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 24 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

DS 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% $Na_V1.1$ 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]

Seizures are not adequately controlled in the majority of patients with DS despite treatment[8–10]

Current therapies do not address non-seizure symptoms including[7,8]

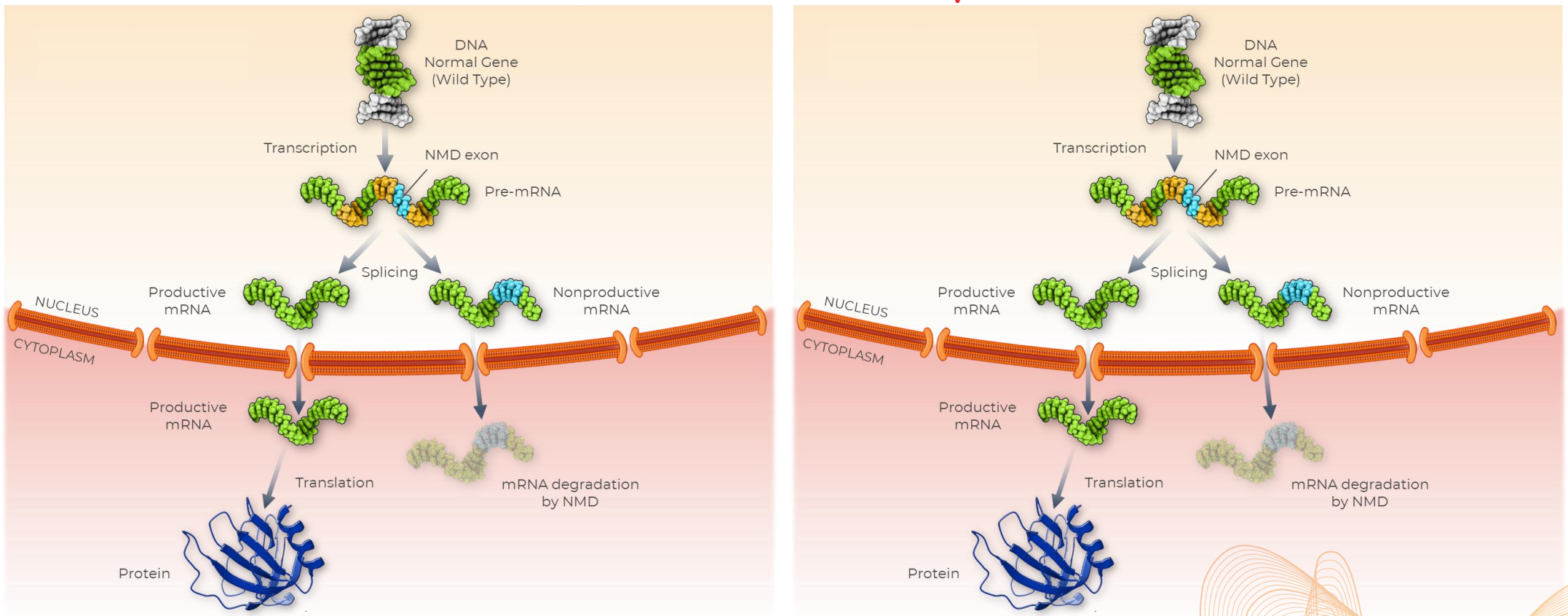
- Intellectual disability
- Language disturbances
- Behavioral difficulties
- Motor and gait issues

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. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72. 9. Gil-Nagel A et al. Sci Rep 2023; 13 (1): 3355. 10. Benitez A et al. Abstract 1.305 from AES Annual Meeting 2023; Orlando, FL, USA, 1–5 December 2023.

Zorevunersen is an investigational ASO designed to upregulate $Na_V1.1$ expression by leveraging the wild-type copy of *SCN1A*

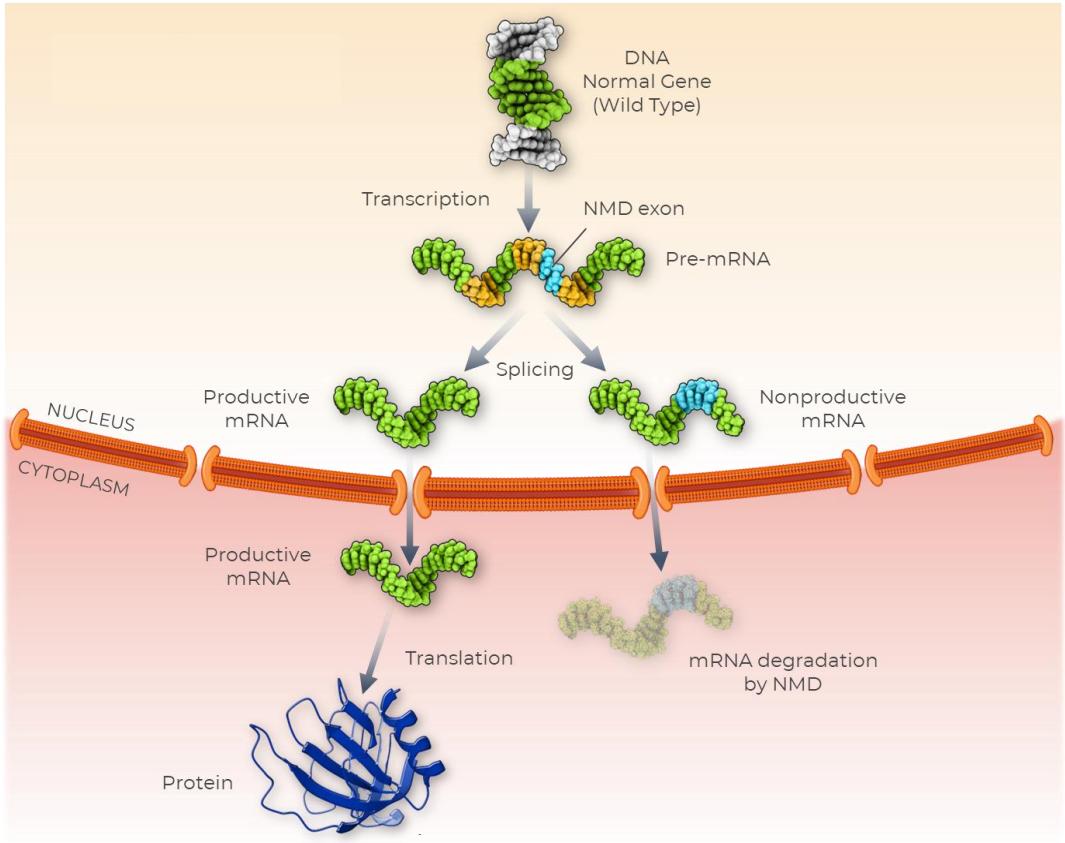
The *SCN1A* gene codes for the $Na_V1.1$ protein

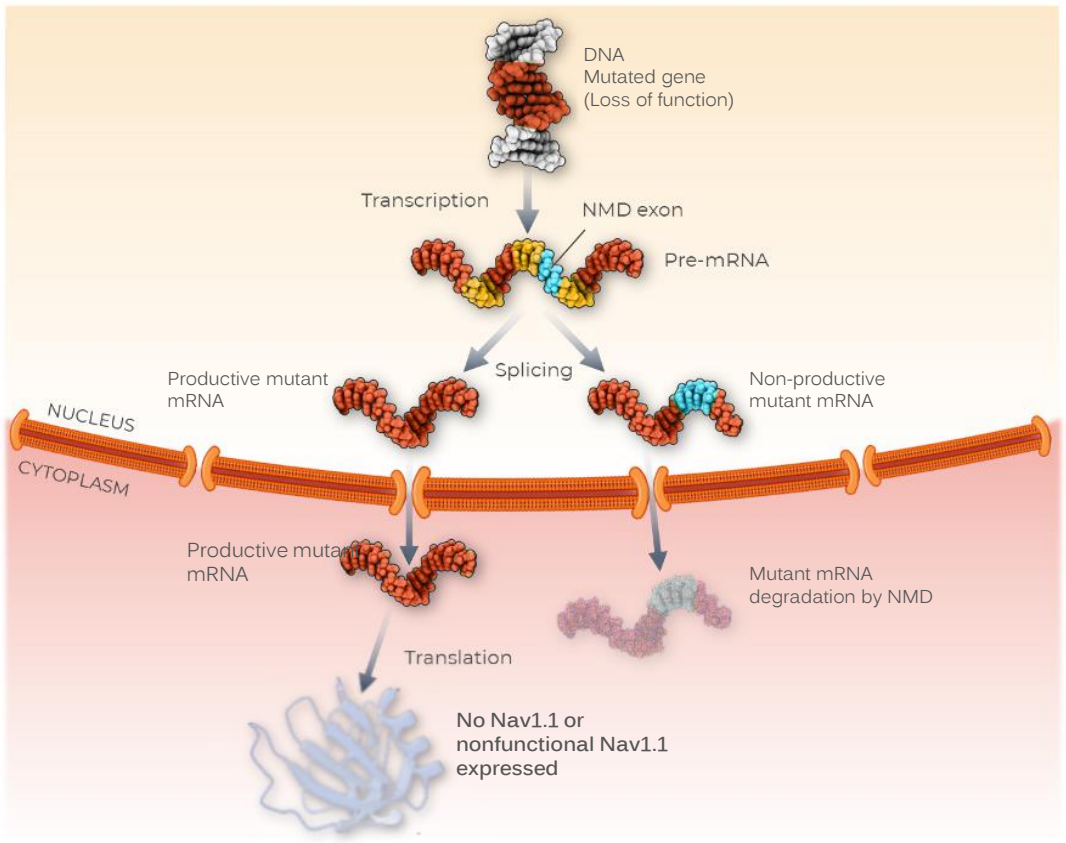


Dravet Syndrome Foundation – Voice of the Patient Report. Available at: https://dravetfoundation.org/wp-content/uploads/2022/05/Voice-of-the-Patient-report-5.31.22_compressed.pdf. Accessed April 2025. 2. Hattori J et al. Epilepsia 2008; 49 (4): 626–633. 3. Gil-Nagel A et al. Sci Rep 2023; 13 (1): 3355. 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. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72. 9 Perry MS et al. Epilepsia 2024; 65 (2): 322–337. ASO, an antisense oligonucleotide; DS, Dravet syndrome; SCN1A, sodium channel protein type 1 alpha subunit; mRNA, messenger RNA; NMD, nonsense-mediated mRNA decay; SUDEP, sudden unexpected death in epilepsy.

Zorevunersen is an investigational ASO designed to upregulate $Na_V1.1$ expression by leveraging the wild-type copy of *SCN1A*

Mechanism of haploinsufficiency

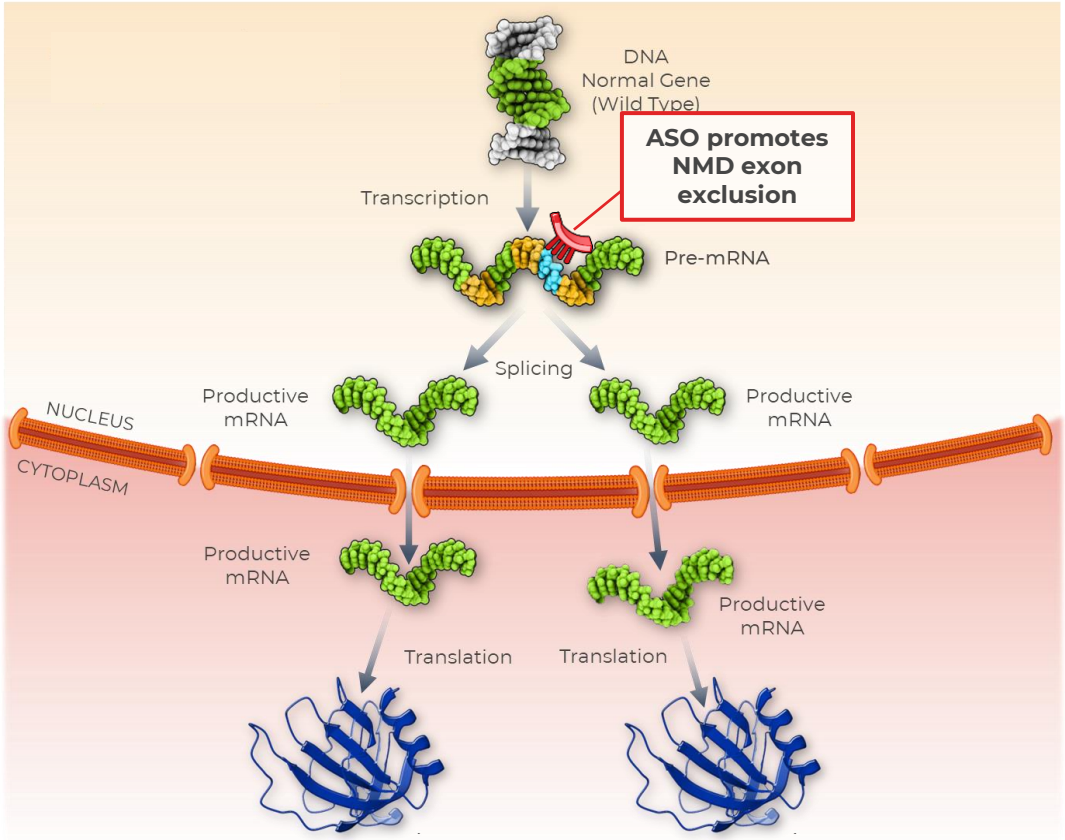


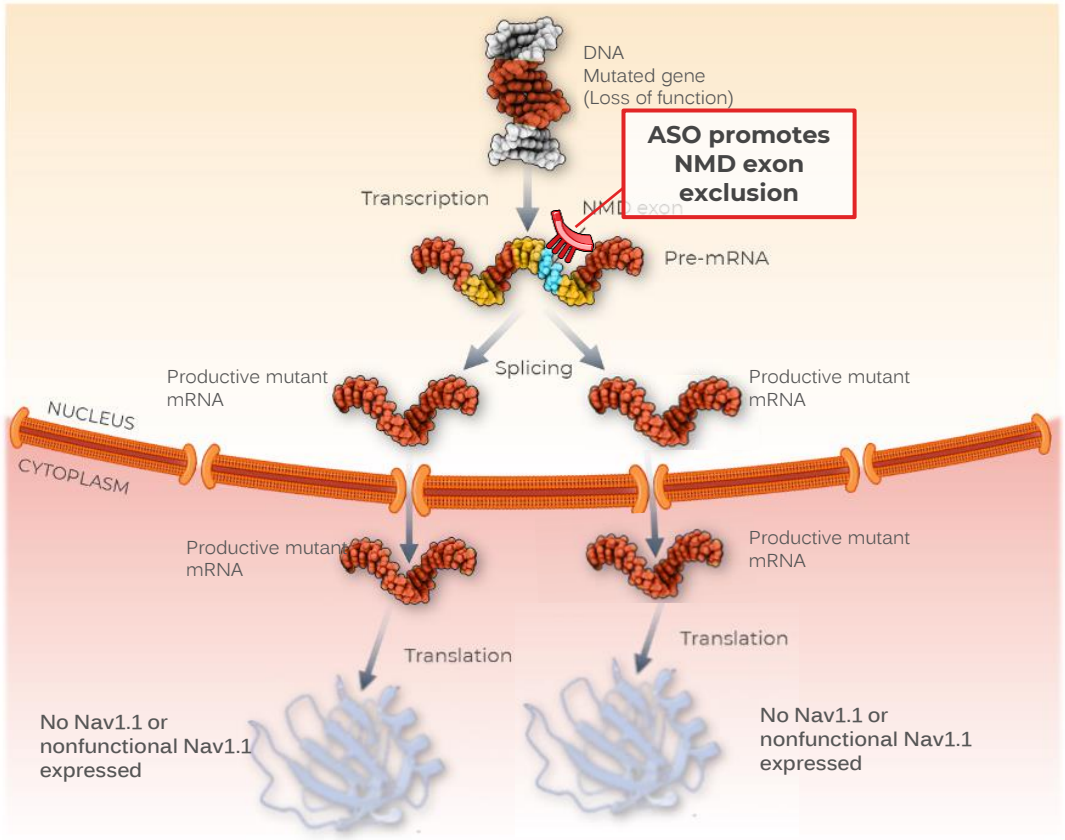


1. Dravet Syndrome Foundation – Voice of the Patient Report. Available at: https://dravetfoundation.org/wp-content/uploads/2022/05/Voice-of-the-Patient-report-5.31.22_compressed.pdf. Accessed April 2025. 2. Hattori J et al. Epilepsia 2008; 49 (4): 626–633. 3. Gil-Nagel A et al. Sci Rep 2023; 13 (1): 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. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72. 9 Perry MS et al. Epilepsia 2024; 65 (2): 322–337. ASO, an antisense oligonucleotide; DS, Dravet syndrome; SCN1A, sodium channel protein type 1 alpha subunit; mRNA, messenger RNA; NMD, nonsense-mediated mRNA decay; SUDEP, sudden unexpected death in epilepsy.

Zorevunersen is an investigational ASO designed to upregulate $Na_V1.1$ expression by leveraging the wild-type copy of *SCN1A*

ASO correction of haploinsufficiency





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 April 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. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72. 9 Perry MS et al. Epilepsia 2024; 65 (2): 322–337. ASO, an antisense oligonucleotide; DS, Dravet syndrome; SCN1A, sodium channel protein type 1 alpha subunit; mRNA, messenger RNA; NMD, nonsense-mediated mRNA decay; SUDEP, sudden unexpected death in epilepsy.

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, likely pathogenic, or variant of uncertain significance in the *SCN1A* gene

MONARCH and ADMIRAL

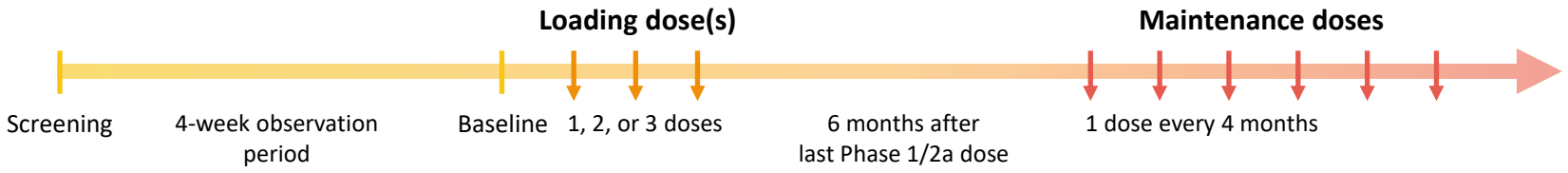
Phase 1/2a studies

- Single/multiple ascending doses between 10 to 70 mg zorevunersen*
- Study Locations: USA (MONARCH) and UK (ADMIRAL)

SWALLOWTAIL and LONGWING

OLE studies

- Ongoing: Maintenance doses of 45 mg zorevunersen every 4 months*
- Study Locations: USA (SWALLOWTAIL) and 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)

81 PATIENTS TREATED

Age at screening, years	
Median (range)	10 (2, 18)
Number of concomitant ASMs at screening, n (%)	
≥3	66 (82%)
≥4	41 (51%)
Concomitant fenfluramine at screening, n (%)	
Yes	40 (49%)
Baseline convulsive seizure frequency per 28 days (n=77†)	
Median (range)	17 (4, 2,335)

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
**Zorevunersen is administered on top of existing antiseizure regimens. †Four patients did not meet criteria for inclusion in seizure analysis.*
ASM, antiseizure medication; CSF, cerebrospinal fluid; OLE, open-label extension; PK; pharmacokinetics.

Loading doses of up to 70 mg zorevunersen followed by maintenance doses up to 45 mg were generally well tolerated

Phase 1/2a studies (n=81)

Drug-related TEAES

- **30%** of patients experienced a study drug–related TEAE
- Most common — CSF protein elevations (14%) and procedural vomiting (5%)

TESAEs

- **22%** of patients experienced a TESAE
- All were unrelated to the study drug except for one patient with SUSARs

OLE studies (n=74)

- Findings consistent with Phase 1/2a, except for higher incidence of CSF protein elevation
- **79%** of patients had CSF protein elevations*
  - No clinical manifestations were observed in these patients
  - One patient discontinued treatment due to elevated CSF protein

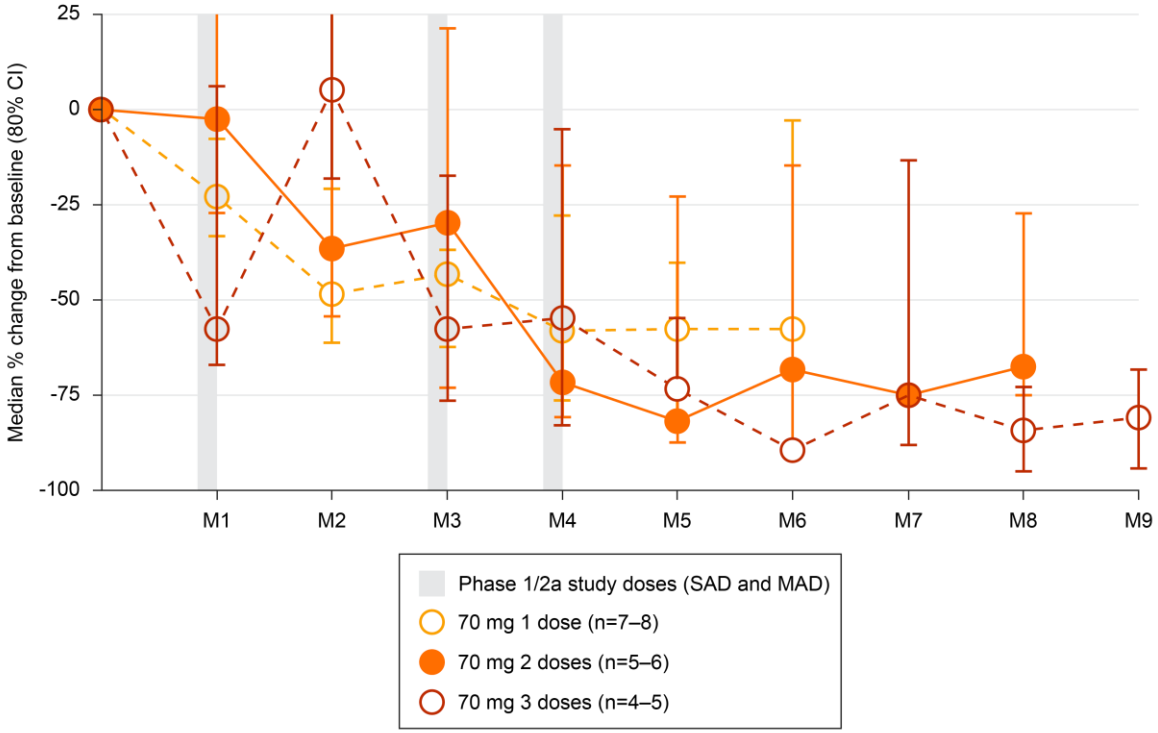
>700 doses†
administered to date

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
**≥1 CSF protein value >50 mg/dL. Percentage based on 71/74 patients who had ≥1 post-baseline CSF protein value in SWALLOWTAIL or LONGWING, of whom 56/71 (79%) had an elevation.*
†Number of doses to date includes doses administered after the June 28, 2024, OLE data cut.
CSF, cerebrospinal fluid; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

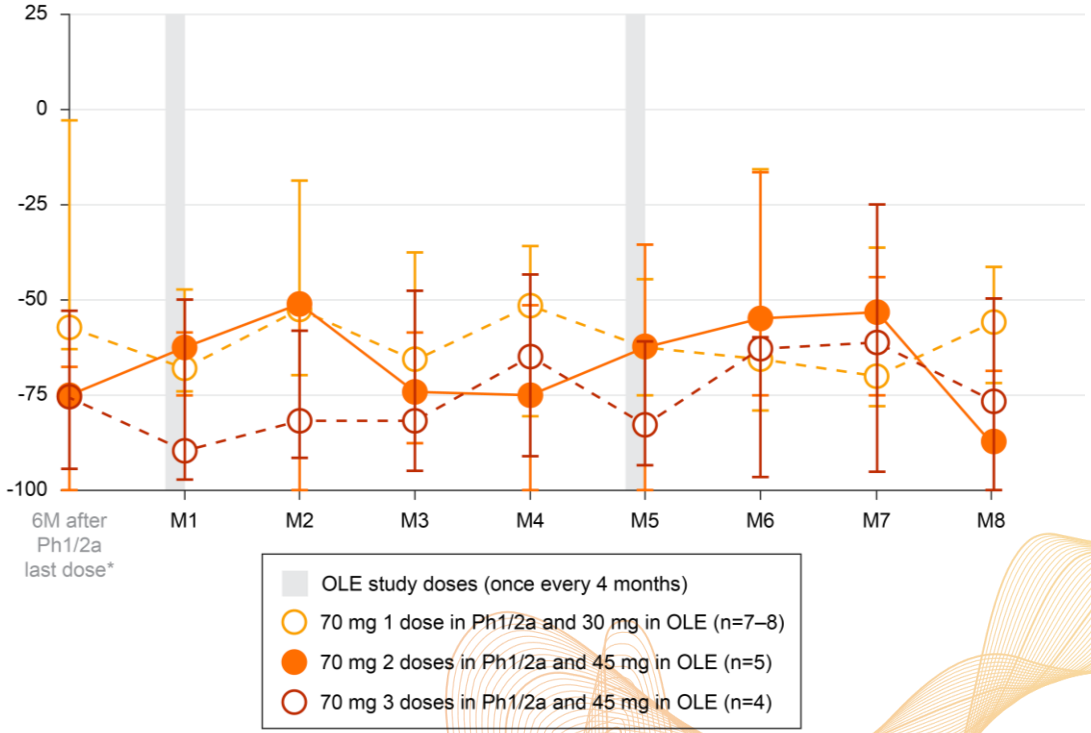
Durable reductions in convulsive seizure frequency with loading doses of 70 mg and maintenance doses of 45 mg zorevunersen

Reductions in convulsive seizure frequency from Phase 1/2a baseline through OLE studies

Phase 1/2a studies (loading doses)



OLE studies (maintenance doses)

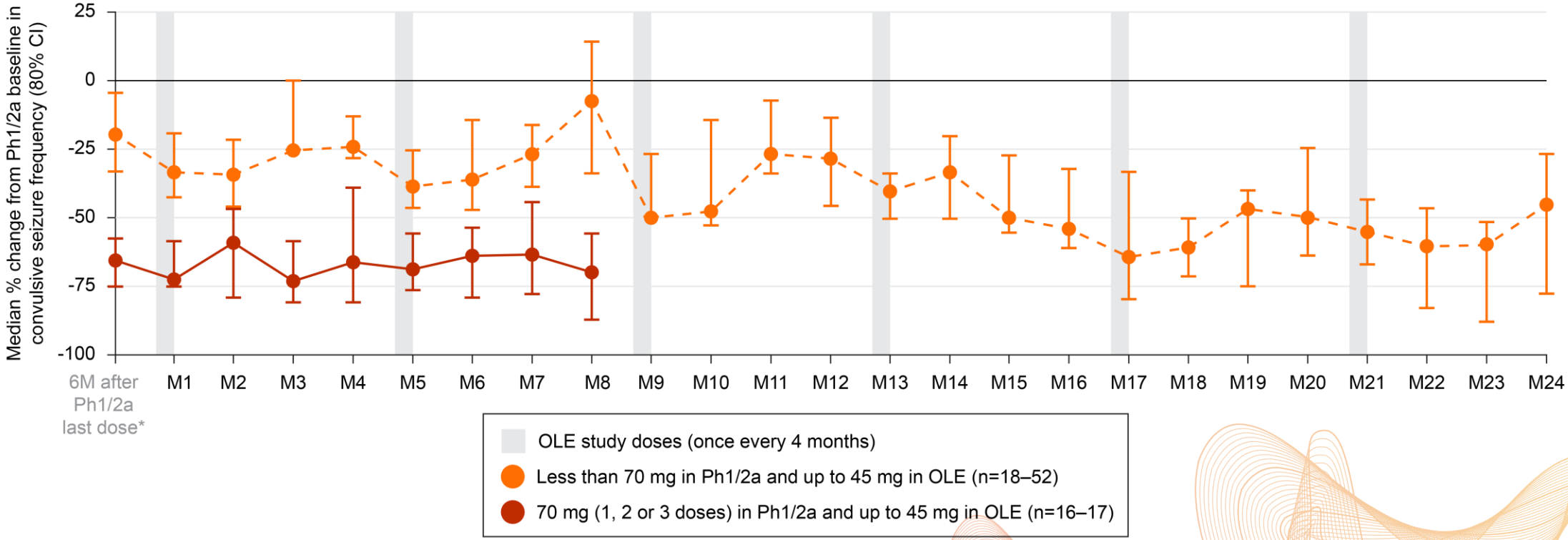


Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
The 70 mg SAD cohort from MONARCH was dosed on Day 1. The 2-dose 70 mg MAD cohort from ADMIRAL was dosed on Days 1 and 57. The 3-dose 70 mg MAD cohort from ADMIRAL was dosed on Days 1, 57, and 85. MONARCH ended at Day 169 for the SAD cohort and Day 225 for the MAD cohort. ADMIRAL ended at Day 253. Patients were followed for 6 months after last dose of study drug. One 70 mg 1-dose patient who experienced <4 seizures during the Phase 1/2 baseline period was excluded. Data were censored if <50% diary data were available for a 28-day interval (D141 to D168 for ONE patient in 70 mg 1 dose) or at time of ASM modification (one patient in 70 mg 2 dose and one patient in 70 mg 3 dose). As of the OLE data cut, SAD patients received 30 mg doses of zorevunersen at Week 1 and Week 16, while MAD patients received 45 mg doses of zorevunersen at Week 1 and Week 16. No exclusion for ASM modification in the OLE studies.
**Excludes patients who did not enter the OLE.*
ASM, antiseizure medication; CI, confidence interval; D, day; M, month; MAD, multiple ascending dose; OLE, open-label extension; Ph1/2a, Phase 1/2a; SAD, single ascending dose.

Reductions in convulsive seizure frequency were maintained through 2 years of the OLE studies

Reductions in convulsive seizure frequency from Phase 1/2a baseline

OLE studies (maintenance doses)

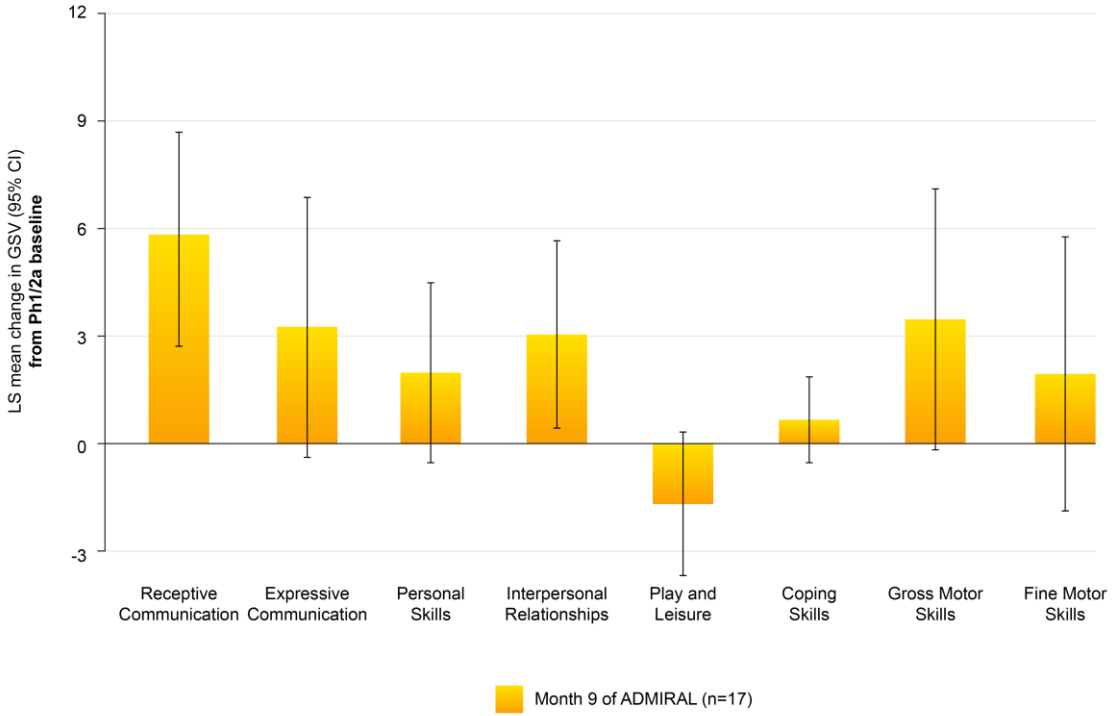


Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
One patient who received an incorrect dose in Phase 1/2a and three patients who experienced <4 seizures during Phase 1/2a baseline were excluded. Patients were not included in 6M after last Ph1/2a dose time point if they did not enter the OLE studies. No exclusions were made for ASM modification in the OLE studies.
CI, confidence interval; M, month; OLE, open-label extension; Ph1/2a, Phase 1/2a.

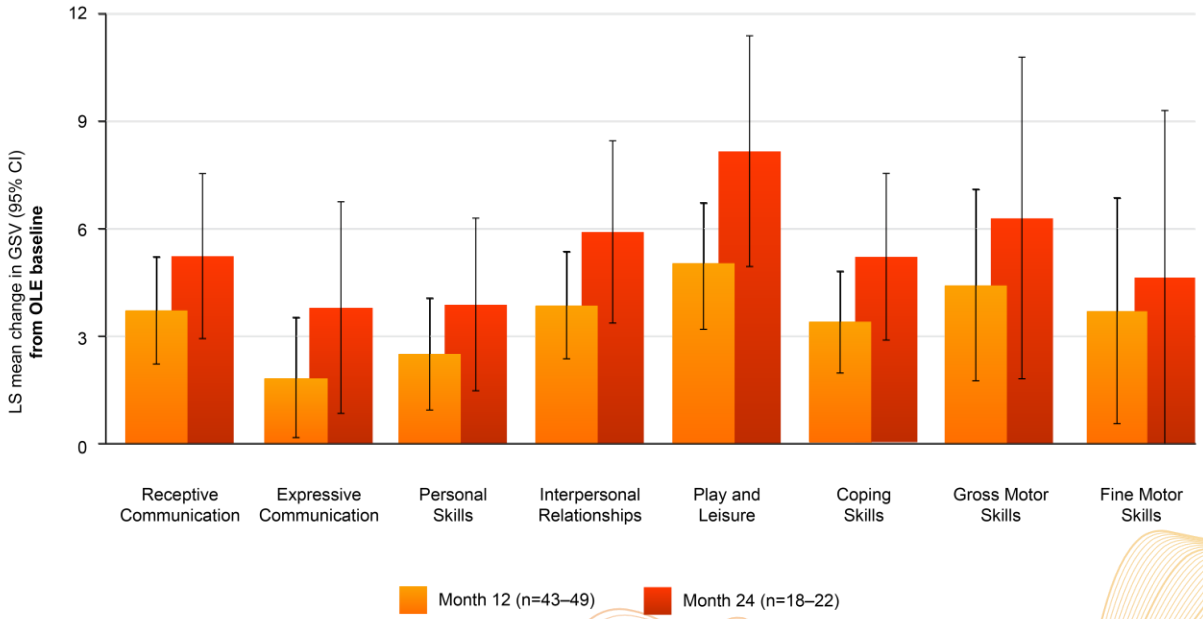
Improvements in cognition and behavior within the first year of treatment in Phase 1/2a and with ongoing treatment in the OLE studies

Vineland-3 improvements at Month 9 of the Phase 1/2a study and Months 12 and 24 of the OLEs

Phase 1/2a study (ADMIRAL) at 9 months



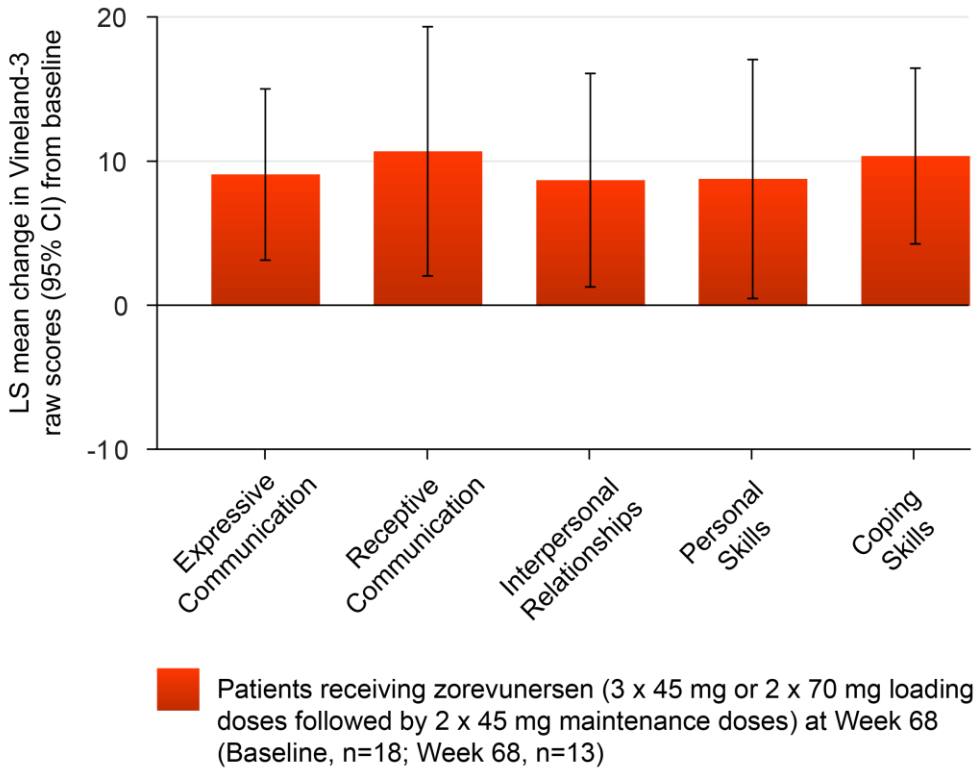
OLE studies at 12 and 24 months



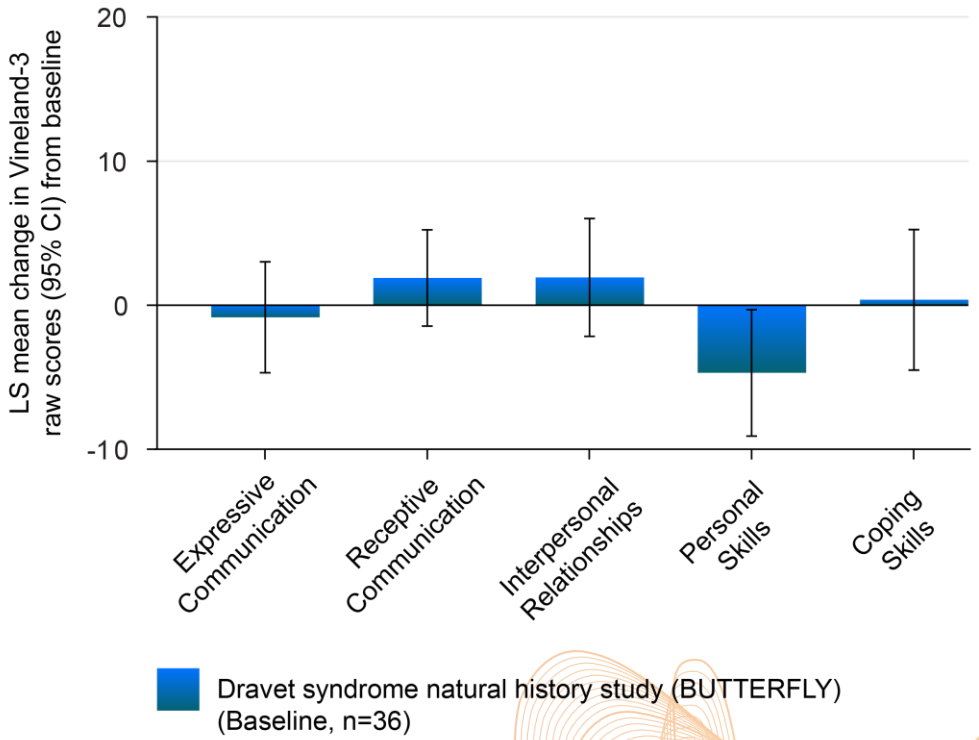
Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
Data from ADMIRAL (all dose cohorts) through Visit 3 (Month 13 from ADMIRAL baseline; data cut November 1, 2023) in LONGWING from pre-treatment/naïve baseline analyzed with machine learning. ADMIRAL sample size: n=18 at screen. Mixed-effects model for repeated measures constructed using data through Month 33 from ADMIRAL baseline of enrolled patients in OLE studies. One patient who received an incorrect dose in the Phase 1/2 study was excluded. One patient had multiple results classified as extreme outliers in the Fine Motor subdomain. SWALLOWTAIL/LONGWING sample sizes across subdomains: n=68–72 at OLE baseline.
CI, confidence interval; GSV, growth scale value; LS, least squares; OLE, open-label extension; Ph1/2a, Phase 1/2a; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Improvements in cognition and behavior in patients treated with zorevunersen contrasted with matched Dravet syndrome natural history patients

Patients treated with zorevunersen



Dravet syndrome natural history study patients

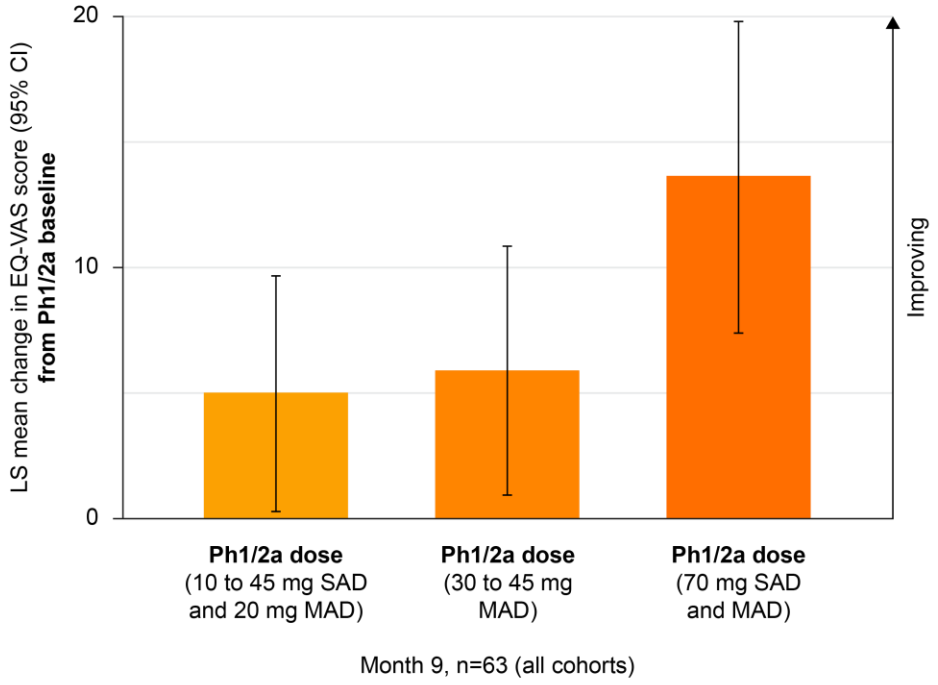


Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
A mixed-effects model for repeated measures (MMRM) analysis was used to evaluate the potential effects of the Phase 3 zorevunersen dosing regimen on patient cognition and behavior at Week 68. The model was developed using clinical data from patients in the Phase 1/2a ADMIRAL study (n=18 at baseline) and the LONGWING OLE study (n=13 at OLE Week 32). A sub-analysis of patients who received a total cumulative dose consistent with the Phase 3 EMPEROR regimen showed improvements in cognition and behavior. A total of 10 patients in the ADMIRAL study received 2 doses of 70mg (n=6) or 3 doses of 45mg (n=4). These are the patients represented in this modeled analysis. A cross-trial comparison analyzed the effects from this analysis with those observed in the BUTTERFLY natural history study through Month 24. Baseline covariates for patients followed in the BUTTERFLY natural history study were matched to the selected ADMIRAL patient population.
LS, least squares; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.
Due to differences between trials, cross-study comparisons may provide limited information on the efficacy or safety of a drug.

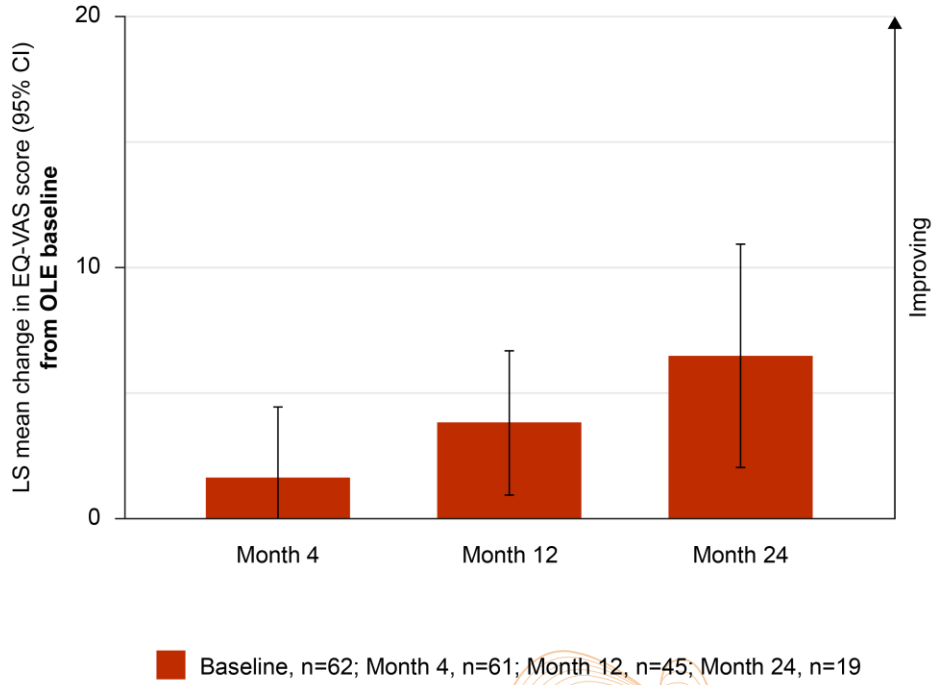
Improvements in patient QoL were observed within the first 9 months of treatment in Phase 1/2a and continued with ongoing treatment in the OLE studies

Improvements in QoL as measured with EQ-VAS

Phase 1/2a studies at approximately 9 months



OLE studies up to 24 months



Additionally, measurable improvements in **overall functioning** were observed within the first 9 months of treatment in Phase 1/2a and through an additional 24 months in the OLE studies

Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
A mixed-effects model for repeated measures for the EQ-VAS was constructed using data from MONARCH and ADMIRAL through Visit 2 (Week 16) in OLEs from pre-treatment/naïve baseline. A mixed-effects model for repeated measures for the EQ-VAS was constructed using data through Month 24 from enrolled patients in SWALLOWTAIL/LONGWING. One patient who received an incorrect dose in Phase 1/2a was excluded.
CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; LS, least squares; MAD, multiple ascending dose; OLE, open-label extension; Ph1/2a, Phase 1/2a; QoL, quality of life; SAD, single ascending dose.

Phase 1/2a and OLE study findings support the potential of zorevunersen to be a durable, disease-modifying therapy for Dravet syndrome

- Patients treated with **loading doses of 70 mg zorevunersen experienced the most substantial reductions in convulsive seizure frequency** within the first 9 months of treatment in Phase 1/2a studies, despite already receiving best-available ASMs
- Overall, reductions in seizure frequency were **sustained through the OLE studies** with ongoing maintenance dosing every 4 months

- Substantial **improvements were detected in measures of cognition and behavior and quality of life** in patients receiving zorevunersen
  - **Improvements in key measures of cognition and behavior** detected in patients receiving zorevunersen were in **contrast to the DS natural history study**

- Loading doses of 70 mg zorevunersen, followed by maintenance doses up to 45 mg, were generally **well tolerated**

Acknowledgements

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: June 28, 2024.
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