Poster #92

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

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Key Findings

1. Patients already receiving best available standard-of-care experienced substantial reductions in major motor seizure frequency upon treatment with zorevunersen. Durable reductions were observed through 36 months in the open-label extension studies with maintenance dosing every 4 months.
2. Patients receiving zorevunersen dosing similar to and consistent with the Phase 3 regimen experienced substantial and durable improvements in cognition, behavior, and functioning as measured by Vineland-3, which contrasted with DS patients receiving the best available standard-of-care over 2 years of observation in a natural history study.
3. Clinicians and caregivers reported consistent and substantial improvements in overall clinical status, cognition, behavior and functioning in zorevunersen-treated patients through 36 months in the open-label extension studies.
4. Treatment with zorevunersen was generally well tolerated across the studies.

Introduction

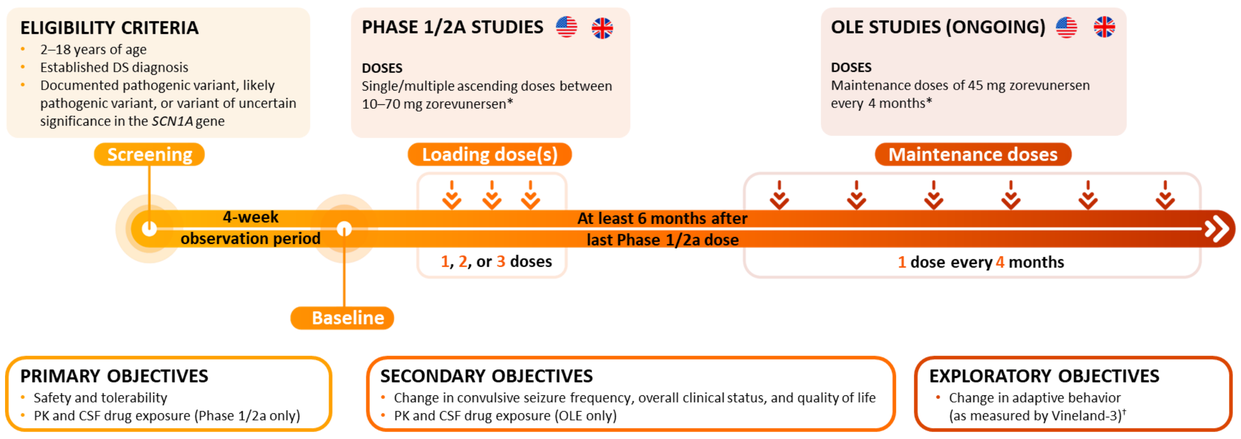
- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused primarily by voltage-gated sodium channel α subunit 1 (*SCN1A*) variants that result in 50% $Na_V1.1$ sodium channel expression.[1–3]
- Patients with DS experience prolonged, refractory seizures and significant developmental, cognitive, and behavioral impairments that impact their quality of life (QoL).[4–7]
- In the BUTTERFLY natural history study (NHS), adaptive functioning and neurodevelopment generally plateaued with a widening developmental gap over time compared with population norms, despite the use of standard-of-care antiseizure medications (ASMs).[8]
- There is an urgent need for disease-modifying therapies that address the seizure burden and improve cognition and behavior in patients with DS.[9]
- Zorevunersen is an investigational antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression by leveraging the wild-type copy of *SCN1A*.[10]
- Here, we present the effects of zorevunersen on seizure burden, cognition, behavior, and overall clinical status as well as its safety in patients with DS who were 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 patients aged 2–18 years with highly refractory DS **(Figure 1)**.

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



Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025. Phase 1/2a studies: MONARCH (NCT04442295 [US]) and ADMIRAL (2020-006016-24 [UK]. OLE studies: SWALLOWTAIL (NCT04740476 [US]) 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 Adaptive Behavior Scales, Third Edition (Vineland-3) in ADMIRAL and SWALLOWTAIL/LONGWING through four key domains: Communication (Receptive, Expressive, and Written subdomains), Daily Living Skills (Personal, Domestic, and Community subdomains), Socialization (Interpersonal Relationships, Play and Leisure, and Coping Skills subdomains), and Motor Skills (Gross Motor and Fine Motor subdomains). Vineland-3 was administered to all patients' parent/caregiver as a semi-structured interview by a trained and certified rater at the specified timepoints. CSF, cerebrospinal fluid; DS, Dravet syndrome; OLE, open-label extension; PK, pharmacokinetics; *SCN1A*, voltage-gated sodium channel α subunit 1; UK, United Kingdom; US, United States.

Results

Baseline characteristics

- 81 patients with DS received single or multiple zorevunersen doses (≤70 mg) **(Table 1)**.
  - 74 patients transitioned to the subsequent OLE studies and received zorevunersen (≤45 mg) every 4 months while continuing standard-of-care ASMs.

Table 1. Summary of baseline clinical characteristics in the Phase 1/2a studies

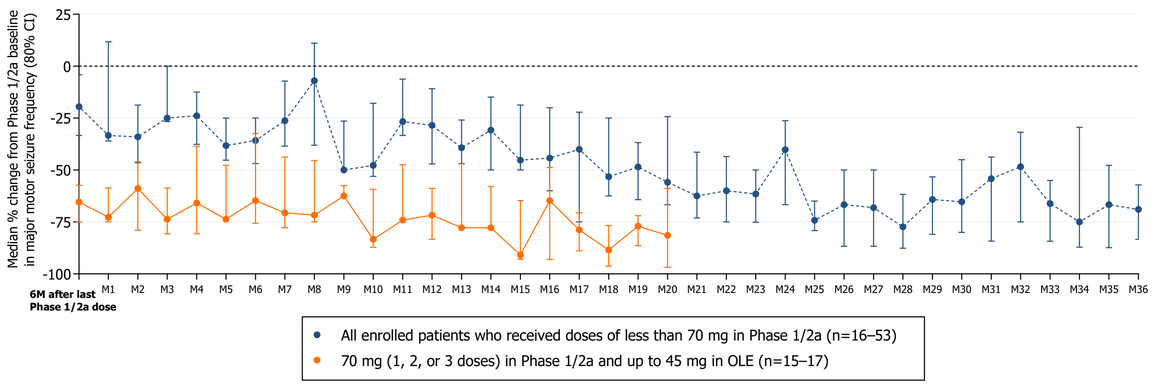
Characteristics	Value (N=81)
Age at screening (years), median (range)	10 (2–18)
Number of concomitant ASMs at screening, n (%)	
≥3	66 (82)
≥4	41 (51)
Receiving concomitant fenfluramine at screening, n (%)	40 (49)
Receiving concomitant cannabidiol at screening, n (%)	36 (44)
Baseline major motor seizure frequency per 28 days (n=77*), median (range)	17 (4–2335)

*Four patients did not meet criteria for inclusion in seizure analysis. ASM, antiseizure medication.

Major motor seizure frequency

- In the Phase 1/2a studies, the most substantial reductions in major motor seizure frequency were in patients treated with 70 mg (1, 2, or 3 doses) zorevunersen **(Figure 2)**.
- Overall, reductions in major motor frequency were maintained through 36 months of the OLE studies.

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

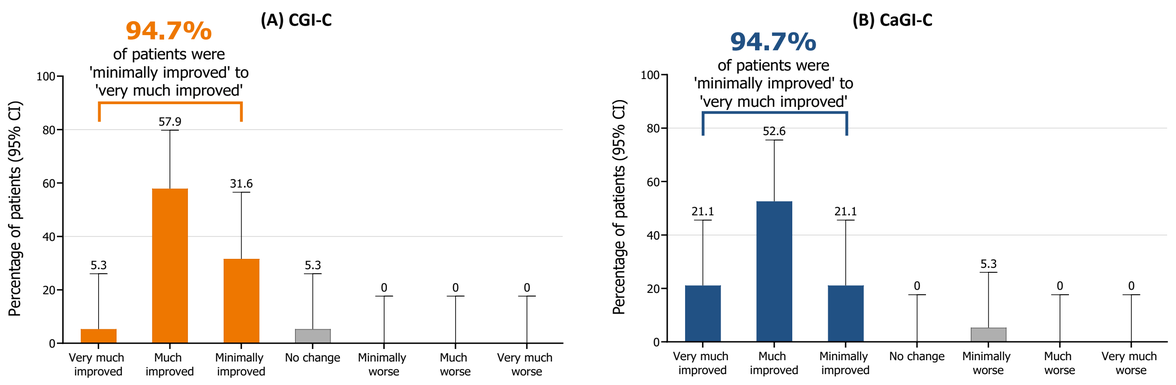


OLE (SWALLOWTAIL and LONGWING) data cut: May 30, 2025. Error bars represent 80% CIs. One patient who received an incorrect dose of zorevunersen in Phase 1/2a, 3 patients who experienced less than the minimum number of major motor seizures during Phase 1/2a baseline, and 1 patient who transferred into 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, antiseizure medication; CI, confidence interval; M, month; OLE, open label extension.

Overall clinical status

- The majority of patients showed improvements in overall clinical status at 36 months of treatment with zorevunersen in the OLE studies **(Figure 3)**.

Figure 3. Clinicians and caregivers report similar improvements in overall clinical status at 36 months as measured by (A) CGI-C and (B) CaGI-C

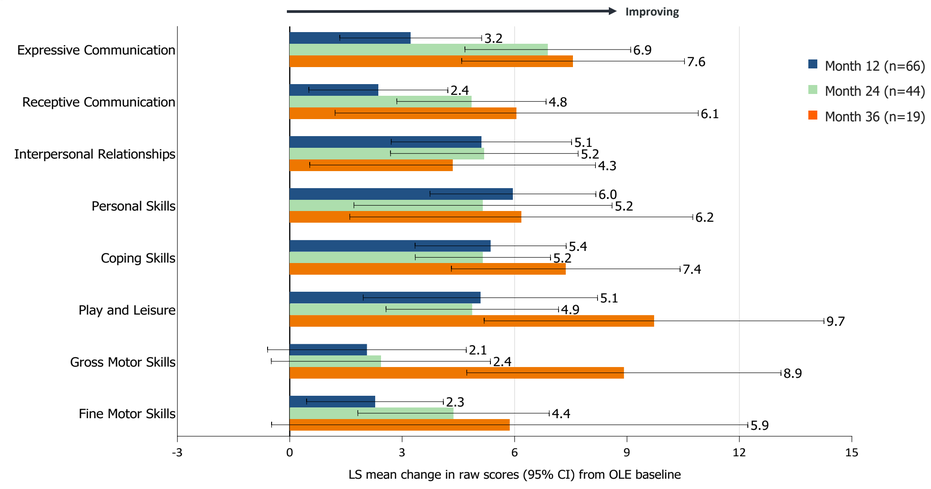


OLE data cut: May 30, 2025. CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), or 7 (Very much worse). OLE sample size: n=19 at Month 36. CaGI-C, Caregiver Global Impression of Change; CGI-C, Clinical Global Impression of Change; CI, confidence interval; OLE, open-label extension.

Cognition and behavior

- Substantial improvements in cognition and behavior were observed through 3 years of treatment with zorevunersen in the OLE studies **(Figure 4)**.

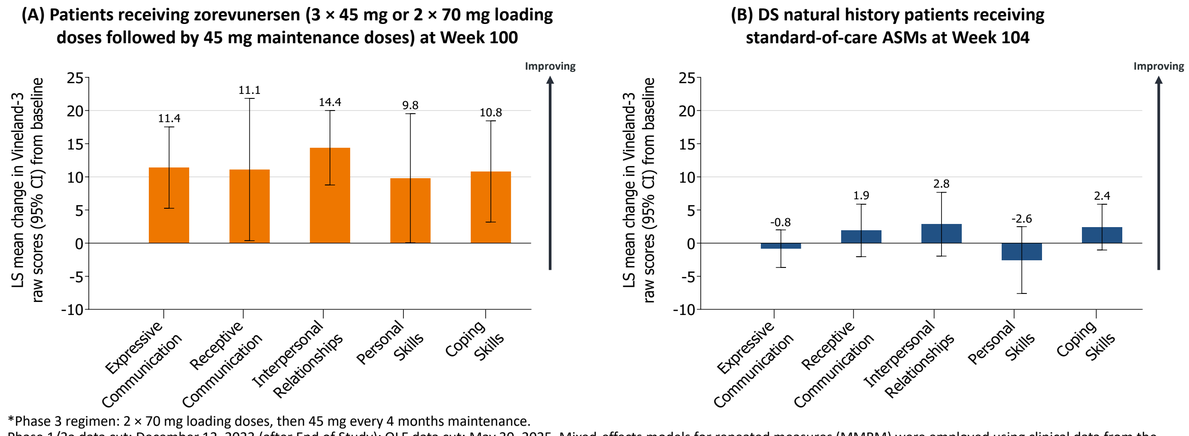
Figure 4. Improvements in Vineland-3 subdomain raw scores from OLE baseline



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. Sample sizes at OLE baseline: n=74. 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.

- A matched-adjusted indirect comparison of DS patients from the BUTTERFLY NHS and zorevunersen-treated patients demonstrates that while natural history patients only experience minimal changes in cognition and behavior, patients treated with zorevunersen experience substantial and durable improvements **(Figure 5).**

Figure 5. Continuing improvements in Vineland-3 subdomains with zorevunersen dosing similar to and consistent with the Phase 3 regimen* contrasted with DS natural history patients at ~2 years



*Phase 3 regimen: 2 × 70 mg loading doses, then 45 mg every 4 months maintenance.
Phase 1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: May 30, 2025. Mixed-effects models for repeated measures (MMRM) were employed using clinical data from the Phase 1/2a ADMIRAL study (n=18 at baseline) and LONGWING OLE study (n=13 at OLE Week 100). Ten patients in ADMIRAL who received 2 doses of 70 mg (n=6) or 3 doses of 45 mg (n=4) are represented on the left. Matching of baseline characteristics was performed using population-adjusted least squares means (LS means) to allow for cross-trial comparison with the BUTTERFLY natural history study (n=36 at baseline; n=25 at Week 104)(right graph). A matched-adjusted indirect comparison (MAIC) was used to compare BUTTERFLY patients with those treated with zorevunersen in ADMIRAL and LONGWING studies. CI, confidence interval; LS, least squares; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Safety and tolerability

- More than 700 doses of zorevunersen have been administered over a maximum of 4.5 years (as of May 2025).
- Study drug–related treatment-emergent adverse events were reported in 30% of patients (24/81) in the Phase 1/2a studies (most common: CSF protein elevations [14%, n=11] and procedural vomiting [5%, n=4]).
- 22% 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 a suspected unexpected serious adverse reactions.
- No new safety concerns have emerged in the OLE studies; results were consistent with those of the Phase 1/2a studies, except for a higher incidence of CSF protein elevation (Phase 1/2a: 42%, n=34/81; OLE: 86%, n=62/72).
  - One patient discontinued treatment due to CSF protein elevation.
  - No clinical manifestations associated with CSF protein elevation were reported.

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