Zorevunersen demonstrates potential as a disease-modifying therapy in patients with Dravet syndrome through durable seizure reduction and improvements in cognition, behavior, and quality of life through 36 months of treatment in open-label extension studies

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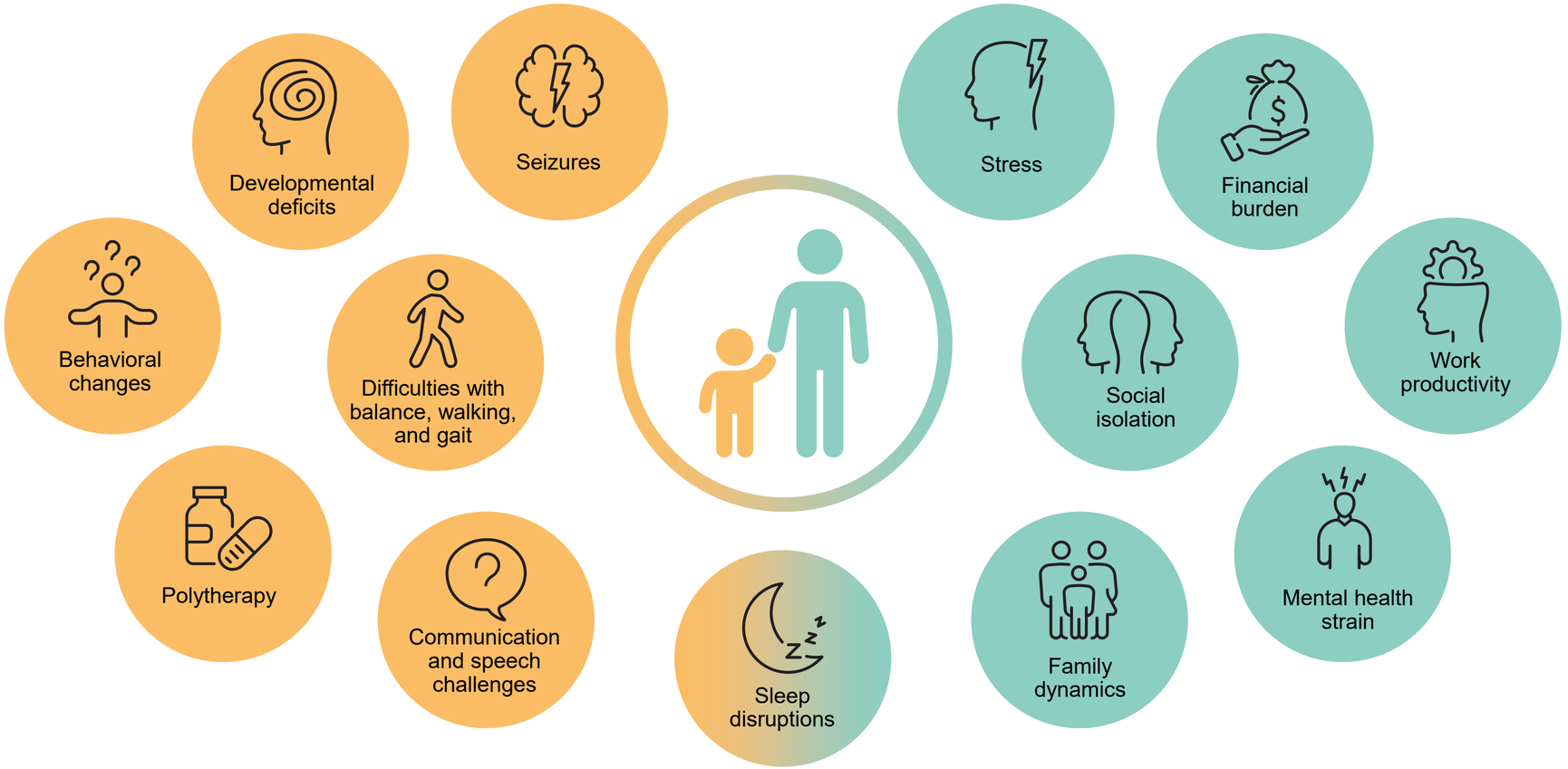
Disclosures

- Speaker
  - Serves as a Principal Investigator for research grants from Stoke Therapeutics, Encoded Therapeutics, Praxis Precision Medicine, and Longboard Pharmaceuticals
  - Receives consulting fees from Stoke Therapeutics and Biocodex
  - Receives payment/honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Stoke Therapeutics, Biocodex, and UCB
  - Receives support for attending meetings and/or travel from Stoke Therapeutics and Biocodex
  - Participates on a Data Safety Monitoring Board or Advisory Board for Stoke Therapeutics
  - Serves in a leadership or fiduciary role at the Dravet Syndrome Foundation Medical Advisory Board

Kelly G Knupp, M.D. has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring board for Harmony and for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Epilepsy Research. Andreas Brunklaus, M.D. has received personal compensation for serving as a consultant for Servier and Stoke Therapeutics; for serving on a Scientific Advisory or Data Safety Monitoring Board for Stoke Therapeutics, Encoded Therapeutics, Biocodex, and UCB; and for serving on a Speakers Bureau for Biocodex and UCB. J Helen Cross, M.B., Ch.B., Ph.D. has nothing to disclose. M Scott Perry, M.D. has received personal compensation for serving as a consultant for Stoke Therapeutics, Neurelis, Marinus, Jazz Pharmaceuticals, UCB, Pyros, Azurity, and Biocodex and for serving on a Scientific Advisory or Data Safety Monitoring Board for Stoke Therapeutics. Dr. Perry has stock in Praxis Precision Medicine, Biohaven, Rapport, and Alto Neurosciences. Dr. Perry also has non-compensated relationships as a president with child neurology foundation and as a President with Pediatric Epilepsy Research Consortium that are relevant to AAN interests or activities. Joseph Sullivan, M.D. has received personal compensation for serving as a consultant for Biocodex, UCB, Ceribell, Xenon, and the Epilepsy Study Consortium. Dr. Sullivan has also received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring Board for Neuropace and for serving as an Expert Witness for various firms. Dr. Sullivan has stock in Harmony. Archana Desurkar, M.D. has received personal compensation for serving on a Scientific Advisory or Data Safety Monitoring Board for Biocodex and Stoke Therapeutics and for serving on a Speakers Bureau for UCB. John M Schreiber, M.D. has received personal compensation for serving as a consultant for Neurocrine, Xenon, and Zogenix. Dr. Schreiber has received research support from the Dravet Syndrome Foundation. Colin M Roberts, M.D. has received personal compensation for serving as a consultant for Neurelis and Stoke Therapeutics and for serving on a Scientific Advisory or Data Safety Monitoring Board for Encoded. James W Wheless, M.D. has received personal compensation for serving as a consultant for Jazz, Neurelis, Azurity, UCB, Biocodex, LivaNova, and Stoke Therapeutics and for serving on a Speakers Bureau for Liva Nova, Jazz, UCB, and Neurelis. Elaine C Wirrell, M.D. has received personal compensation for serving as a consultant for Biocodex and for serving on a Scientific Advisory or Data Safety Monitoring Board for Encoded, Neurocrine, and GRIN. Dr. Wirrell has received publishing royalties from a publication relating to health care. Pam Ventola, Ph.D. has received personal compensation for serving as an employee of Cogstate and research support from the NIH. Jessie Lynch, M.S. and Kimberly A. Parkerson, M.D., Ph.D. have received personal compensation for serving as employees of Stoke Therapeutics. They also have stock in Stoke Therapeutics. Brian Werneburg, Ph.D., Fei Wang, Ph.D., and Barry Ticho, M.D., Ph.D. have received personal compensation for serving as employees of Stoke Therapeutics.

Dravet syndrome: A severe developmental and epileptic encephalopathy

The effects of Dravet syndrome **go beyond just seizures**, impacting **all aspects of life**, not only for the individual living with Dravet syndrome but also for their caregivers and families



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Voice of the patient report. Externally-Led Patient-Focused Drug Development Meeting on Dravet Syndrome. Available at: https://dravetfoundation.org/dsf-funded-research/externally-led-pfdd-meeting/. Accessed February 2026.

An urgent need for disease-modifying therapies addressing the underlying genetic cause of Dravet syndrome

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

During a 5-year period, **60% of caregivers of adults with Dravet syndrome report a decline in skills**, such as cognition, speech, motor skills, and interaction with others[3]

>90% of Dravet syndrome cases are caused by ***SCN1A* gene variants → 50% reduction in $Na_V1.1$ sodium channel expression**[4–6]

Current antiseizure medications only target seizures; **up to 57% of patients fail to achieve ≥50% reduction in seizure frequency**[7–9]

No approved treatments for non-seizure symptoms[10–12]

There is an urgent need for **disease-modifying therapies** addressing the **underlying genetic cause** of Dravet syndrome 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

ASO, antisense oligonucleotide; *SCN1A*, voltage-gated sodium channel alpha subunit 1.

1. Wu YW *et al. Pediatrics* 2015; 136 (5): e1310–e1315. 2. Symonds JD *et al. Brain* 2019; 142 (8): 2303–2318. 3. Selvarajah A *et al. Epilepsia* 2025; 66: 1975–1987. 4. Gil-Nagel A *et al. Sci Rep* 2023; 13 (1): 3355. 5. Bechi G *et al. Epilepsia* 2012; 53 (1): 87–100. 6. Gertler TS *et al. Seizure* 2020; 75: 1–6. 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. Lagae L *et al. Dev Med Child Neurol* 2018; 60 (1): 63–72. 11. Perry *et al. Epilepsia* 2024; 65 (2): 322–347. 12. Isom LL *et al. Neurotherapeutics* 2021; 18 (3): 1524–1534.

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Cognition and behavior are commonly evaluated in Dravet syndrome using the Vineland-3 assessment tool

Domains	COMMUNICATION	MOTOR SKILLS	SOCIALIZATION	DAILY LIVING SKILLS
Subdomains	**Receptive:** Responds upon hearing name called **Expressive:** Says “Dada”, “Mama”, or caregiver name **Written:** Writes alphabet letters using correct orientation	**Gross Motor:** Moves, scoots, or crawls across the floor **Fine Motor:** Picks up small objects with thumb and fingers	**Interpersonal Relationships:** Tries to interact with others **Play and Leisure:** Responds when parent or caregiver is playful **Coping Skills:** Transitions easily from one activity to another	**Personal:** Cooperates in dressing and undressing **Domestic:** Puts away books, toys, etc. when done **Community:** Talks with a familiar person using a phone

Maladaptive Behavior is an additional optional domain of the Vineland-3 depending on age and developmental requirements. Its subdomains include Externalizing, Internalizing, and Other.

Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Sparrow SS *et al*. Vineland Adaptive Behavior Scales – Third Edition. Pearson; 2016.

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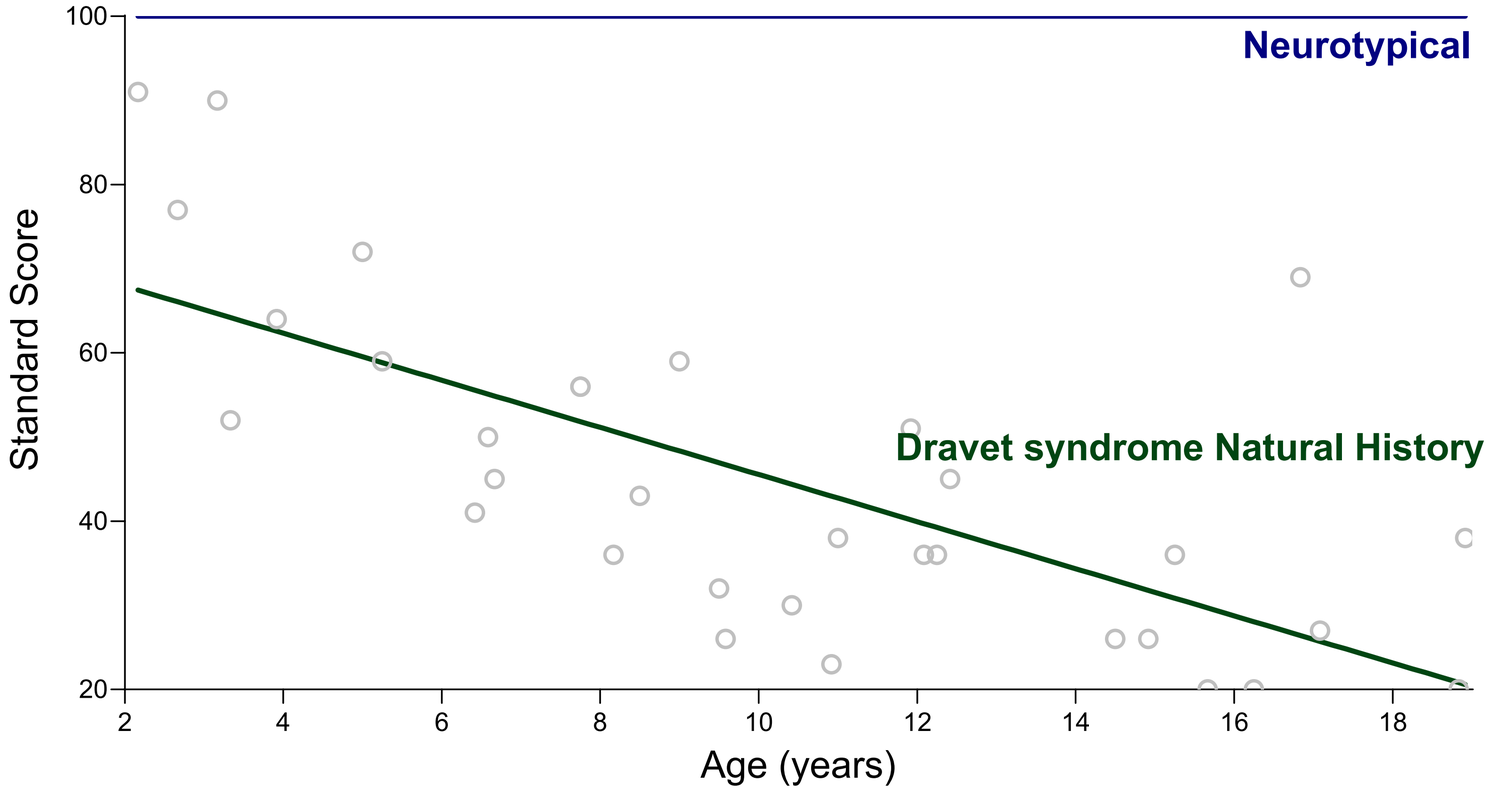
Substantial neurodevelopmental gap between patients with Dravet syndrome and neurotypical peers that widens with age

Regression analysis of adaptive behavior composite score for all Vineland-3 domains at baseline*



*Regression analysis of adaptive behavior composite score for individual patients with all Vineland-3 domains completed at baseline (n=33/36). Regression analysis statistics: F(1,31)=29.76; $P \leq 0.0001$; $r^2=0.4898$. The patients with scores of 91 and 90 were aged 2 years and 2 months, and 3 years and 2 months, respectively, at screening. The adaptive behavior composite score only included the motor component for patients aged 2 years to 9 years and 11 months. The neurotypical score is 100±15 SD.

Adapted from Sullivan J *et al. Epilepsy Behav* 2022; 137 (Pt A): 108955.

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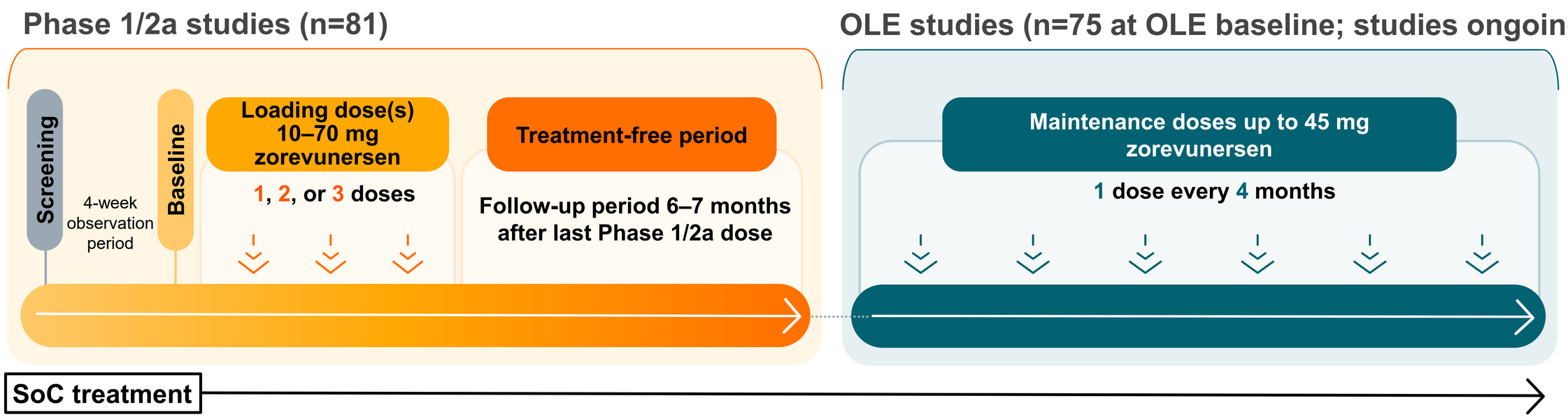
Phase 1/2a and OLE studies investigating zorevunersen safety, PK, and efficacy in children and adolescents with Dravet syndrome

PRIMARY ENDPOINTS[1]	SECONDARY ENDPOINTS[1]	EXPLORATORY ENDPOINTS[1]
• 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)



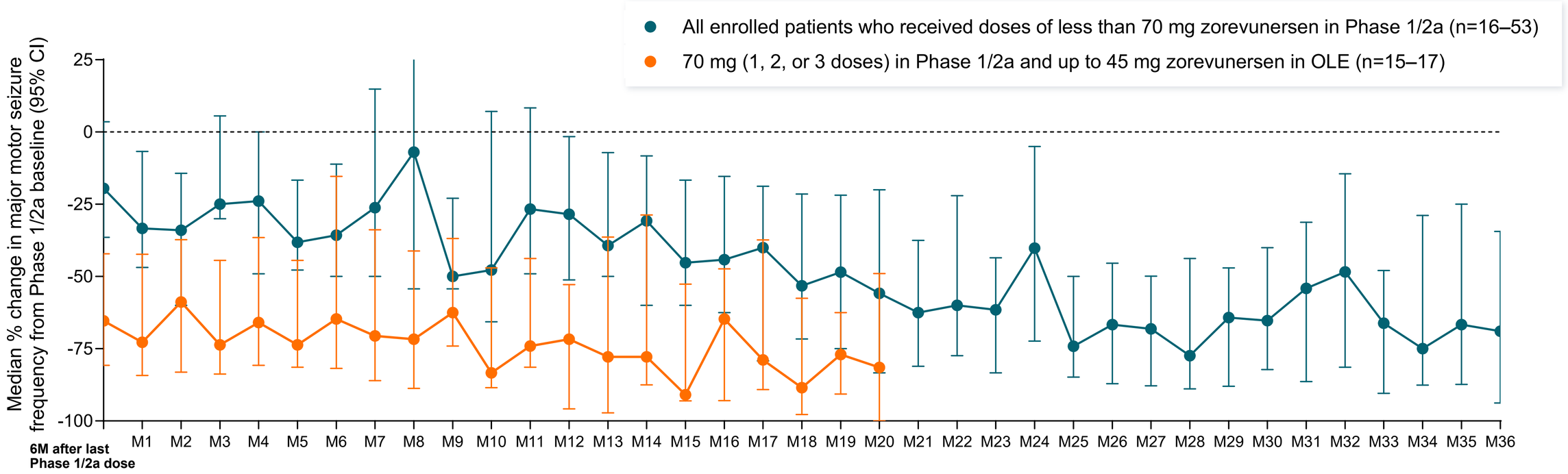
Baseline concomitant antiseizure medications (ASMs)[1]

- **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).
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.

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

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



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

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 95% CIs. One patient who received an incorrect dose of zorevunersen in Phase 1/2a, three patients who experienced less than the minimum number of convulsive seizures during Phase 1/2a baseline, and one 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 did not enter the OLE studies. No exclusions were made for antiseizure medication modification. Intervals with <50% diary data were excluded for individual patients. All enrolled patients received up to 45 mg zorevunersen in the OLE studies, and OLE study doses were administered once every 4 months.

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

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

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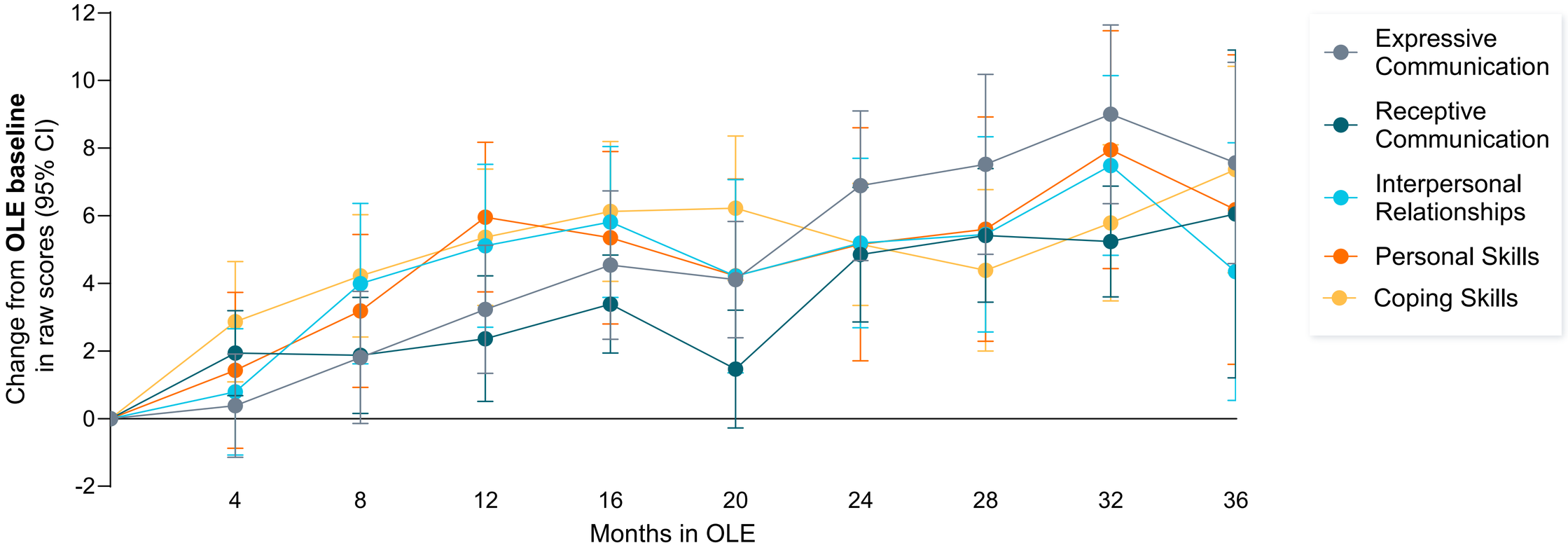
After Phase 1/ 2a, continuing improvements in cognition and behavior were observed through 3 years of treatment in the OLE studies*



*Data shown are changes from the OLE baseline, 6 months after the last Phase 1/2a dose among all patients who entered the OLE

OLE data cut: May 30, 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; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

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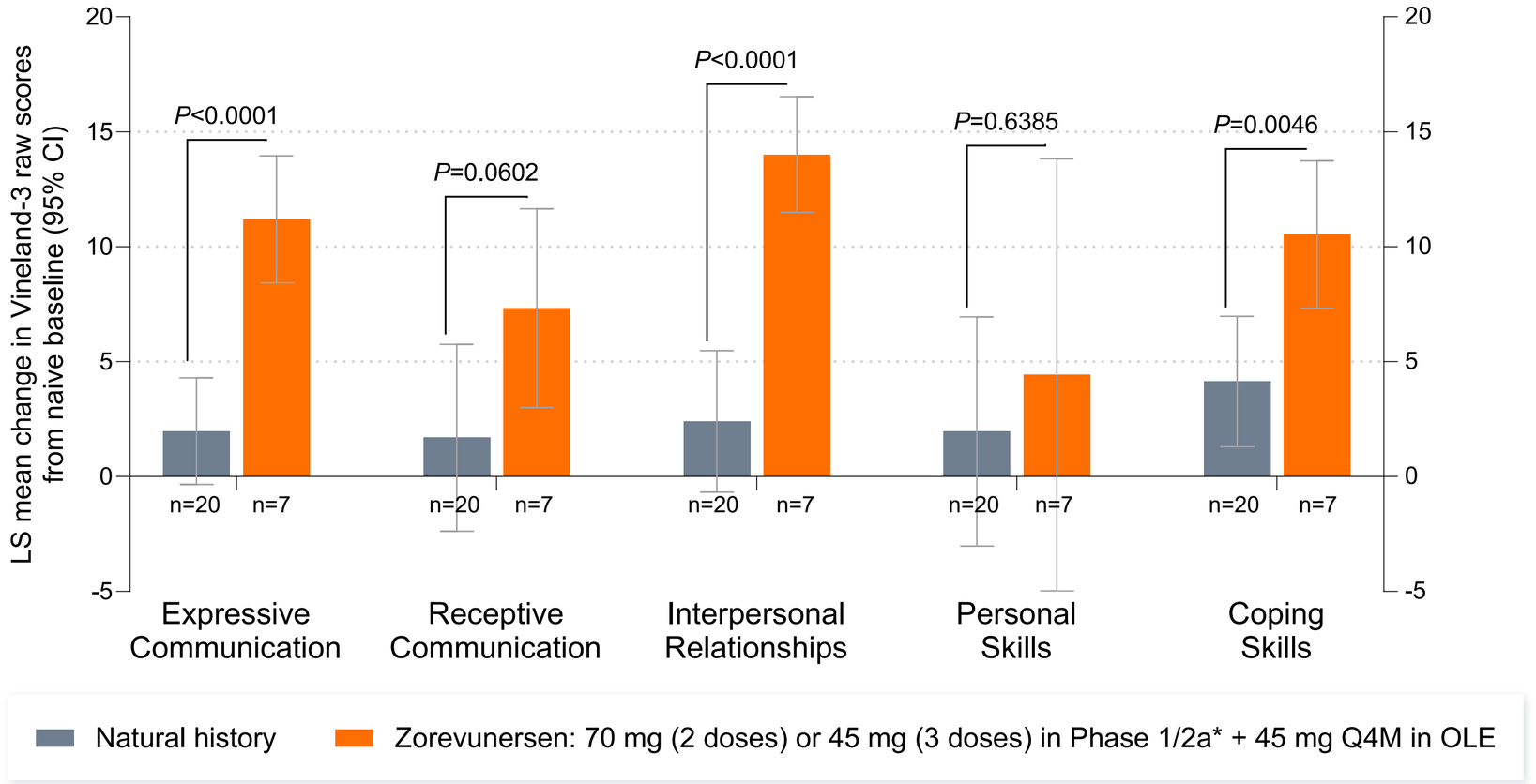
Significant and durable improvement in cognition and behavior at 24 months with zorevunersen, compared to natural history

Propensity score weight (PSW) analysis of Vineland-3 subdomains 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. PSW with weighted 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; MMRM, mixed model repeated-measures; OLE, open-label extension; PSW, propensity score weighting; Q4M, every 4 months; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

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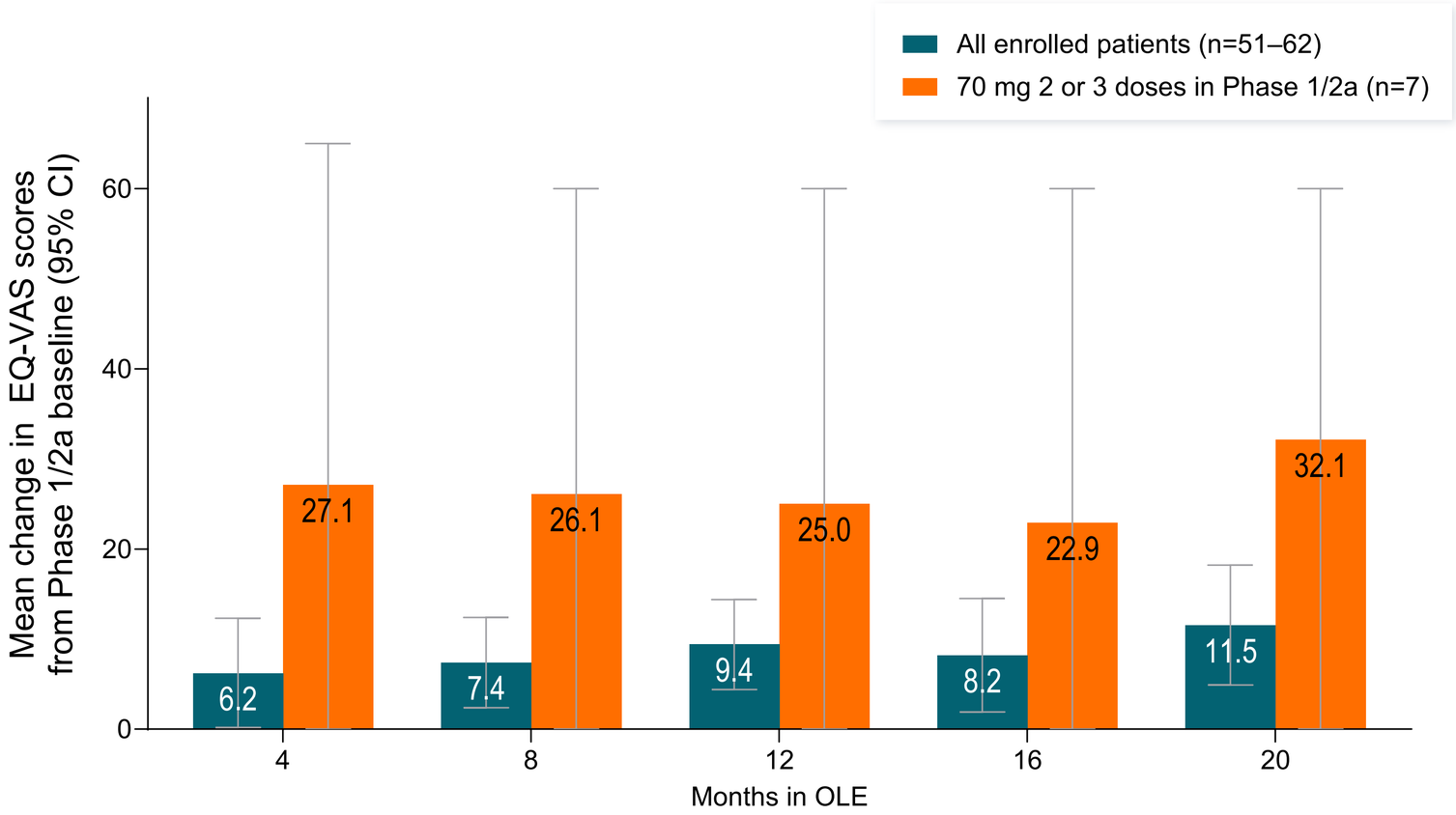
Patients who received multiple loading doses of 70 mg in Phase 1/2a showed the greatest improvements in quality of life



EQ-VAS is a validated, visual analogue scale ranging from 0 to 100 (worst to best imaginable health)

Continuing improvements in quality of life were observed through the OLE studies

OLE data cut: May 30, 2025.
CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; OLE, open-label extension.

Zorevunersen was generally well tolerated with long-term dosing

Phase 1/2a studies (n=81)[1]

- **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 because of SUDEP, **unrelated to zorevunersen**

OLE studies (n=75)[1]

- **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 because of SUDEP and 1 because of malnutrition; both deaths were **unrelated to zorevunersen**

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

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

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

There is an **urgent need for disease-modifying therapies** to address the **underlying genetic cause** of Dravet syndrome as developmental gaps widen over time despite use of current ASMs

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

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 Dravet syndrome

Acknowledgments

We thank the investigators, healthcare providers, research staff, patients, and caregivers who participated in the MONARCH/ADMIRAL and SWALLOWTAIL/LONGWING studies. These studies were funded by Stoke Therapeutics.

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025.
ASM, antiseizure medication; OLE, open-label extension; SoC, standard of care.