Patients with Dravet syndrome in open-label extension studies of zorevunersen (STK-001) have durable reductions in seizure frequency and ongoing improvements in cognition and behavior

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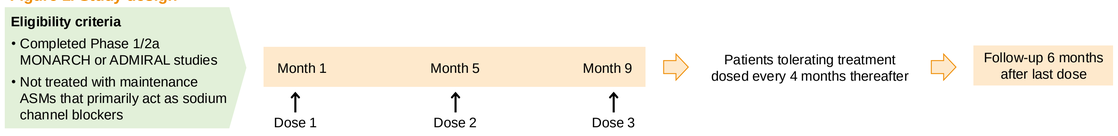
INTRODUCTION

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by severe, recurrent seizures as well as significant cognitive and behavioral impairments[1–3]
- In the BUTTERFLY natural history study, despite being on standard of care treatment with best available antiseizure medications (ASMs), patients with DS experienced ongoing high seizure rates and continued to fall further behind in aspects of cognition and behavior over 24 months compared to neurotypical peers[4]
- Zorevunersen is an investigational antisense oligonucleotide designed to treat the underlying cause of DS — $Na_V1.1$ protein haploinsufficiency caused by variants of the sodium channel type 1 alpha subunit (*SCN1A*) gene
- In the Phase 1/2a MONARCH/ADMIRAL studies, zorevunersen was generally well tolerated and resulted in seizure reductions and improvements in cognition and behavior, overall clinical status, and quality of life[5]
- The SWALLOWTAIL/LONGWING open-label extensions (OLEs) expand upon the Phase 1/2a studies to provide additional insights into the long-term effects of zorevunersen on safety, seizures, and non-seizure impairments in patients with DS

METHODS

- SWALLOWTAIL and LONGWING are ongoing OLEs of the MONARCH and ADMIRAL studies conducted in the USA and UK, respectively (Figure 1)
- Patients were administered maintenance doses of zorevunersen as an intrathecal slow bolus injection every 4 months

Figure 1. Study design



Primary objective: Long-term safety and tolerability of repeated doses of zorevunersen administered every 4 months

Selected secondary and exploratory objectives: Effect of zorevunersen on percentage change from baseline in convulsive seizure frequency, cognition and behavior (Vineland-3), overall clinical status (CGI-C/CaGI-C with a focus on DS symptoms), and QoL (EQ-VAS component of EuroQol-5D Youth)

ASM, antiseizure medication; CaGI-C, Caregiver Global Impression of Change; CGI-C, Clinical Global Impression of Change; DS, Dravet syndrome; EQ-VAS, EuroQol visual analogue scale; QoL, quality of life; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

Key Findings

1. Long-term OLE data support the **potential for zorevunersen to be the first disease-modifying medicine for DS**
2. **Substantial and durable reductions in convulsive seizure frequency were observed through Month 24 in patients already receiving best available ASMs,** with the largest reductions in patients who received doses of 70 mg in Phase 1/2a followed by 30 or 45 mg in the OLEs
3. Patients treated with zorevunersen experienced **durable improvements in multiple measures of cognition, behavior, quality of life, and overall clinical status, which continued to improve through 24 months of the OLEs** with ongoing maintenance dosing
4. Multiple maintenance doses of zorevunersen up to 45 mg were generally **well tolerated**

RESULTS

Baseline characteristics

- As of June 28, 2024, 58/61 (95.1%) MONARCH completers enrolled in SWALLOWTAIL, with 47/58 (81.0%) remaining in study, and 16/19 (84.2%) ADMIRAL completers enrolled in LONGWING, with 14/16 (87.5%) remaining in study
- Patient demographics were generally comparable across both OLEs (Table 1)
- Overall, 52.7% (39/74) patients were concomitantly on fenfluramine

Table 1. Summary of baseline characteristics

Parameter	SWALLOWTAIL (n=58)	LONGWING (n=16)	All enrolled (N=74)
Age at screening, years			
Median (range)	11 (2, 19)	7 (4, 17)	11 (2, 19)
Age group, n (%)			
2–12 years	31 (53.4)	11 (68.8)	42 (56.8)
≥13 years	27 (46.6)	5 (31.3)	32 (43.2)
Gender, n (%)			
Female	29 (50.0)	8 (50.0)	37 (50.0)
Male	29 (50.0)	8 (50.0)	37 (50.0)
Race*, n (%)			
Asian	5 (8.6)	0	5 (6.8)
Black or African American	5 (8.6)	0	5 (6.8)
White	48 (82.8)	16 (100.0)	65 (87.8)
Prefer not to answer	4 (6.9)	0	3 (4.1)

*Multiple selections for race could be entered.

Safety and tolerability

- Zorevunersen was generally well tolerated across both OLEs (Table 2), with the most commonly reported treatment-emergent adverse events (TEAEs) being cerebrospinal fluid (CSF) protein increased (n=23, 31.1%), pyrexia (n=22, 29.7%), and COVID-19 (n=19, 25.7%)
- All drug-related and procedure-related TEAEs were non-serious and mild or moderate in severity; drug-related TEAEs reported in >1 patient were CSF protein increased (n=20, 27.0%) and proteinuria (n=2, 2.7%)
- No patients experienced clinical manifestations associated with increased CSF protein, although one patient withdrew due to elevated CSF protein
- Of the 71 patients with ≥1 post-baseline CSF value (<50 mg/dL is considered normal[6]), 78.9% patients had at least 1 value >50 mg/dL, and 7.0% had a value >250 mg/dL

Table 2. Summary of TEAEs*

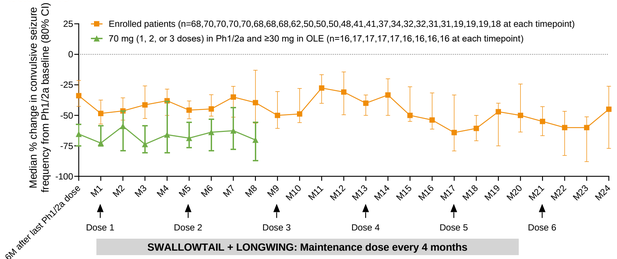
TEAE Category Number of patients (%)	SWALLOWTAIL (n=58)	LONGWING (n=16)	All enrolled (N=74)
Any TEAE	58 (100)	15 (93.8)	73 (98.6)
Drug-related TEAEs	25 (43.1)	2 (12.5)	27 (36.5)
Procedure-related TEAEs	30 (51.7)	8 (50.0)	38 (51.4)
≥Grade 3 TEAE	5 (8.6)	1 (6.3)	6 (8.1)
TESAE	12 (20.7)	2 (12.5)	14 (18.9)
Drug-related TESAE	0	0	0
Potential DLT	0	0	0
TEAE leading to study withdrawal	1 (1.7)	0	1 (1.4)
TEAE leading to death	0	0	0†

*TEAE is defined as an adverse event first identified, or is identified to worsen in intensity, at a time occurring after the first dose of study drug.
†Following the data cut, 1 patient in SWALLOWTAIL died due to sudden unexpected death in epilepsy (SUDEP) that was assessed as unrelated to zorevunersen.
DLT, dose limiting toxicity; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Convulsive seizure frequency

- Reductions in convulsive seizure frequency were sustained through Month 24 of the OLEs (Figure 2)
- Patients who received doses of 70 mg zorevunersen in the Phase 1/2a studies followed by maintenance doses of ≥30 mg in the OLEs experienced greater magnitudes of reduction

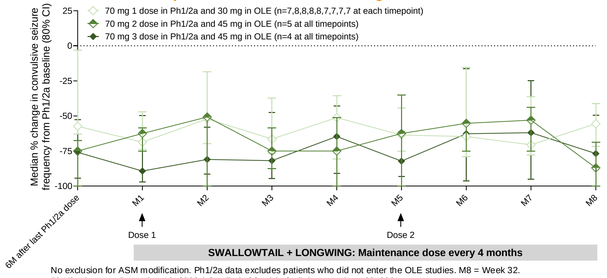
Figure 2. Durable reductions in convulsive seizure frequency from Phase 1/2a baseline



No exclusion for ASM modification. Ph1/2a data excludes patients who did not enter the OLE studies. Of the patients enrolled in the OLEs, one patient was excluded due to receiving an incorrect dose during the Ph1/2a study, and three patients were excluded for not meeting the minimum convulsive seizure frequency requirement at the Ph1/2a baseline. M24 = Week 96. Ph1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024. ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open-label extension; Ph1/2a, Phase 1/2a.

- In patients treated with 1, 2, or 3 doses of 70 mg zorevunersen in the Phase 1/2a studies, ≥50% reductions in median convulsive seizure frequency were observed in the OLEs through Month 8 (Figure 3)

Figure 3. Substantial and durable reductions in convulsive seizure frequency from Phase 1/2a baseline in patients who received 70 mg zorevunersen in Phase 1/2a

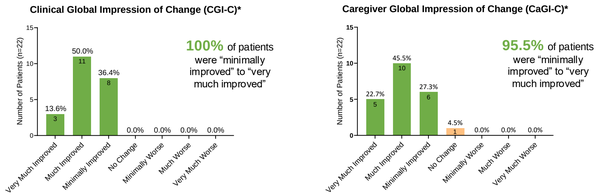


No exclusion for ASM modification. Ph1/2a data excludes patients who did not enter the OLE studies. M8 = Week 32.
Ph1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open-label extension; Ph1/2a, Phase 1/2a.

Overall clinical status

- Clinical and Caregiver Global Impression of Change (CGI-C and CaGI-C) scales indicate substantial and ongoing improvements in overall clinical status through Month 24 of the OLEs (Figure 4)

Figure 4. Improvements from OLE baseline in overall clinical status at Month 24

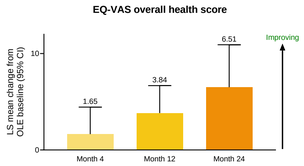


*CGI-C and CaGI-C assessments are scored on a Likert scale with seven response options: 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), or 7 (Very much worse).
OLE data cut: June 28, 2024.
OLE, open-label extension.

Quality of life

- Model outcomes from the EQ-VAS component of the EuroQol-5D Youth indicate ongoing improvements in quality of life through Month 24 of the OLEs (Figure 5)

Figure 5. Improvements in quality of life through Month 24 of the OLEs

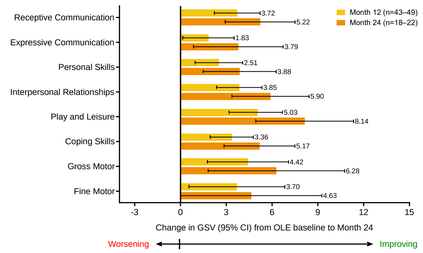


Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies. One patient who received an incorrect dose in Phase 1/2a study was excluded. OLE data cut: June 28, 2024.
SWALLOWTAIL/LONGWING sample sizes at OLE baseline: n=62.
CI, confidence interval; LS, least-squares; EQ-VAS, EuroQol visual analogue scale; OLE, open-label extension.

Cognition and behavior

- Model outcomes from the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) indicate ongoing improvements in cognition and behavior through Month 24 of the OLEs, with interval improvements across Vineland-3 subdomains between Months 12 and 24 (Figure 6)

Figure 6. Continuing improvements in Vineland-3 subdomain growth scale values from OLE baseline



Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies. One patient who received incorrect dose in Phase 1/2a study was excluded; 1 patient had multiple results classified as extreme outliers in Fine Motor subdomain.
OLE data cut: June 28, 2024. SWALLOWTAIL/LONGWING sample sizes at OLE baseline: n=68–72.
CI, confidence interval; GSV, growth scale value; OLE, open-label extension; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

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. Sullivan J *et al.* Poster P788 presented at EEC 2024; Rome, Italy, 7–11 September 2024. 5. Laux L *et al.* Poster 2.379 presented at AES 2024; Los Angeles, USA, 6–10 December 2024. 6. Shahan B *et al. Am Fam Physician* 2021; 103 (7): 422–428.
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