Poster 1.379

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Zorevunersen demonstrates disease-modifying potential in patients with Dravet syndrome with increases in seizure-free days, improvements in quality of life, and benefits in overall clinical status

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Key Findings

1. Patients receiving zorevunersen on top of standard-of-care experienced substantial increases in the number of days free of major motor seizures through 36 months of treatment in the open-label extension studies.
2. Improvements in quality of life were observed; the greatest improvements were seen for patients treated with loading doses of 70 mg zorevunersen.
3. Clinicians and caregivers reported consistent and substantial improvements in overall clinical status in zorevunersen-treated patients through 36 months in the open-label extension studies.
4. Zorevunersen was generally well tolerated, with some patients treated up to 4.5 years.

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Introduction

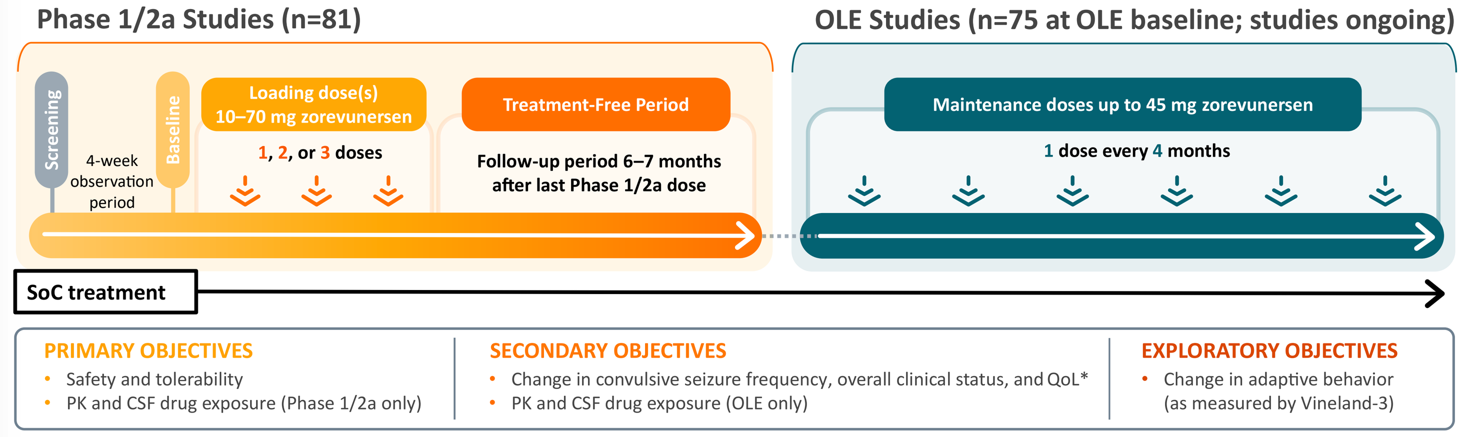
- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy. More than 90% of DS cases are caused by voltage-gated sodium channel α subunit 1 (*SCN1A*) variants that result in 50% $Na_V1.1$ sodium channel expression, causing refractory seizures and significant developmental, cognitive, and behavioral impairments that impact quality of life.[1–7]
- There is an urgent need for disease-modifying therapies that can address the seizure burden and improve QoL in patients with DS.[8]
- Zorevunersen is an investigational antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression by leveraging the wild-type copy of *SCN1A*.[9]
- Here, we present the effects of zorevunersen on seizures and measures of QoL in patients with DS.

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 children and adolescents with highly refractory DS (**Figure 1**).
- Eligible patients were aged 2–18 years old with an established DS diagnosis and documented *SCN1A* gene variant.

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: NCT04442295 (USA) and 2020-006016-24 (UK). OLE studies: NCT04740476 (USA) and 2021-005626-14 (UK). *Overall clinical status was assessed using the clinical and caregiver global impression of change scales (CGI-C and CaGI-C, respectively). QoL was measured by the EuroQol visual analogue scale (EQ-VAS) component of the EuroQoL 5-dimension (Youth) instrument. CSF, cerebrospinal fluid; DS, Dravet syndrome; OLE, open-label extension; PK, pharmacokinetics; QoL, quality of life; SoC, standard-of-care; Vineland-3, Vineland Adaptive Behavior Scales–Third Edition.

Results

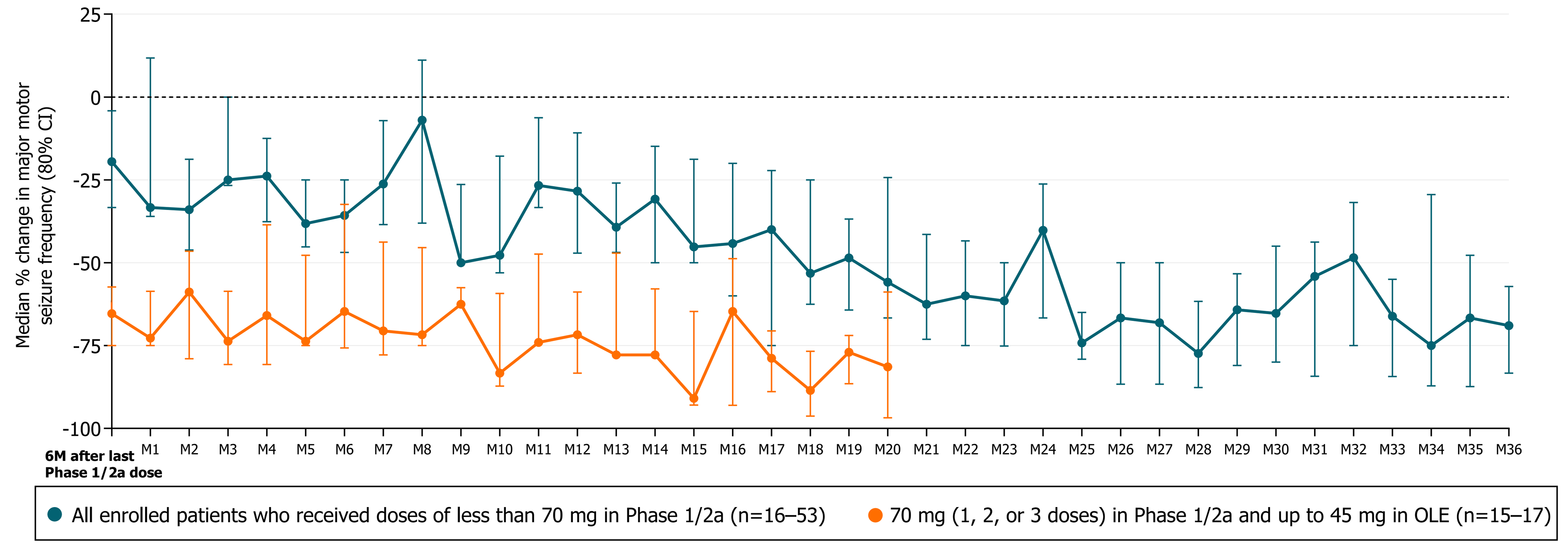
Baseline characteristics

- 81 patients with DS received single or multiple zorevunersen doses (≤70 mg) on top of standard-of-care antiseizure medications.
  - 75 patients transitioned to the subsequent OLE studies and received zorevunersen (≤45 mg) every 4 months while continuing standard-of-care antiseizure medications (ASMs).
- 82% patients were on ≥3 ASMs, and 51% were on ≥4 ASMs at baseline
- 49%, 44%, and 36% patients were receiving fenfluramine, cannabidiol, and stiripentol, respectively, at baseline.
- For additional details on the baseline characteristics please scan the QR code.

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; overall, reductions in major motor seizure frequency were maintained through 36 months of the OLEs (**Figure 2**).

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

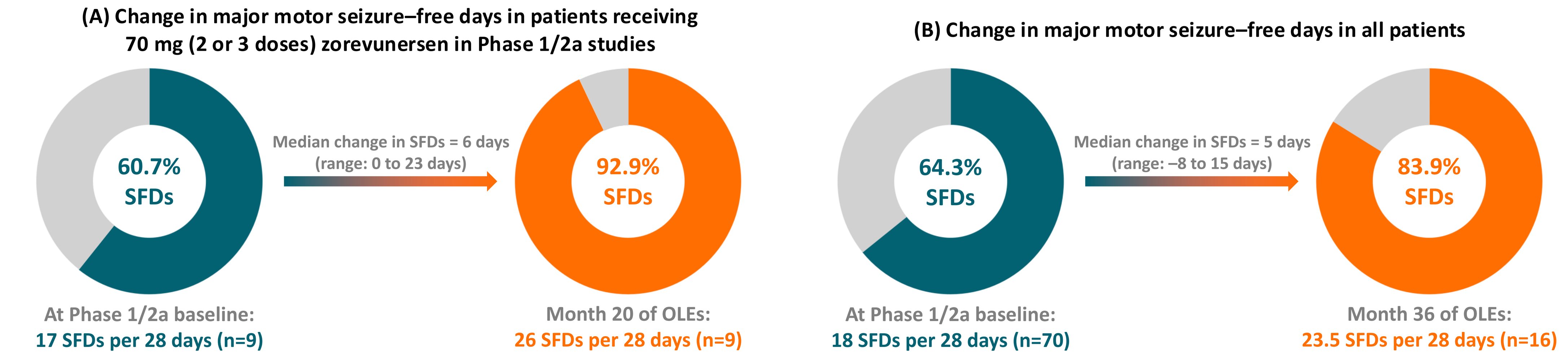


OLE data cut: May 30, 2025. Figure demonstrates an as-treated analysis and major motor seizure frequency was calculated for the 28-day interval preceding each M time point. Error bars show 80% CIs. One patient who received an incorrect dose of zorevunersen in Phase 1/2a, 3 patients who experienced less than the minimum number of major motor seizures during Phase 1/2a baseline, and 1 patient who transferred into the OLE with a delay of about 10 months were excluded. Patients were not included in 6M after last Phase 1/2a dose time point if they didn't enter the OLE. No exclusions were made for ASM modification. Intervals with <50% diary data were excluded for individual patients. All enrolled patients received ≤45 mg zorevunersen in the OLEs and doses were administered once every 4 months. ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open label extension.

Major motor seizure–free days

- Patients who received multiple doses of 70 mg zorevunersen in the Phase 1/2a studies gained a median (range) of 6 (0–23) major motor seizure–free days per 28 days from Phase 1/2a baseline to Month 20 of the OLEs, leading to a median (range) of 26 (0–28) major motor seizure-free days per 28 days per patient (**Figure 3**).
- Similarly, all patients gained a median (range) of 5 (-8–15) major motor seizure–free days per 28 days from Phase 1/2a baseline to Month 36 of the OLEs, leading to 23.5 (2–28) major motor seizure–free days per 28 days per patient.

Figure 3. Median major motor SFDs at baseline and at Month 20 (A: 70 mg zorevunersen group) and Month 36 (B: all patients) of the OLE studies

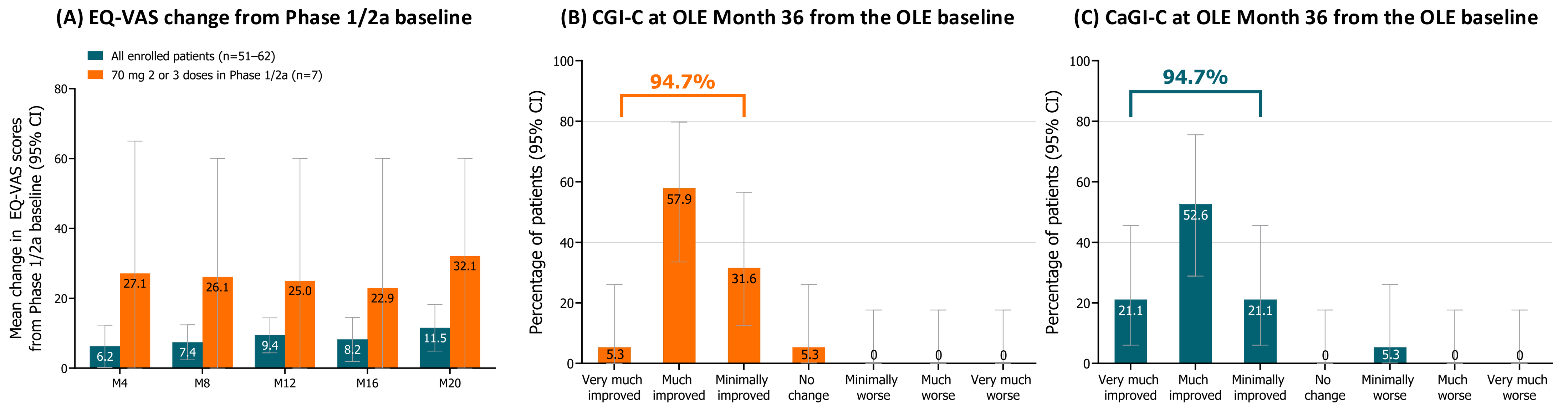


Phase 1/2a data cut: December 12, 2023 (after End of Study). OLE data cut: May 30, 2025. Percentages represent the proportion of days without seizures per 28 days. OLE, open-label extension; SFD, seizure-free day.

Quality of life and overall clinical status

- Improvements in QoL, measured by EQ-VAS scores, were observed over 80 weeks in the OLEs, with those receiving 2 or 3 doses of 70 mg in Phase 1/2a showing the greatest improvement from Phase 1/2a baseline (**Figure 4A**).
- Most patients showed improvements in overall clinical status at 36 months of treatment with zorevunersen in the OLEs, as measured by the CGI-C assessment (**Figure 4B**) and CaGI-C assessment (**Figure 4C**), from the OLE baseline.

Figure 4. Improvements in QoL and overall clinical status as measured by (A) EQ-VAS, (B) CGI-C, and (C) CaGI-C.



OLE data cut: May 30, 2025. EQ-VAS is a validated visual analogue scale (part of EQ-5D-Y) ranging from 0 to 100. 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). For CGI-C and CaGI-C, OLE sample size: n=19 at Month 36. CaGI-C, Caregiver Global Impression of Change; CGI-C, Clinical Global Impression of Change; EQ-VAS, EuroQol visual analogue scale; M, month; OLE, open-label extension.

Safety and tolerability*

- Study drug–related treatment-emergent adverse events were reported in 30% of patients (n=24/81) in the Phase 1/2a studies (most common: cerebrospinal fluid [CSF] protein elevations [14%, n=11] and procedural vomiting [5%, n=4]).
- 22% (n=18/81) 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 suspected unexpected serious adverse reactions.
- CSF protein elevation† occurred in 86% of patients and it was classified as a TEAE in 45%. No hydrocephalus associated with CSF protein elevation was reported. One patient discontinued treatment because of CSF protein elevation.
- 3 deaths have occurred during the Phase 1/2a and OLE studies (2 due to sudden unexpected death in epilepsy, 1 due to malnutrition); all were unrelated to zorevunersen.
- More than 800 doses of zorevunersen have been administered to date in the Phase 1/2a and OLE studies, for up to 4.5 years (as of November 2025).

*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.

References: 1. Hattori J *et al. Epilepsia* 2008; 49 (4): 626–633. 2. Gil-Nagel A *et al. Sci Rep* 2023; 13 (1): 3355. 3. Bechi G *et al. Epilepsia* 2012; 53 (1): 87–100. 4. Zuberi *SM et al. Epilepsia* 2022; 63 (6): 1349–1397. 5. Villas N *et al. Epilepsy Behav* 2017; 74: 81–86. 6. Sinoo C *et al. Epilepsy Behav* 2019; 90: 217–227. 7. Brunklaus A *et al. Epilepsia* 2011; 52(8): 1476–1482. 8. Wirrell EC *et al. Epilepsia* 2022; 63(7): 1761–1777. 9. Lim KH *et al. Nat Commun* 2020; 11(1): 3501.

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