using MAIC weighting to improve comparability between studies. (Right) For each subdomain, an unweighted mixed-effects model for repeated measures (MMRM) with an unstructured covariance matrix was fitted using available data from ADMIRAL/LONGWING patients with a baseline assessment and at least one post-baseline assessment (N=17). The figure displays the 2 × 70 mg and 3 × 45 mg dose cohorts, with 7–10 patients contributing evaluable change-from-baseline data at individual visits. (Left) For each subdomain, an unweighted MMRM with an unstructured covariance matrix was fitted using available data from BUTTERFLY patients with a baseline assessment and at least one post-baseline assessment (N=34), with 20–34 patients contributing evaluable change-from-baseline data at individual visits. The legend shown below the left graph applies to both graphs.

*Phase 3–like regimen: 2 × 70 mg or 3 × 45 mg loading doses, followed by 45 mg maintenance every 4 months. CI, confidence interval; DS, Dravet syndrome; LS, least squares; OLE, open-label extension.

Clinically meaningful improvements in cognition, behavior, and functioning continuing through 4 years of treatment in the OLE studies

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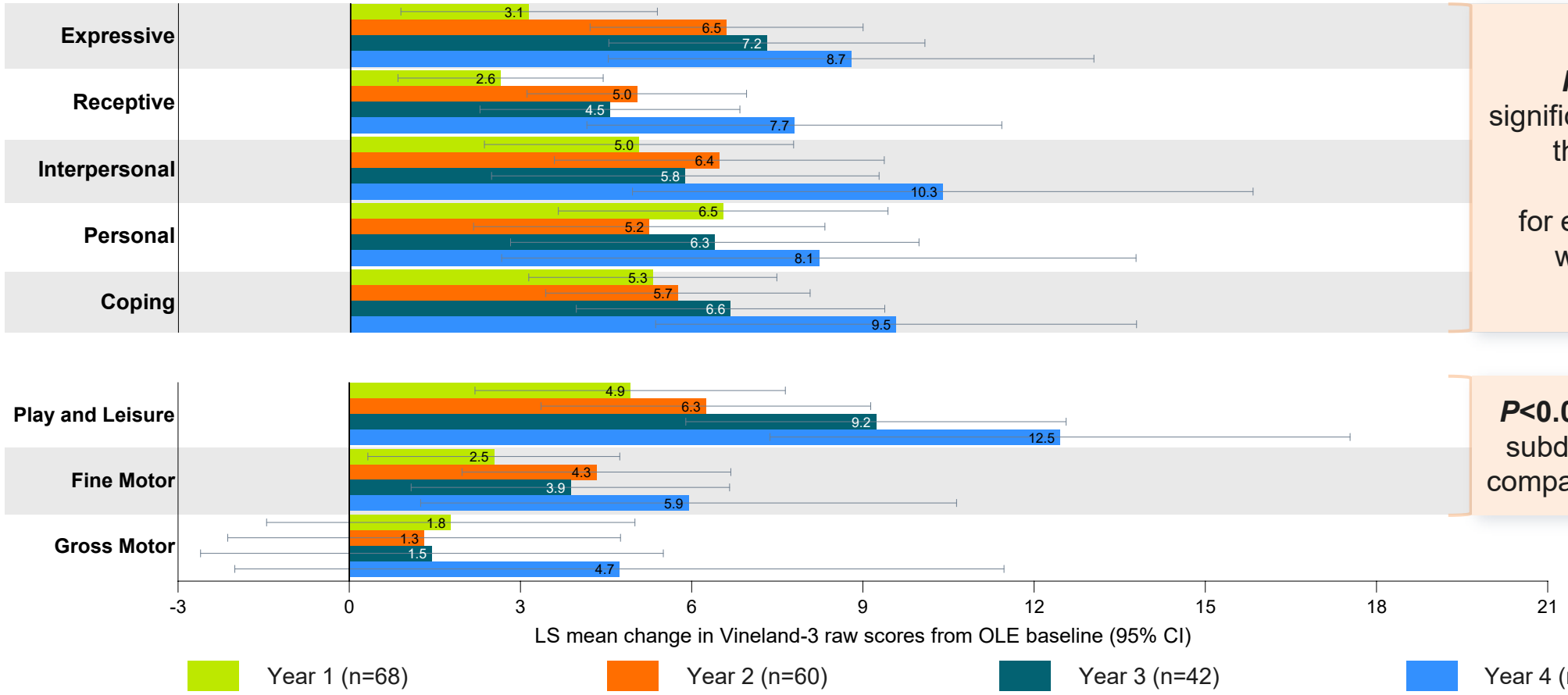
Change in Vineland-3 subdomain scores from OLE baseline



***P*<0.01** statistical significance was achieved in the **5 key Phase 3 subdomains** for each year compared with OLE baseline

***P*<0.03** achieved in 2 other subdomains for each year compared with OLE baseline

Data cut date: 19 February 2026. Mixed-effects model for repeated measures (MMRM) for each subdomain were fit using available data from patients with baseline and at least one post baseline assessment in the SWALLOWTAIL and LONGWING OLE studies, with n representing the number of completed patient visits at each timepoint shown. Statistical analyses are post hoc and exploratory. 1 year = 48 weeks.
CI, confidence interval; LS, least squares; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.
Condon C *et al. Epilepsy Behav* 2025; 167: 110381.

Improvements in quality of life following treatment with zorevunersen

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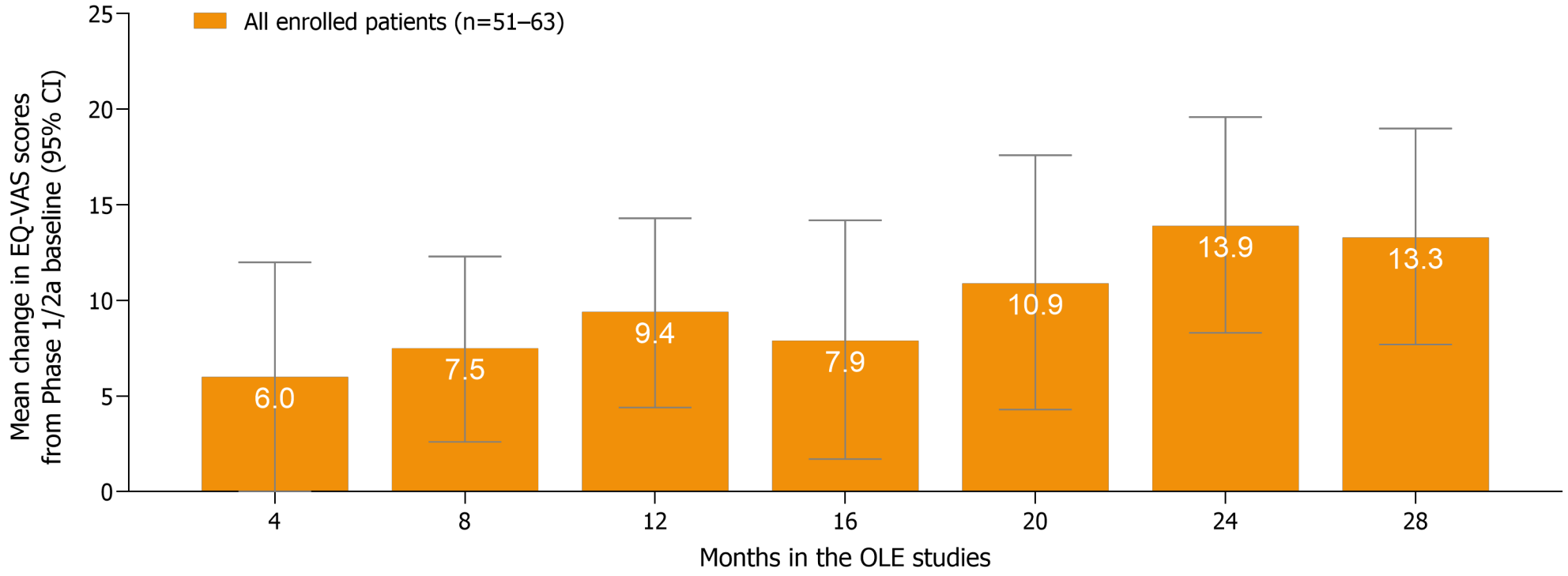
Change in EQ-VAS scores from Phase 1/2a baseline



Substantial increases in quality of life were observed in addition to reductions in seizure frequency and improvements in cognition, behavior, and functioning

Data cut date: 19 February 2026. Analysis performed using available data from patients enrolled in the SWALLOWTAIL and LONGWING OLE studies (N=75), with n=51 to 63 patients having evaluable change-from-baseline data across visits. EQ-VAS is a validated visual analogue scale ranging from 0 to 100 (worst to best imaginable health). 1 month = 4 weeks.
CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; OLE, open-label extension.

The safety profile of zorevunersen with long-term dosing

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55th ANNUAL MEETING
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Phase 1/2a studies (N=81)[1]

- **30%** (24/81) of patients experienced a study drug–related TEAE
  - Most common: CSF protein elevations (14%) and procedural vomiting (5%)
- **22%** (18/81) of patients experienced a TESAE
  - TESAEs for 17/18 patients were assessed as unrelated to study drug
  - 1 patient had study drug-related SUSARs
- 1 patient died because of SUDEP, **unrelated to study drug**

OLE studies (N=75)

- **56%** (42/75) of patients experienced a study drug–related TEAE
- **31%** (23/75) of patients experienced a TESAE; all unrelated to study drug
- **CSF protein elevation*** occurred in **94%** (68/72) of patients and was **classified as a TEAE in 59%** (40/68)
  - No serious or severe clinical manifestations associated with CSF protein elevation were observed
  - 1 patient discontinued treatment because of CSF protein elevation
- 1 patient died because of SUDEP and 1 because of malnutrition; both **unrelated to study drug**

Phase 1/2a data cut: 12 December 2023 (after End of Study). OLE data cut: 19 February 2026.
*≥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.
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.
1. Laux L *et al. N Engl J Med* 2026; 394 (10): 969–982.

Dosing, exposure, and understanding of zorevunersen long-term safety profile is now continuing past 5 years

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Phase 1/2a (N=81) and OLE (N=75) studies

Parameter	Result
Median treatment days per patient	1,255
Median doses per patient	11
Total exposure, patient-years	260.7
Maximum duration of years	5.33
Patients on treatment at data cutoff*	58

>930 doses administered in the Phase 1/2a and OLE studies as of 31 July 2026

Phase 1/2a data cut: 12 December 2023 (after End of Study). OLE data cut: 19 February 2026.
*As of the 19 February 2026 data cut, 58/75 (77%) of patients remained in the OLE studies. Most discontinuations were in the lower dose groups.
OLE, open-label extension.

Key findings

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- Patients receiving zorevunersen on top of SoC had durable reductions in major motor seizure frequency, including reductions in severe seizure types that increase risk for SUDEP
- Patients on a Phase 3–like regimen of zorevunersen on top of SoC had substantial improvements in cognition, behavior, and functioning relative to the natural history of patients with DS
- Improvements in quality of life accompanied improvements in seizures, cognition, behavior, and functioning
- Treatment with zorevunersen has been generally well tolerated over more than 260 patient-years of exposure, with some patients treated for more than 5 years
- Zorevunersen is now being studied in a global Phase 3 double-blind, randomized, sham-controlled trial in children and adolescents with DS

Acknowledgements: We thank the patients, caregivers, investigators, healthcare providers, and research staff who participated in the Phase 1/2a and OLE studies

Phase 3 Study EU CT: 2024-519555-28-00; ClinicalTrials.gov ID: NCT06872125.
DS, Dravet syndrome; OLE, open-label extension; SoC, standard of care; SUDEP, sudden unexpected death in epilepsy.

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