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Zorevunersen demonstrates potential as a disease-modifying therapy in patients with Dravet syndrome through durable seizure reduction and improvements in cognition, behaviour, and quality of life through 48 months of treatment in open-label extension studies

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KEY TAKEAWAYS:

1. Patients receiving zorevunersen on top of standard of care (SoC) experienced substantial reductions in major motor seizure frequency through 4 years of treatment in the open-label extension (OLE) studies
2. Patients receiving zorevunersen in the OLEs experienced substantial reductions in the frequency of the most severe seizure types, the leading risk factor for sudden unexpected death in epilepsy (SUDEP)
3. Adaptive functioning and behaviour were significantly improved from the OLE baseline in patients receiving zorevunersen through 4 years of treatment
4. Substantial increases in quality of life were observed in addition to the improvements in seizure frequency, adaptive functioning, and behaviour, highlighting the disease-modifying potential of zorevunersen in Dravet syndrome
5. 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
6. 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 SoC antiseizure medications (ASMs) (mean of 3.7 ASMs, 44% of patients on fenfluramine), patients with DS in the 2-year BUTTERFLY natural history 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]
- The results presented here build upon the published zorevunersen clinical data.[14]

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

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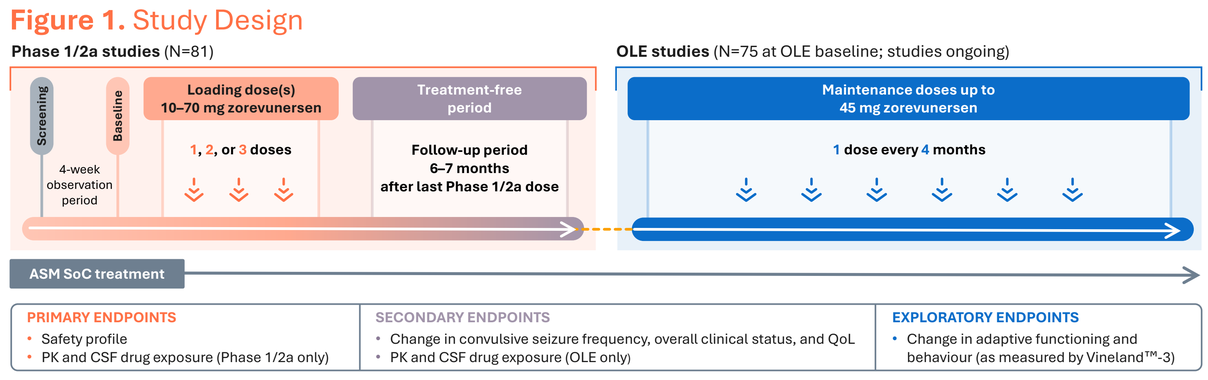
METHODS

- The Phase 1/2a open-label, multicentre studies and their corresponding ongoing OLE studies 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

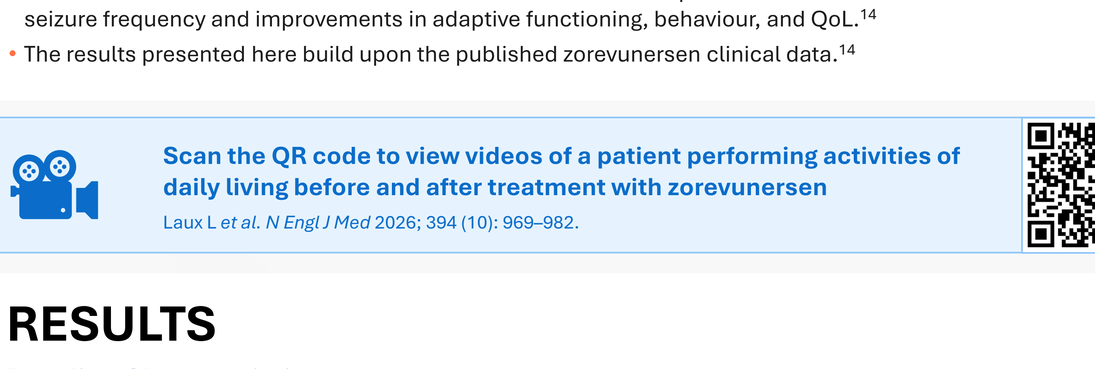
Baseline Characteristics

- 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%).

Major Motor Seizure Frequency

- Reductions in major motor seizure frequency were maintained through 4 years of treatment with zorevunersen on top of SoC in the OLE studies (**Figure 2**).
- Patients who received doses of 70 mg in the Phase 1/2a studies experienced 66% to 84% median reduction in major motor seizures during the first 28 months of the OLE studies.

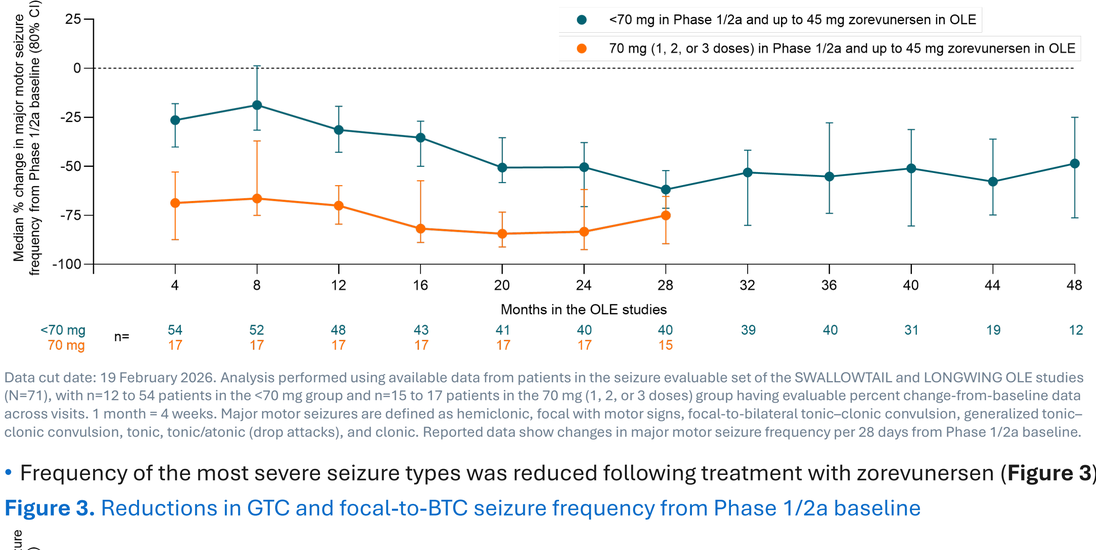
Figure 2. Reductions in major motor seizure frequency from Phase 1/2a baseline



Data cut date: 19 February 2026. Analysis performed using available data from patients in the seizure evaluable set of the SWALLOWTAIL and LONGWING OLE studies (N=71), with n=12 to 54 patients in the <70 mg group and n=15 to 17 patients in the 70 mg (1, 2, or 3 doses) group having evaluable percent change-from-baseline data across visits. 1 month = 4 weeks. Major motor seizures are defined as hemiclonic, focal with motor signs, focal-to-bilateral tonic–clonic convulsion, generalized tonic–clonic convulsion, tonic, tonic/atonic (drop attacks), and clonic. Reported data show changes in major motor seizure frequency per 28 days from Phase 1/2a baseline.

- Frequency of the most severe seizure types was reduced following treatment with zorevunersen (**Figure 3**).

Figure 3. Reductions in GTC and focal-to-BTC seizure frequency from Phase 1/2a baseline

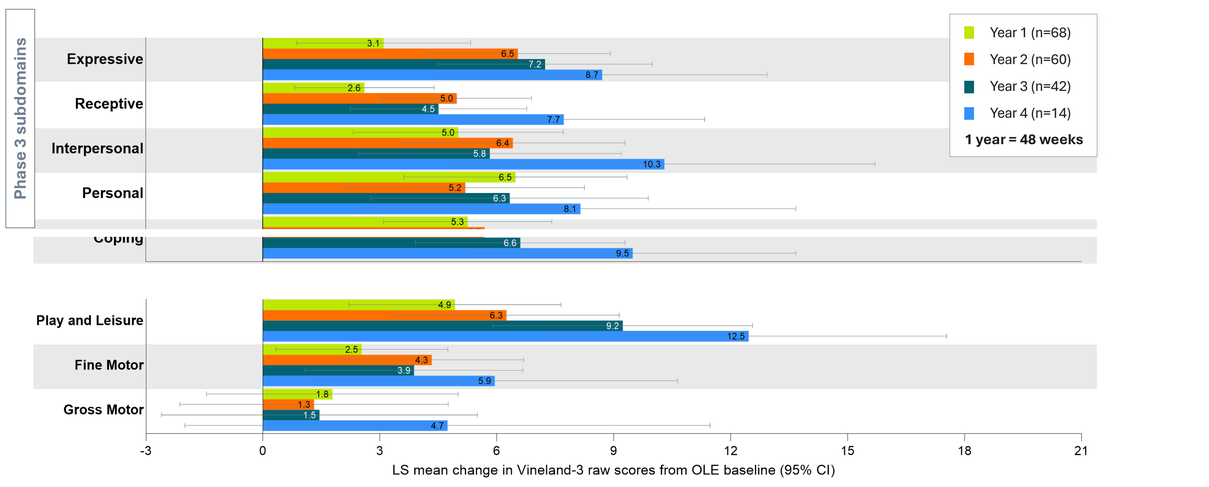


Data cut date: 19 February 2026. Analysis performed using available data from patients in the seizure evaluable set of the SWALLOWTAIL and LONGWING OLE studies (N=71), with n=34 to 47 patients in the <70 mg group and n=14 to 15 patients in the 70 mg (1, 2, or 3 doses) group having evaluable percent change-from-baseline data across visits. 1 month = 4 weeks. Reported data show changes in GTC and focal-to-BTC seizure frequency per 28 days from Phase 1/2a baseline.

Adaptive Functioning and Behaviour

- Clinically meaningful improvements[15] in adaptive functioning and behaviour continuing through 4 years of treatment with zorevunersen in the OLE studies (**Figure 4**).
  - $P<0.01$ 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 4. Improvements in Vineland-3 subdomain raw scores from OLE baseline

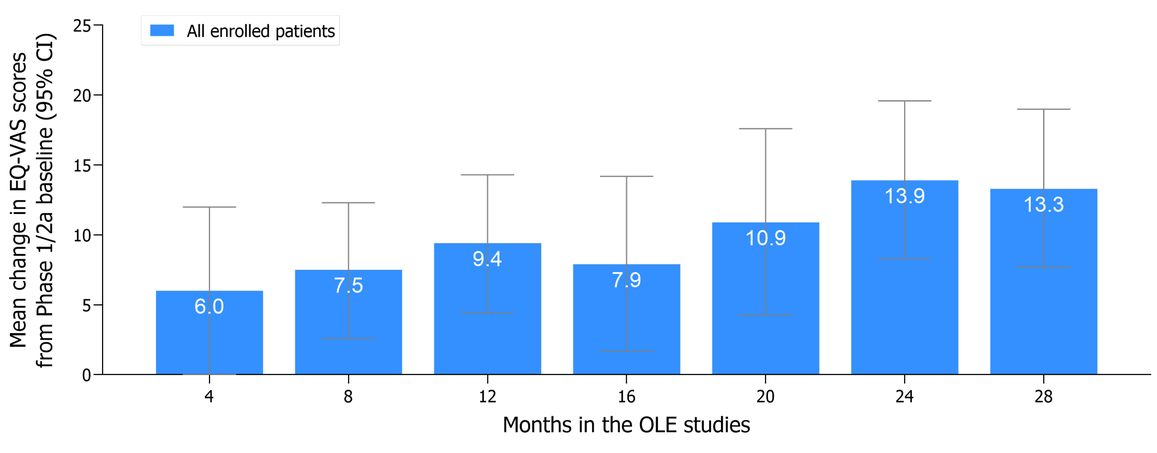


Data cut date: 19 February 2026. Mixed-effects models for repeated measures (MMRMs) for each subdomain were fit using available data from patients with baseline and at least one post baseline assessment in the SWALLOWTAIL and LONGWING OLE studies, with n representing the number of completed patient visits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

Quality of Life

- Improvements in quality of life, as measured by the change in EuroQol visual analogue scale (EQ-VAS) scores, were observed among patients treated with zorevunersen through 28 months of treatment in the OLE studies relative to the Phase 1/2a baseline (**Figure 5**).

Figure 5. Improvements in quality of life from Phase 1/2a baseline



Data cut date: 19 February 2026. Analysis performed using available data from patients enrolled in the SWALLOWTAIL and LONGWING OLE studies (N=75), with n=51 to 63 patients having evaluable change-from-baseline data across visits. EQ-VAS is a validated visual analogue scale ranging from 0 to 100 (worst to best imaginable health). 1 month = 4 weeks.

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 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). OLE data cut: 19 February 2026. Phase 3 Study EU CT: 2024-519555-28-00; NCT06872125. ASM, antiseizure medication; BTC, bilateral tonic–clonic; CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; GTC, generalised tonic–clonic; LS, least squares; OLE, open-label extension; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

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