P0803

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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KEY TAKEAWAYS:

1. Adaptive functioning and behaviour were significantly improved from the OLE baseline in patients receiving zorevunersen through 4 years of treatment
2. Patients receiving zorevunersen with a Phase 3-like regimen experienced substantial and durable improvements in adaptive functioning and behaviour, contrasted with the natural history of patients with Dravet syndrome
3. Treatment with zorevunersen has been generally well tolerated over more than 260 total patient-years of exposure and some patients have been treated for more than 5 years
4. Zorevunersen is being investigated in a global, Phase 3, double-blind, randomised, sham-controlled study to assess the efficacy, safety profile, and tolerability among children and adolescents with Dravet syndrome

INTRODUCTION

- Dravet syndrome (DS) is a severe, genetic developmental and epileptic encephalopathy characterised by frequent seizures and substantial cognitive, behavioural, and motor impairments, which lead to poor quality of life (QoL).[1–5]
- More than 90% of DS cases are caused by voltage-gated sodium channel alpha subunit 1 (*SCN1A*) gene variants that result in reduced functional $Na_V1.1$ expression.[2,4–8]
- Despite treatment with standard of care (SoC) antiseizure medications (ASMs; mean of 3.7 ASMs, 44% of patients on fenfluramine), patients with DS in the 2-year BUTTERFLY natural history (NH) study experienced frequent seizures and widening gaps in adaptive functioning and behaviour relative to population norms.[9]
- There is an urgent need for therapies that target the underlying genetic cause and improve all aspects of DS beyond seizure management, including adaptive functioning, behaviour, and QoL.[10,11]
- Zorevunersen is an investigational antisense oligonucleotide that upregulates $Na_V1.1$ protein expression via the wild-type copy of the *SCN1A* gene.[12,13]
- Phase 1/2a and OLE studies of zorevunersen administered on top of SoC have demonstrated reductions in seizure frequency and improvements in adaptive functioning, behaviour, and QoL.[14]
  - Patients with DS receiving zorevunersen experienced substantial and durable reductions in seizure frequency through 4 years of treatment in the OLE studies (**Poster #0797**).[15]
- The results presented here build upon the published zorevunersen clinical data and provide context of adaptive functioning and behaviour improvements relative to NH with SoC treatment.

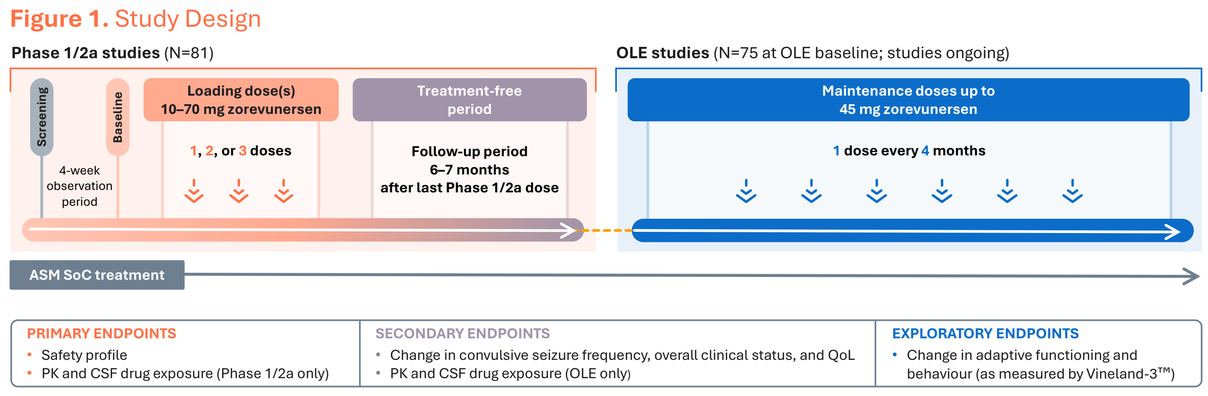
Scan the QR code to view videos of a patient performing activities of daily living before and after treatment with zorevunersen

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

METHODS

- The Phase 1/2a open-label, multicentre studies and their corresponding ongoing OLEs aim to evaluate the effects of zorevunersen in children and adolescents with refractory DS (**Figure 1**).[14]
  - Eligible patients were aged 2–18 years old with an established DS diagnosis and documented *SCN1A* gene variant.

Figure 1. Study Design



Phase 1/2a studies: NCT04442295 (USA) and 2020-006016-24 (UK). OLE studies: NCT04740476 (USA) and 2021-005626-14 (UK). 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.

RESULTS

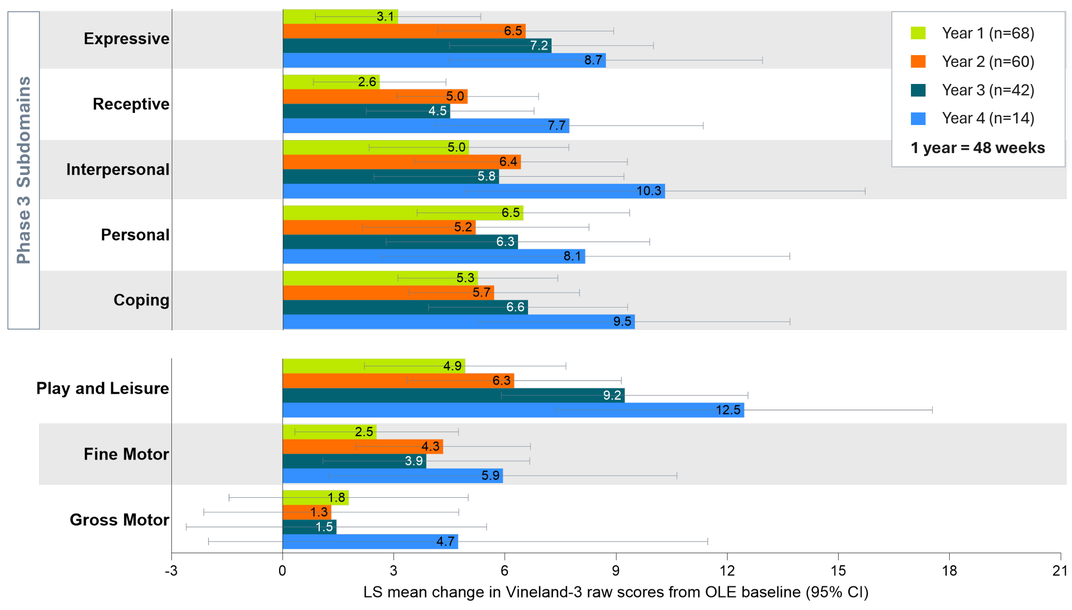
Baseline Characteristics

- In the Phase 1/2a studies, 81 patients with DS (median [range] age: 10 [2–18] years) received at least one dose of zorevunersen; 75 patients (median [range] age: 11 [2–19] years) continued treatment every 4 months in the OLE studies.[14]
- At baseline, 81% of patients were on ≥3 ASMs; 51% were on ≥4 ASMs.[14]
  - Most common ASMs: clobazam (70%), fenfluramine (49%), cannabidiol (44%), and valproate compounds (44%).

Adaptive Functioning and Behaviour

- Clinically meaningful improvements[16] in adaptive functioning and behaviour continued through 4 years of treatment with zorevunersen in the OLE studies (**Figure 2**).
  - $P<0.01$ statistical significance was achieved in the 5 key Phase 3 subdomains for each year compared with OLE baseline.
  - $P<0.01$ and $P<0.03$ were achieved in Play and Leisure and Fine Motor, respectively, for each year compared with OLE baseline.

Figure 2. Improvements in Vineland-3 subdomain raw scores from OLE baseline

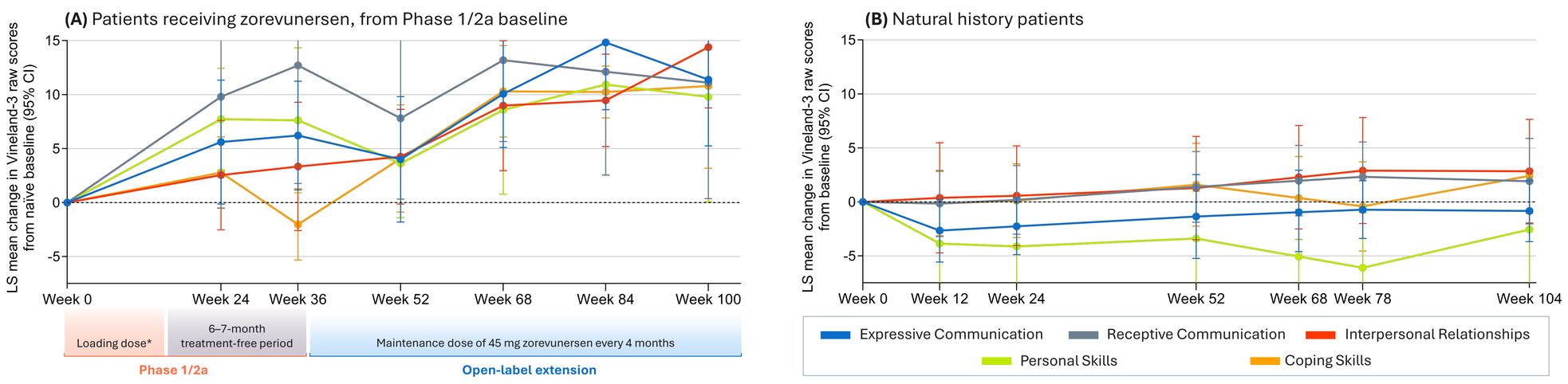


Data cut date: 19 February 2026. Mixed-effects models for repeated measures (MMRMs) for each subdomain were fit using available data from patients with baseline and at least one post-baseline assessment in the SWALLOWTAIL and LONGWING OLE studies, with n representing the number of completed patient visits at each timepoint shown. Statistical analyses are post-hoc and exploratory. 1 year = 48 weeks.

Zorevunersen-Treated Patients Versus Natural History

- A matching-adjusted indirect comparison of zorevunersen-treated patients (**Figure 3A**) and patients with DS from the BUTTERFLY NH study (**Figure 3B**) demonstrated that while NH patients experience minimal changes in adaptive functioning and behaviour, patients receiving zorevunersen experience substantial and durable improvements.

Figure 3. Improvements in Vineland-3 subdomains raw scores in patients receiving zorevunersen (Phase 3-like dosing regimen*) contrasted with DS natural history patients over ~2 years



A matching-adjusted indirect comparison (MAIC) was conducted to compare BUTTERFLY natural history patients with zorevunersen-treated patients from the UK Phase 1/2a and OLE studies (ADMIRAL and LONGWING, respectively). Baseline characteristics were balanced using MAIC weighting to improve comparability between studies. Longitudinal efficacy was evaluated using mixed-effects models for repeated measures (MMRMs) with an unstructured covariance matrix. **(A)** MMRMs for each subdomain were fit using available data from patients with baseline and at least one post-baseline assessment in the ADMIRAL and LONGWING studies (N=17). The figure displays the 2 × 70 mg and 3 × 45 mg dose cohorts, with n=7–10 patients having evaluable change-from-baseline data across visits. **(B)** MMRMs for each subdomain were fit using available data from patients with baseline and at least one post-baseline assessment in the BUTTERFLY study (N=34), with n=20–34 patients having evaluable change-from-baseline data across visits.
OLE data cut: 30 May 2025.
*Phase 3-like regimen: 2 × 70 mg or 3 × 45 mg loading doses, followed by 45 mg maintenance every 4 months.

Safety Profile of Zorevunersen with Long-Term Dosing Over 5 Years (Table 1)

Phase 1/2a studies[14]

- 30% (24/81) of patients experienced a study drug–related TEAE (most common: cerebrospinal fluid [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 suspected unexpected serious adverse reactions.
- 1 patient died because of sudden unexpected death in epilepsy (SUDEP), unrelated to study drug.

OLE studies*

- 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.

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

*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.

Table 1. Long-term exposure to zorevunersen in the 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

OLE data cut: 19 February 2026. *As of the 19 February 2026 data cut, 58/75 (77%) of patients remained in the OLEs. Most discontinuations were in the lower dose groups.

Data have been updated since abstract acceptance. Phase 1/2a data cut: 12 December 2023 (after End of Study). Phase 3 Study EU CT: 2024-519555-28-00; NCT06872125. CI, confidence interval; LS, least squares; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

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