Zorevunersen demonstrates potential as a disease-modifying therapy in patients with Dravet syndrome through durable seizure reduction and improvements in cognition, behavior, and functioning with up to 36 months of maintenance dosing in open-label extension studies

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Speaker disclosures

- Received honoraria for presenting at educational events and advisory boards
- Consultancy work for Biocodex, GW / Jazz Pharma, Encoded Therapeutics, Servier, Stoke Therapeutics, and Zogenix/UCB

Dravet syndrome is a severe developmental and epileptic encephalopathy with a burdensome and challenging treatment paradigm[1]

About 85% of DS cases are caused by SCN1A gene variants that result in 50% NaV1.1 sodium channel expression[2–4]

1 out of 15,500–16,000 babies are born with DS[5,6]

Of those children and adolescents with DS, **up to 20% die before adulthood** due to SUDEP, seizure-related accidents, or infections[7]

Despite being on currently approved ASMs for DS, up to 57% of patients fail to achieve ≥50% reduction in seizure frequency[8–10]

Current therapies do not target non-seizure symptoms including[7,11]

Results from the BUTTERFLY 24-month natural history study demonstrated that **adaptive behavior and neurodevelopment in patients with DS plateaued with a widening developmental gap** as compared with population norms[12]

These findings support the urgent need for disease-modifying therapies that address the underlying genetic cause of DS to improve long-term outcomes

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; DS, Dravet syndrome; SCN1A, sodium channel protein type 1 alpha subunit; SUDEP, sudden unexpected death in epilepsy.

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 July 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. Wu YW et al. Pediatrics 2015; 136 (5): e1310–e1315. 6. Symonds JD et al. Brain 2019; 142 (8): 2303–2318. 7. Cooper MS et al. Epilepsy Res 2016; 128: 43–47. 8. Devinsky O et al. N Engl J Med 2017; 376 (21): 2011–2020. 9. Sullivan J et al. Epilepsia 2023; 64 (10): 2653–2666. 10. Guerrini R et al. Neurol Ther 2024; 13 (3): 869–884. 11. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72..
12. Sullivan J et al. Poster P788 presented at the15th European Epilepsy Congress (EEC); Rome, Italy 7–11 September 2024.

Safety, pharmacokinetics, and effectiveness of zorevunersen in children and adolescents were evaluated in Phase 1/2a and OLE studies

ELIGIBILITY CRITERIA

- 2–18 years of age
- Established DS diagnosis
- Documented pathogenic variant, likely pathogenic variant, or variant of uncertain significance in the *SCN1A* gene

MONARCH and ADMIRAL

Phase 1/2a studies

DOSES
Single/multiple ascending doses between 10–70 mg zorevunersen*

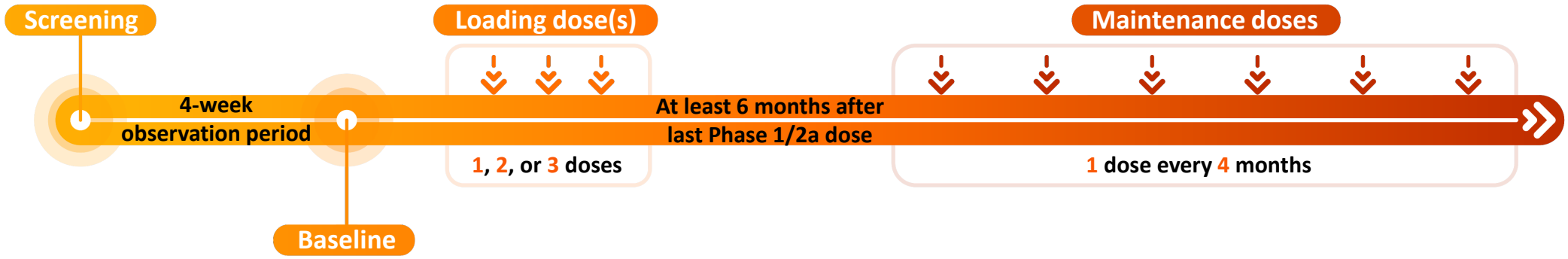
STUDY LOCATIONS
USA (MONARCH)
UK (ADMIRAL)

SWALLOWTAIL and LONGWING

OLE studies (ongoing)

DOSES
Maintenance doses of 45 mg zorevunersen every 4 months*

STUDY LOCATIONS
USA (SWALLOWTAIL)
UK (LONGWING)



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 quality of life
- PK and CSF drug exposure (OLE only)

EXPLORATORY OBJECTIVES

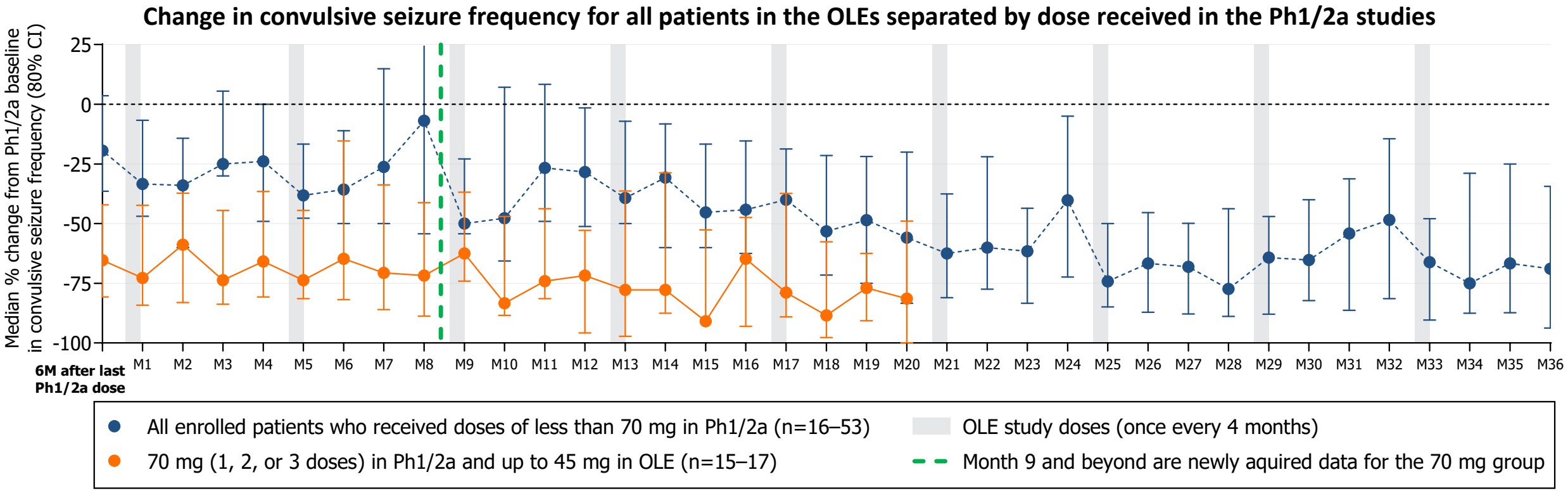
- Change in adaptive behavior (as measured by Vineland-3)†

PATIENTS AND BASELINE ASMs

- 81 patients were enrolled in Phase 1/2a and 75 patients rolled over into the OLEs
- At baseline, 81.5% patients were taking at least three ASMs and 50.6% were taking at least four
- Most commonly used ASMs were clobazam (70.4%), fenfluramine (49.4%), cannabidiol (44.4%), and valproate compounds (44.4%)

*Phase 1/2a data cut: December 12, 2023 (after End of Study). OLE data cut: June 28, 2024. Phase 1/2a studies: MONARCH (NCT04442295 [USA]) and ADMIRAL (2020-006016-24 [UK]). OLE studies: SWALLOWTAIL (NCT04740476 [USA]) and LONGWING (2021-005626-14 [UK]).*Zorevunersen is administered on top of existing antiseizure regimens; some patients initially received doses as low as 10 mg. †Adaptive behavior was assessed using the Vineland-3 in ADMIRAL and SWALLOWTAIL/LONGWING. CSF, cerebrospinal fluid; DS, Dravet syndrome; OLE, open-label extension; PK pharmacokinetics; SCN1A, voltage-gated sodium channel αsubunit 1; UK, United Kingdom; USA, United States of America; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.*

Reductions in convulsive seizure frequency were maintained through 3 years of treatment with zorevunersen on top of standard of care in the OLE studies

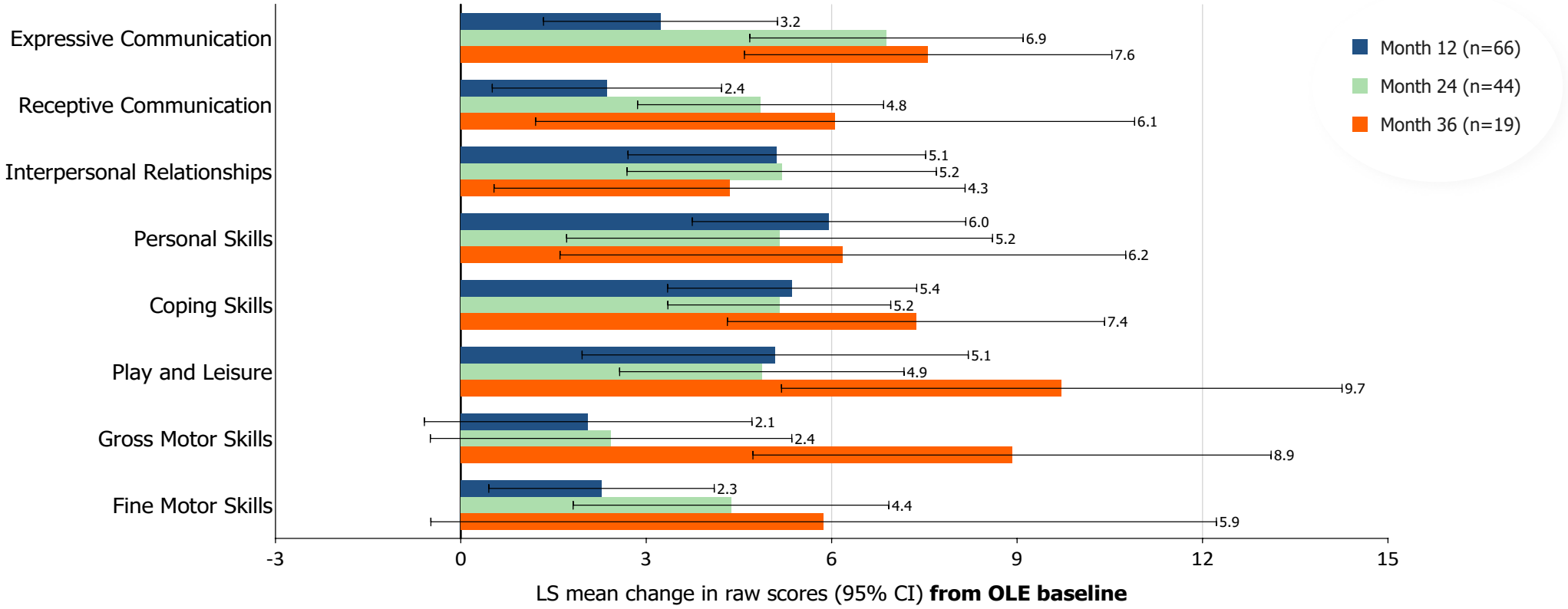


Reductions were greater in patients who received loading doses of 70 mg followed by maintenance doses of ≤45 mg

OLE (SWALLOWTAIL and LONGWING) data cut 30 May 2025. 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 Ph1/2a 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. For all enrolled patients who received doses of less than 70 mg in Ph1/2a, n = 52, 53, 53, 53, 53, 52, 52, 52, 46, 46, 47, 47, 45, 45, 45, 41, 38, 41, 41, 40, 38, 39, 39, 39, 36, 36, 36, 36, 32, 30, 30, 30, 25, 20, 19, 19, 16 for each time point. For patients who received 70 mg (1, 2, or 3 doses) in Ph1/2a and up to 45 mg in OLE, n = 16, 17, 17, 17, 17, 17, 17, 17, 17, 17, 17, 17, 16, 17, 17, 17, 15, 16, 16, 16, 16 at each time point. All enrolled patients received up to 45 mg zorevunersen in the OLEs.
ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open label extension; Ph1/2a, Phase 1/2a.

Substantial improvements in cognition and behavior continued through 3 years of treatment with zorevunersen in the OLE studies

Change in Vineland-3 subdomain raw scores at 12, 24, and 36 months compared to OLE baseline

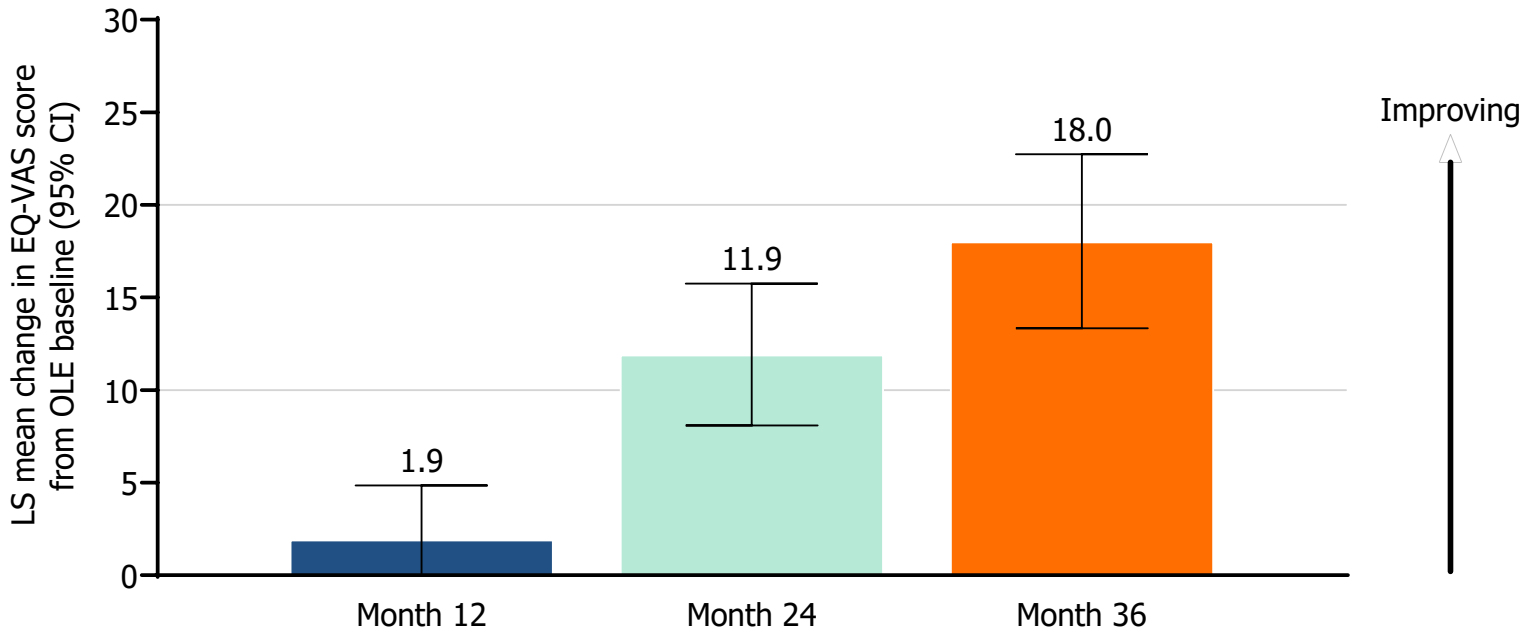


Continued improvements in Vineland-3 subdomains were observed through 36 months of the OLE studies

OLE data cut: 30 May 2025. Mixed-effects model for repeated measures constructed using available data from enrolled patients in OLE studies. One patient who received incorrect dose in Ph1/2a study 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 in the OLEs.
CI, confidence interval; OLE, open-label extension; LS, least square; Ph1/2a, Phase 1/2a; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Substantial improvements in quality of life continued through 3 years of treatment with zorevunersen in the OLE studies

Change in EQ-VAS scores at 12, 24, and 36 months compared to OLE baseline



Improvements in EQ-VAS continued through 36 months of the OLE studies

OLE data cut: May 30, 2025. EQ-VAS is a validated, easy-to-administer visual analogue scale ranging from 0 to 100 (worst to best imaginable health) commonly used across diverse populations/settings.
A mixed-effects model for repeated measures for the EQ-VAS was constructed using available data from enrolled patients in OLE studies. OLE sample sizes: n=65 at OLE baseline, n=62 at Month 12, n=41 at Month 24, and n=18 at Month 36. All enrolled patients received up to 45 mg zorevunersen in the OLEs.

CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; LS, least squares; OLE, open-label extension; QoL, quality of life.

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

OLE studies (n=75)

- No new safety concerns have emerged
- **CSF protein elevation*** occurred in **86%** of patients and was **classified as a TEAE in 45%**
  - No clinical manifestations associated with CSF protein elevation were observed
  - One patient discontinued treatment due to elevated CSF protein

>700 doses administered to date

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.*
CSF, cerebrospinal fluid; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

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

- Patients already receiving best-available ASMs **experienced substantial reductions in convulsive seizure frequency upon treatment with zorevunersen**
- Overall, **durable reductions in seizure frequency were observed throughout 36 months in the OLE studies,** with patients receiving maintenance dosing every 4 months.

- Substantial **improvements were reported in measures of cognition and behavior and in quality of life** in patients receiving zorevunersen
  - **Improvements continued to increase over time,** with patients generally showing greater improvements at Month 36 of the OLE studies than at Months 12 or 24

- Treatment with zorevunersen was generally **well tolerated**

Acknowledgements

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