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Substantial improvements in overall seizure burden and seizure-free days in patients with Dravet syndrome treated with zorevunersen: Results from Phase 1/2a and open-label extension studies

Cross J.H.,[1] Brunklaus A.,[2] Laux L.,[3] Sullivan J.,[4] Perry M.S.,[5] Desurkar A.,[6] Schreiber J.M.,[7] Roberts C.M.,[8] Knupp K.G.,[9] Wheless J.W.,[10] Wirrell E.C.,[11] Condon C.,[12] Brathwaite C.,[12] Fitzpatrick D.,[12] Lynch J.,[12] Stutely J.,[12] Wang F.,[12] Parkerson K.A.,[12] Ticho B.[12]

[1]UCL Great Ormond Street Institute of Child Health, London, UK; [2]University of Glasgow, Glasgow, Scotland, UK; [3]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; [4]University of California San Francisco, San Francisco, CA, USA; [5]Cook Children's Medical Center, Fort Worth, TX, USA; [6]Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK; [7]Children's National Hospital, Washington DC, USA; [8]Oregon Health & Science University, Portland, OR, USA; [9]Children's Hospital Colorado, Aurora, CO, USA; [10]Le Bonheur Children's Hospital, University of Tennessee Health Science Center, Memphis, TN, USA; [11]Mayo Clinic, Rochester, MN, USA; [12]Stoke Therapeutics, Bedford, MA, USA

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Key Findings

1. In patients with highly refractory Dravet syndrome, loading doses of 70 mg zorevunersen in Phase 1/2a studies, followed by ongoing maintenance doses in open-label extension studies, led to substantial and durable reductions in major motor seizure frequency on top of best-available antiseizure medications.
2. The most substantial improvements in major motor seizure-free days and quality of life were observed in patients treated with loading doses of 70 mg zorevunersen.
3. Zorevunersen was generally well tolerated across the Phase 1/2a and open-label extension studies.
4. These findings support further evaluation of the effects of zorevunersen on seizure outcomes as well as behavior, cognition, and quality of life outcomes in patients in the ongoing EMPEROR Phase 3 study.

Introduction

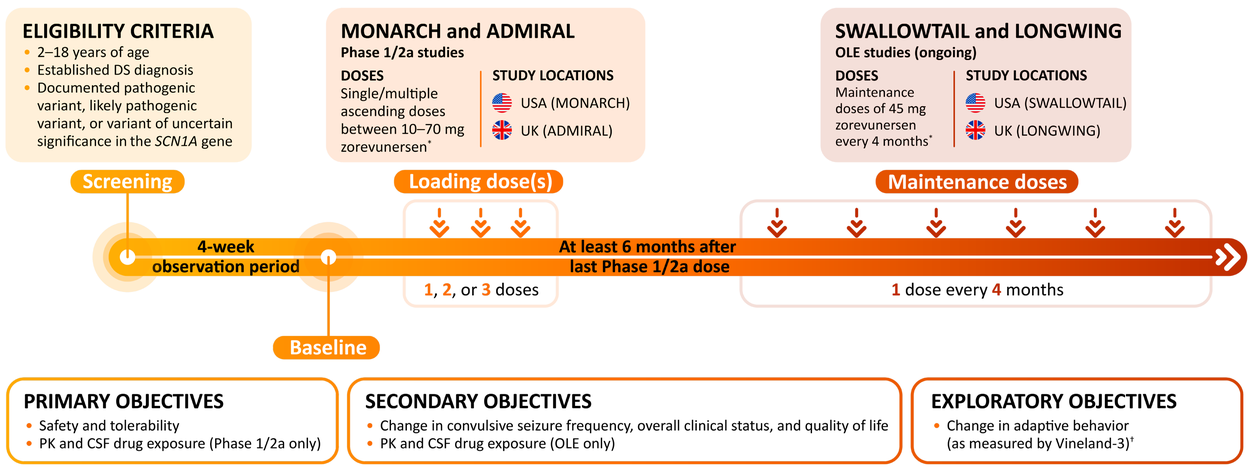
- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused primarily by voltage-gated sodium channel α subunit 1 (*SCN1A*) haploinsufficiency.[1]
- In addition to prolonged refractory seizures, patients with DS experience significant developmental, cognitive, and behavioral impairments that impact their quality of life (QoL).[2–5]
- There is a need for disease-modifying therapies that reduce the seizure burden and improve behavior and cognition in patients with DS.[6]
- Zorevunersen is an investigational antisense oligonucleotide designed to upregulate $Na_V1.1$ by leveraging the *SCN1A* wild-type copy.[7]
- Here, we present the effects of zorevunersen on seizure burden and QoL in patients with highly refractory DS who are already on the best-available antiseizure medications (ASMs), such as fenfluramine and cannabidiol.

Methods

Study Design

- The open-label, multicenter, Phase 1/2a studies and their corresponding open-label extensions (OLEs) evaluated the effects of zorevunersen in patients with highly refractory DS aged 2–18 years. **(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: June 28, 2024. Phase 1/2a studies: MONARCH (NCT04442295 [USA]) and ADMIRAL (2020-006016-24 [UK]). OLE studies: SWALLOWTAIL (NCT04740476 [USA]) 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-3 in ADMIRAL and SWALLOWTAIL/LONGWING. CSF, cerebrospinal fluid; DS, Dravet syndrome; OLE, open-label extension; PK, pharmacokinetics; *SCN1A*, voltage-gated sodium channel α subunit 1; UK, United Kingdom; USA, United States of America; Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Results

Baseline Characteristics

- In the Phase 1/2a studies, 81 patients with DS received single or multiple zorevunersen doses (≤70 mg). **(Table 1)**
  - 74 patients transitioned to the 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

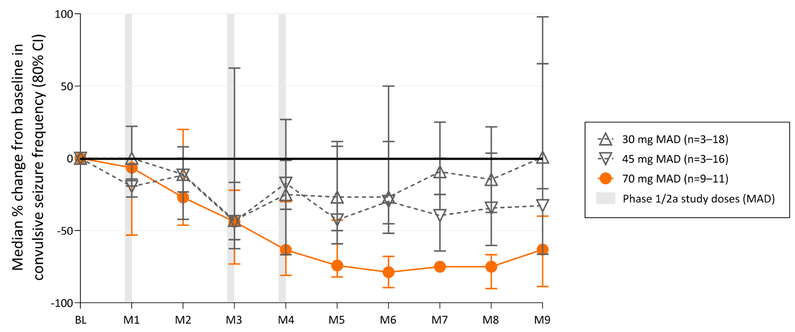
Characteristics	Value (N=81)
Age at screening in years, median (range)	10 (2–18)
Number of concomitant ASMs at screening, n (%)	
≥3	66 (82)
≥4	41 (51)
Receiving concomitant fenfluramine at screening, n (%)	40 (49)
Receiving concomitant cannabidiol at screening, n (%)	36 (44)
Baseline major motor seizure frequency per 28 days (n=77*), median (range)	17 (4–2,335)

*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 reduction in major motor seizure frequency was in patients treated with an initial 2 or 3 doses of 70 mg zorevunersen. **(Figure 2)**
- Patients who received 70 mg zorevunersen (2 or 3 doses; n=11) achieved median reductions in major motor seizure frequency of 84.8% (n=10) at 3 months after the last dose of zorevunersen in the Phase 1/2a studies.

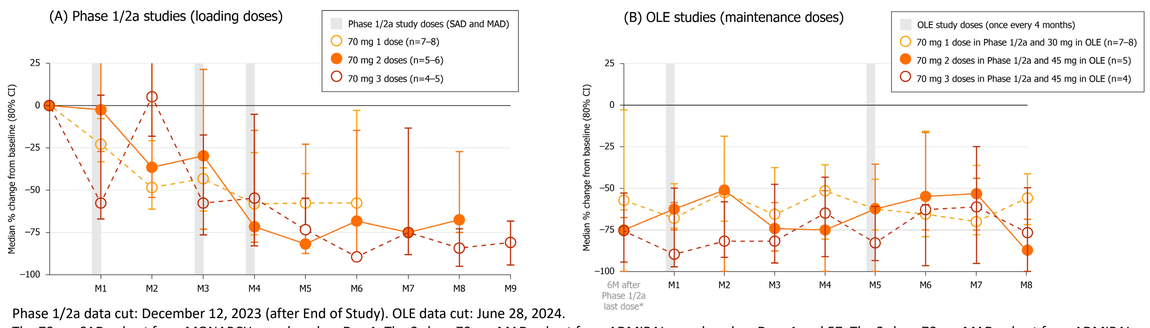
Figure 2. Change from baseline in major motor seizure frequency in Phase 1/2a studies



Phase 1/2a data cut: December 12, 2023 (after End of Study). MONARCH MAD cohorts were dosed on Days 1, 29, and 57. ADMIRAL included 30, 45, and 3-dose 70 mg MAD cohorts with drug administration on Days 1, 57, and 85 and a 2-dose 70 mg MAD cohort with drug administration on Days 1 and 57. BL, baseline; CI, confidence interval; M, month; MAD, multiple ascending doses.

- Patients treated with 70 mg zorevunersen in the Phase 1/2a studies followed by 30 or 45 mg maintenance doses in the OLEs experienced substantial and durable reductions in median major motor seizure frequency, ranging from 50.8% to 89.3%, through Month 8 of the OLEs. **(Figure 3)**

Figure 3. Reduction in major motor seizure frequency from (A) Phase 1/2a baseline to (B) the OLE studies



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. Data show follow-up for 6 months after last zorevunersen dose. 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 the 70 mg 1-dose cohort) or in the Phase 1/2a studies at time of ASM modification (one patient in the 70 mg 2-dose cohort and one patient in the 70 mg 3-dose cohort). 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. *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; SAD, single ascending dose.

Dose Relationship

- Up to 80% of patients receiving multiple ascending doses of zorevunersen experienced ≥50% reductions in major motor seizure frequency from baseline to 3 months after the last dose of zorevunersen in the Phase 1/2a studies. **(Table 2)**

Table 2. Reduction in major motor seizure frequency from baseline to 3 months after the last dose of zorevunersen in the Phase 1/2a studies

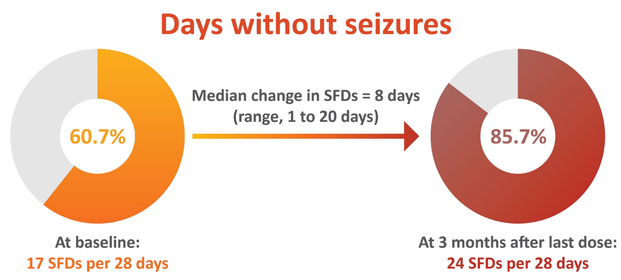
Reduction in convulsive seizure frequency	Loading doses		
	30 mg (n=16)	45 mg (n=13)	70 mg* (n=10)
≥50%	6 (37.5)	5 (38.5)	8 (80)
≥75%	4 (25)	4 (30.8)	6 (60)
100%	1 (6.3)	1 (7.7)	1 (10)
No seizures reported	1 (6.3)	1 (7.7)	2 (20)

Phase 1/2a data cut: December 12, 2023 (after End of Study). Data are shown as n (%). *Includes 2 or 3 doses.

Major Motor Seizure-free Days

- The most substantial improvements in major motor seizure-free days (SFDs) were in patients who received 70 mg zorevunersen (2 or 3 doses), with a median increase of 8 SFDs per 28 days at 3 months after the last dose of zorevunersen. **(Figure 4)**
- Patients had a median of 24 SFDs per 28 days at 3 months after the last dose of 70 mg zorevunersen compared with 17 SFDs at baseline; the median number of SFDs at 3 months was sustained at 6 months. **(Figure 4)**

Figure 4. Median major motor SFDs at baseline and 3 months after the last dose of 70 mg zorevunersen in Phase 1/2a studies

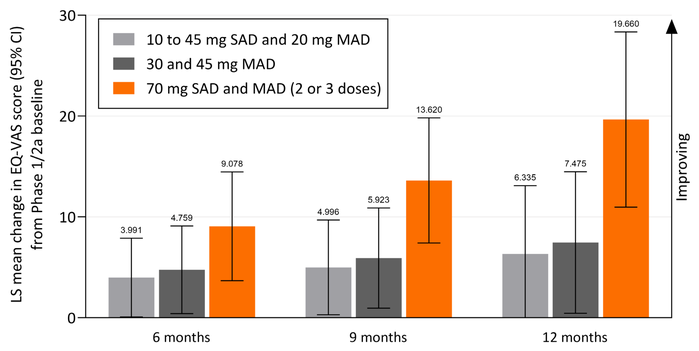


Phase 1/2a data cut: December 12, 2023 (after End of Study). Percentages represent the proportion of days without seizures per 28 days. SFD, seizure-free day.

QoL

- Patients who received 70 mg zorevunersen through the Phase 1/2a studies showed the most substantial improvements in QoL outcomes from the EuroQol visual analogue scale (EQ-VAS) component of the EuroQol-5D Youth. **(Figure 5)**

Figure 5. Improvements in QoL since start of Phase 1/2a studies



Phase 1/2a data cut: December 12, 2023 (after End of Study). OLE data cut: June 28, 2024. Timepoints indicate months after last zorenuversen dose. A mixed effect model repeat measurement analysis was conducted to evaluate the change from baseline in EQ-VAS scores, employing an unstructured covariance matrix to model within-subject correlations; the model included sex, log-transformed age, baseline EQ-VAS score, age at onset, and log-transformed baseline seizure frequency as covariates. Sample sizes were n=71 at baseline, n=15 at Month 9, and n=13 at Month 12. CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; LS, least squares; MAD, multiple ascending dose; QoL, quality of life; SAD, single ascending dose.

Safety and Tolerability

- Over 700 doses of zorevunersen have been administered to date (as of May 2025).
- Study drug–related treatment-emergent adverse events were reported in 30% (24/81) of patients in the Phase 1/2a studies, of which cerebrospinal fluid (CSF) protein elevations (14%, n=11) and procedural vomiting (5%, n=4) were most common.
- In the OLE studies, results were consistent with those of the Phase 1/2a studies, except for a higher incidence of CSF protein elevation (27%, n=20/74).
  - No clinical manifestations associated with CSF protein elevation were observed, and one patient discontinued treatment due to elevated CSF protein value.

References: 1. Steel D *et al. Epilepsia* 2017; 58 (11): 1807–1816; 2. Zuberi *SM et al. Epilepsia* 2022; 63 (6): 1349–1397; 3. Villas N *et al. Epilepsy Behav* 2017; 74: 81–86; 4. Sinoo C *et al. Epilepsy Behav* 2019; 90: 217–227; 5. Brunklaus A *et al. Epilepsia* 2011; 52 (8): 1476–1482; 6. Wirrell EC *et al. Epilepsia* 2022; 63 (7): 1761–1777; 7. Lim KH *et al. Nat Commun* 2020; 11 (1): 3501.

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