SWALLOWTAIL and LONGWING

Open-label Extension Studies for Children and Adolescents with Dravet Syndrome who Previously Participated in a Study of Antisense Oligonucleotide Zorevunersen (STK-001)

Poster P875

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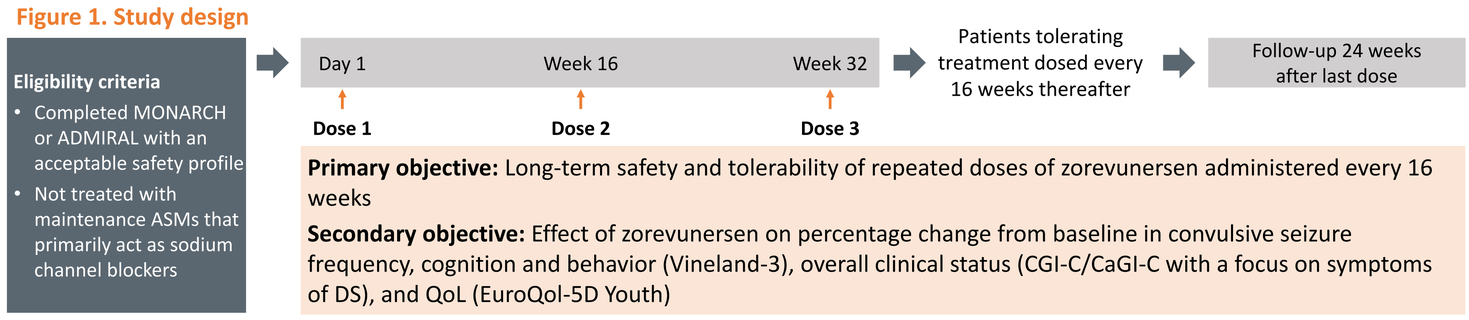
BACKGROUND

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused primarily by sodium channel type 1 alpha subunit (*SCN1A*) gene variants[1]
- Patients with DS experience refractory seizures along with significant cognitive and behavioral comorbidities[2,3]
- Despite treatment, 90% of children and adolescents experience uncontrolled seizures[4]
- In the BUTTERFLY natural history study, despite standard of care treatment with the best antiseizure medications (ASMs), patients with DS experienced ongoing high rates of seizures and fell behind in aspects of cognition and behavior over 24 months relative to neurotypical peers
- Disease-modifying therapies targeting the underlying pathophysiology of DS are needed to improve long-term outcomes
- Zorevunersen is an investigational antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression by leveraging the wild-type copy of the *SCN1A* gene to restore physiological $Na_V1.1$ protein levels in the brain
- **The SWALLOWTAIL/LONGWING open-label extensions (OLEs) expand upon the MONARCH/ADMIRAL Phase 1/2a data to provide further insights into the long-term effects of zorevunersen on seizures and non-seizure comorbidities**

METHODS

- SWALLOWTAIL and LONGWING are ongoing OLEs of the MONARCH and ADMIRAL studies conducted in the USA and UK, respectively (**Figure 1**)
- In both OLEs, patients are administered zorevunersen as an intrathecal slow bolus injection every 16 weeks, with patients currently receiving 45 mg per dose
- Except for baseline characteristics and safety, the data presented here are from a subset of patients who cumulatively received at least 30 mg in the Phase 1/2a studies and continued treatment in the OLEs with 30 or 45 mg per dose

Figure 1. Study design



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

Key Findings

1. **The 12-month OLE data support the potential for zorevunersen as the first disease-modifying medicine for DS**
2. **Multiple doses of zorevunersen up to 45 mg per dose every 4 months were generally well tolerated**
3. **Substantial and durable reductions in seizure frequency were observed on top of best available ASMs**
4. **Substantial improvements were detected in multiple measures of cognition, behavior, and overall clinical status**

RESULTS

Baseline characteristics

- 54 of 57 (94.7%) MONARCH completers and 14 of 17 (84.2%) ADMIRAL completers were enrolled in SWALLOWTAIL and LONGWING, respectively as of November 1, 2023, with 15 patients having been treated for ≥2 years and having received up to 10 doses total (**Table 1**)
- Overall, 49% (33/68) of patients were concomitantly on fenfluramine

Table 1. Summary of baseline characteristics and patient demographics

Parameter	SWALLOWTAIL (n=54)	LONGWING (n=14)	All enrolled (N=68)
Age at screening, years			
Median (min, max)	12 (2, 19)	7.5 (4, 17)	10 (2, 18)
Age group, n (%)			
2–12 years	27 (50.0)	9 (64.3)	38 (55.9)
≥13 years	27 (50.0)	5 (35.7)	30 (44.1)
Gender, n (%)			
Female	29 (53.7)	7 (50.0)	36 (52.9)
Male	25 (46.3)	7 (50.0)	32 (47.1)
Race*, n (%)			
Asian	4 (7.4)	0 (0.0)	4 (5.9)
Black or African American	5 (9.3)	0 (0.0)	5 (7.4)
White	45 (83.3)	14 (100.0)	60 (88.2)
Prefer not to answer	4 (7.4)	0 (0.0)	3 (4.4)

*Multiple selections for race could be entered.

Safety and tolerability

- Zorevunersen was generally well tolerated across patients in both OLEs (**Table 2**), with the most commonly reported treatment-emergent adverse events (TEAEs) being cerebrospinal fluid (CSF) protein increased, pyrexia, and COVID-19
- All drug-related TEAEs were non-serious and mild or moderate in severity; CSF protein elevation was the only drug-related TEAE reported in >1 patient and resulted in one study withdrawal
- CSF protein elevation was observed in 74% (50/68) of patients, no patients experienced any associated clinical manifestations

Table 2. Summary of TEAEs*

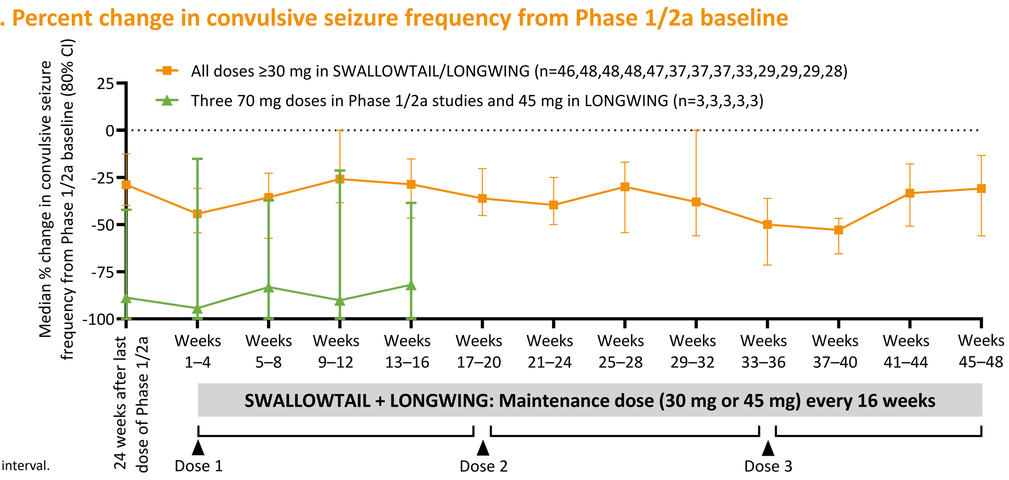
TEAE Category	SWALLOWTAIL	LONGWING	All enrolled
Number of patients (%)	**(n=54)**	**(n=14)**	**(N=68)**
Any TEAE	47 (87.0)	10 (71.4)	57 (83.8)
Drug-related TEAEs	21 (38.9)	2 (14.3)	23 (33.8)
Study procedure-related TEAEs	23 (42.6)	4 (28.6)	27 (39.7)
≥Grade 3 TEAE	3 (5.6)	1 (7.1)	4 (5.9)
Serious TEAE	8 (14.8)	2 (14.3)	10 (14.7)
Drug-related serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Potential dose limiting toxicity	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to study withdrawal	1 (1.9)	0 (0.0)	1 (1.5)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)

*TEAE is defined in this study as an adverse event first identified, or identified to worsen in intensity, at a time occurring after first dose of study drug.

Convulsive seizure frequency

- Reductions in convulsive seizure frequency were sustained throughout Week 48 (**Figure 2**)
- More substantial reductions were observed in the initial three patients who received multiple doses of 70 mg zorevunersen in the Phase 1/2a studies followed by a single dose of 45 mg in the OLE

Figure 2. Percent change in convulsive seizure frequency from Phase 1/2a baseline

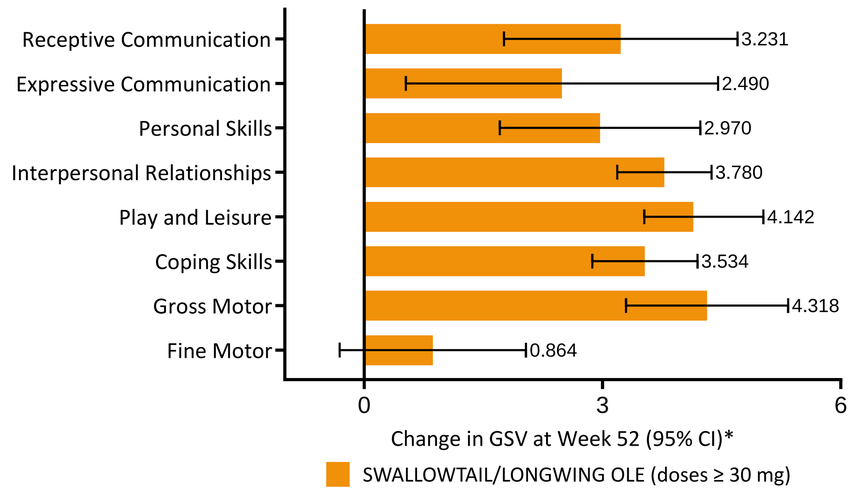


CI, confidence interval.

Cognition, behavior, and overall status

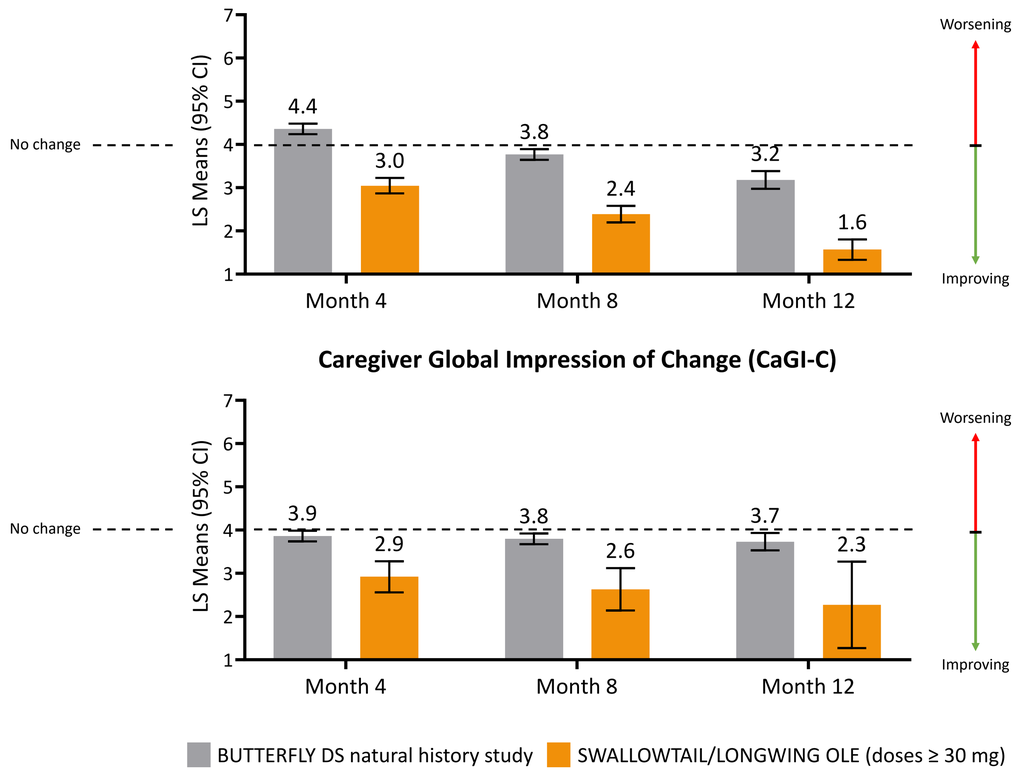
- Model outcomes derived from Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) data indicate substantial improvements in cognition and behavior by Month 12 of the OLEs (**Figure 3**)
- Similarly, data from the Clinical and Caregiver Global Impression of Change for Cognition (CGI-C and CaGI-C) indicate substantial improvements in overall clinical status
  - These improvements were in stark contrast to estimated change based on BUTTERFLY natural history study data (**Figure 4**)

Figure 3. Change in Vineland-3 subdomain growth scale values from SWALLOWTAIL/LONGWING OLE baseline



*Change in GSV for SWALLOWTAIL/LONGWING is from the OLE baseline. Analysis was based on a mixed-effects model for repeated measures with an unstructured covariance structure. Sample size: n=48 at screen, n=28 at Week 48 and n=15 at Week 64, except in Fine Motor where n=45 at screen, n=28 at Week 48, and n=14 at Week 64. CI, confidence interval; GSV, growth scale value; OLE, open-label extension.

Figure 4. Change in overall clinical status from SWALLOWTAIL/LONGWING compared with the BUTTERFLY DS natural history study



For both assessments, change was scored on a 7-point scale with improvement ranging from "very much improved" (scored as 1) to "very much worse" (scored as 7). SWALLOWTAIL/LONGWING analysis was based on a mixed-effects model for repeated measures with an unstructured covariance structure. Data from the BUTTERFLY natural history study through Month 24 were analyzed with machine learning. Baseline covariates in BUTTERFLY including baseline score, convulsive seizure onset age, BMI, age, weight, and baseline seizure frequency were matched to SWALLOWTAIL/LONGWING patient population means. For CGI-C, BUTTERFLY sample size: n=31 at 1st visit post-screen and n=27 at Month 12; SWALLOWTAIL/LONGWING sample size: n=46 at 1st visit post-screen, n=28 at Week 48, and n=14 at Week 64. For CaGI-C, BUTTERFLY sample size: n=34 at 1st visit post-screen and n=29 at Month 12; SWALLOWTAIL/LONGWING sample size: n=46 at 1st visit post-screen, n=29 at Week 48, and n=14 at Week 64. CGI-C and CaGI-C in BUTTERFLY focused on cognition, whereas CGI-C and CaGI-C in SWALLOWTAIL/LONGWING focused on overall symptoms of DS.
CI, confidence interval; DS, Dravet syndrome; LS, least squares.

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