MONARCH and ADMIRAL: Open-label, Phase 1/2a studies in USA and UK investigating safety, drug exposure, and clinical effect of zorevunersen (STK-001), an antisense oligonucleotide, in children and adolescents with Dravet syndrome

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Speaker disclosures

- Investigator for studies with GW Pharmaceuticals (Jazz Pharmaceuticals), Ovid Therapeutics, Zogenix (UCB), Vitaflo, Marinus Pharmaceuticals, Stoke Therapeutics, and Ultragenyx
- Speaker and on advisory boards for GW Pharmaceuticals (Jazz Pharmaceuticals), Zogenix (UCB), Biocodex, Takeda, UCB, and Nutricia; all remuneration has been paid to her department
- Endowed chair at UCL Great Ormond Street Institute of Child Health
- Current chair of the Medical Boards for Dravet Syndrome UK, Hope for Hypothalamic Hamartoma, and Matthew's Friends
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EPSRC, Engineering and Physical Sciences Research Council; ERUK, Epilepsy Research UK; GOSH, Great Ormond Street Hospital; NIHR, National Institute for Health and Care Research; UCL, University College London.

DS is a severe developmental and epileptic encephalopathy with a burdensome and challenging treatment paradigm[1]

DS is characterized by **frequent**, **prolonged**, and **refractory seizures**; its comorbidities include developmental delays, motor/gait issues, sleep abnormalities, and speech impairments[2]

1 out of **16,000**

babies are born with DS[3]

85%

of cases caused by a HAPLOINSUFFICIENCY of the *SCN1A* gene[4,5]

resulting in

50%

$Na_V1.1$ protein expression[6]

Up to

20%

of children and adolescents with DS die before adulthood due to SUDEP, prolonged seizures, seizure-related accidents or infections[7]

Patients with DS and their caregivers have **poor quality of life**[8]

~90% of patients have seizures that are not adequately controlled by ASMs; these therapies also do not address the comorbidities of the disease[9]

→

A substantial unmet need exists for therapies that directly target the most common root cause of DS — neuronal *SCN1A* haploinsufficiency[10]

1. Dravet Syndrome Foundation – Voice of the Patient Report. Available at: https://dravetfoundation.org/wp-content/uploads/2022/05/Voice-of-the-Patient-report-5.31.22_compressed.pdf; 2. Villas N et al. Epilepsy Behav 2017; 74: 81–86; 3. Wu YW et al. Pediatrics 2015; 136 (5): e1310–e1315; 4. Hattori J et al. Epilepsia 2008; 49 (4): 626–633; 5. Gil-Nagel A et al. Sci Rep 2023; 13 (1): 3355; 6. Bechi G et al. Epilepsia 2012; 53 (1): 87–100; 7. Cooper MS et al. Epilepsy Res 2016; 128: 43–47; 8. Sullivan J et al. Epilepsy Behav 2022; 130: 108661; 9. Lagae L et al. Dev Med Child Neurol 2018; 60 (1): 63–72; 10. Han Z et al. Sci Transl Med 2020; 12 (558): eaaz6100.

ASMs, anti-seizure medications; DS, Dravet syndrome; SCN1A, sodium voltage-gated channel protein type 1 alpha subunit gene; SUDEP, sudden unexpected death in epilepsy; USA, United States of America.

MONARCH/ADMIRAL were Phase 1/2a studies evaluating zorevunersen on top of SOC anti-seizure medications in patients with DS

Zorevunersen is a novel antisense oligonucleotide designed to restore physiological $Na_V1.1$ protein levels in the brain

	monarch	Evaluation of zorevunersen in children and adolescents with DS	admiral
Design	Study location: USA SAD: Up to 70 mg per dose MAD: Up to 45 mg per dose		Study location: UK MAD: Up to 70 mg per dose
Primary Endpoint	Safety and tolerability of SAD and MAD levels		Safety and tolerability of MAD levels
	Characterize PK and CSF drug exposure		
Secondary Endpoint	Change in convulsive seizure frequency, overall clinical status, and quality of life		
Open Label Extension	Dosing ongoing in USA: 45 mg per dose every 4 months	swallowtail	Dosing ongoing in UK: 45 mg per dose every 4 months

CSF, cerebrospinal fluid; DS, Dravet syndrome; MAD, multiple ascending dose; PK, pharmacokinetics; SAD, single ascending dose; SOC, standard of care; UK; United Kingdom; USA, United States of America.

Baseline characteristics were comparable in both studies

Characteristic	MONARCH (n=62)	ADMIRAL (n=19)	All enrolled (N=81)
Age at screening, years			
Mean (SD)	10.1 (4.98)	9.3 (5.35)	9.9 (5.05)
Gender, n (%)			
Female	30 (48.4)	10 (52.6)	40 (49.4)
Male	32 (51.6)	9 (47.4)	41 (50.6)
Race*, n (%)			
White	52 (83.9)	19 (100)	71 (87.7)
Asian	5 (8.06)	0	5 (6.17)
Black/African American	5 (8.06)	0	5 (6.17)
***SCN1A* variant type, n (%)**			
Missense	29 (46.8)	8 (42.1)	37 (45.7)
Nonsense	33 (53.2)	11 (57.9)	44 (54.3)
Number of concomitant ASMs, n (%)			
≥3	55 (88.7)	14 (73.7)	69 (85.2)
≥4	36 (58.1)	8 (42.1)	44 (54.3)
Concomitant fenfluramine, n (%)			
Yes	31 (50.0)	9 (47.4)	40 (49.4)
Baseline convulsive seizure frequency per 28 days†			
Median (min, max)	16 (4, 630.0)	21.3 (4, 2335.4)	17 (4, 2335.4)

- Overall, 97 patients were screened, and **81 patients** were enrolled across both studies
- **More than 85%** of patients were taking 3 or more ASMs including clobazam, stiripentol and fenfluramine
- **About half of the patients** were taking fenfluramine as a part of their ASM regimen
- **Despite being on best available ASMs**, baseline median convulsive seizure frequency per 28 days was 17, highlighting the refractory nature of seizures

**Multiple selections for race were allowed to be entered. Four patients (4.9%) preferred to not report race. †Includes only patients that met the clinically evaluable study criteria for seizure analysis per statistical analysis plan. n=58, n=19, and N=77 for MONARCH, ADMIRAL, and all enrolled, respectively.*
ASM, antiseizure medications; SCN1A, sodium voltage-gated channel protein type 1 alpha subunit gene; SD, standard deviation.

Single and multiple doses of zorevunersen up to 70 mg were generally well tolerated

Safety

- **30%** of patients experienced a study drug-related TEAE
  - Most common - CSF protein elevations and procedural vomiting
- **22%** of patients experienced a TESAE
  - All were unrelated to study drug except for 1 patient with SUSARs

Summary of combined TEAEs in MONARCH and ADMIRAL

Event, n (%)	All enrolled N=81
Any TEAE	**78 (96.3)**
Any study drug-related TEAE	24 (29.6)
Any TESAE	**18 (22.2)**
Any study drug-related TESAE	1 (1.23)
Any ≥Grade 3 TEAE	**13 (16.0)**
DLT	**1 (1.23)**
Any TEAE related to study procedure	**43 (53.1)**
Any TEAE leading to study withdrawal	**0**
Any TEAE leading to death*	**1 (1.23)**

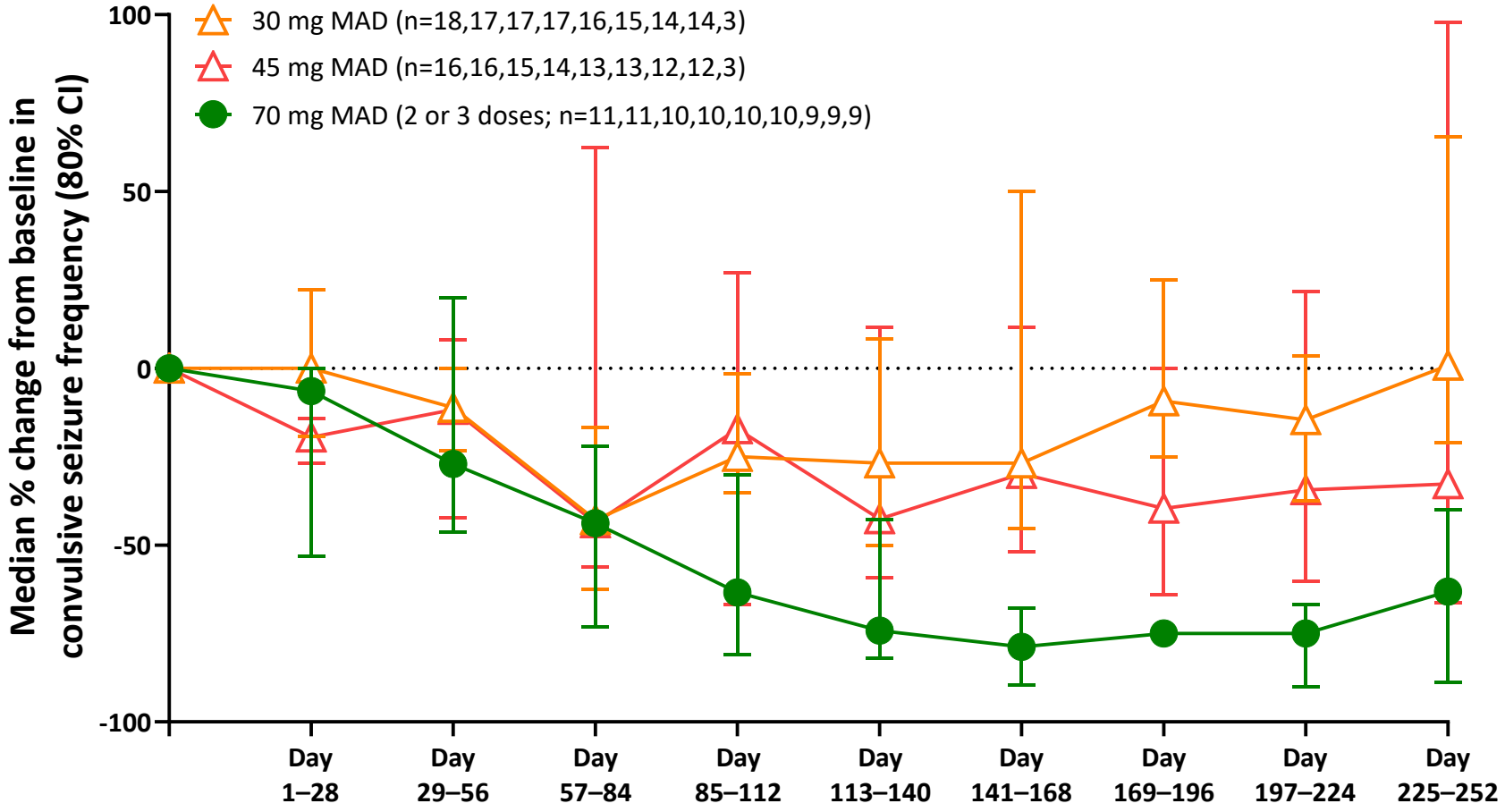
Pharmacokinetics

- **Drug distributes rapidly** in CNS tissues and to systemic circulation after intrathecal injection
- **Plasma drug exposure was dose-dependent** in patients treated with zorevunersen
- **Predicted drug exposure-seizure relationship showed a significant negative trend** demonstrating that higher zorevunersen brain exposure leads to higher reduction in seizure frequency

**1 fatal event of presumed SUDEP was not related to study drug.*
CNS, central nervous system; CSF, cerebrospinal fluid; DLT, dose-limiting toxicity; SUDEP, sudden unexpected death in epilepsy; SUSARs, suspected unexpected serious adverse reactions; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Zorevunersen substantially reduced seizure frequency

Greater reductions in convulsive seizure frequency were observed in the 70 mg MAD cohort

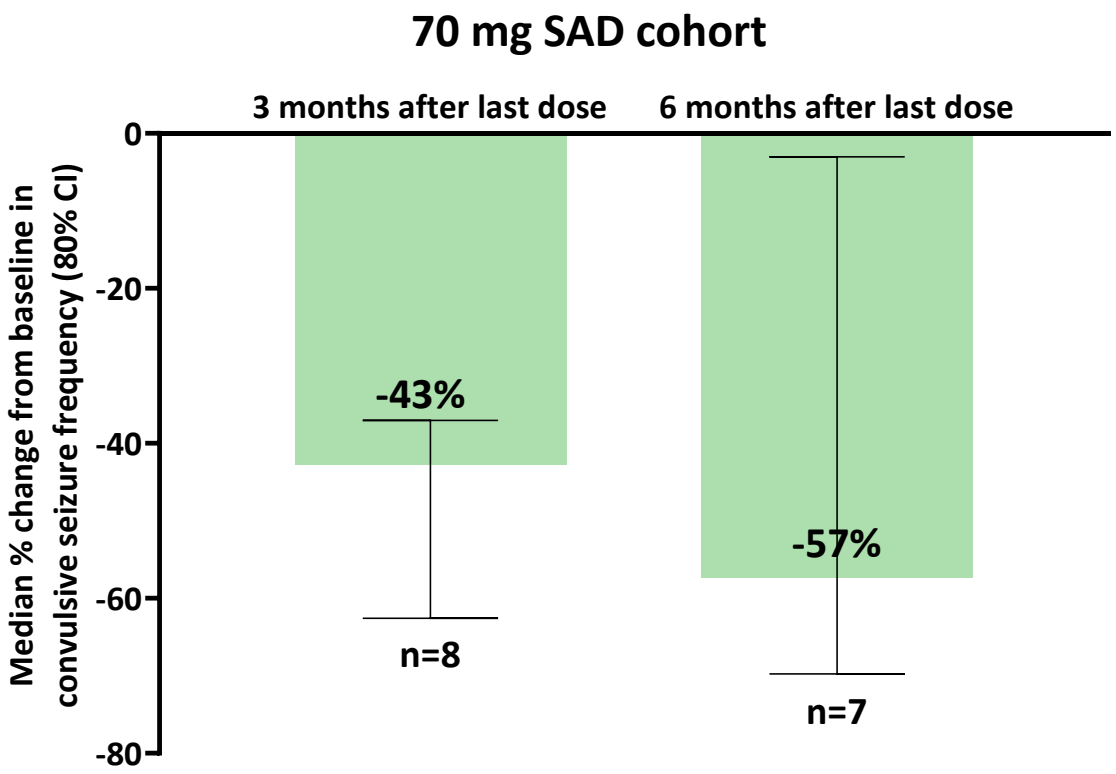


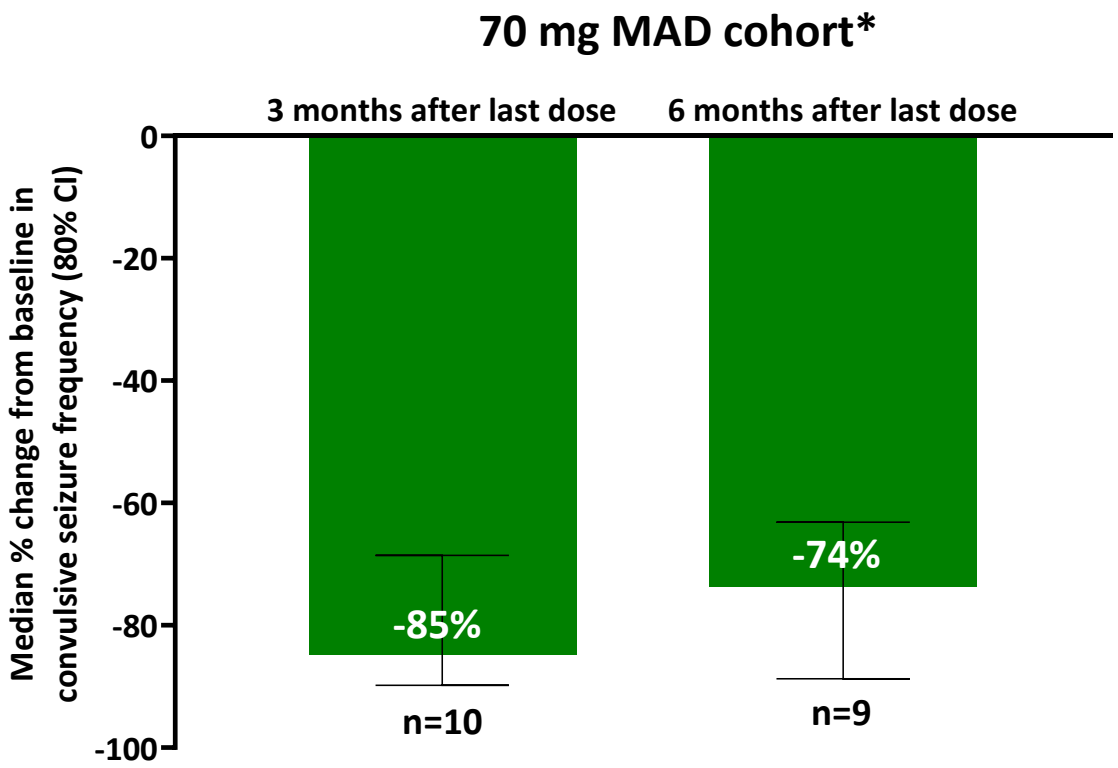
Zorevunersen was administered on Days 1, 29 and 57 in MONARCH, and on Days 1, 57 and 85 in ADMIRAL. Additionally, the MONARCH study ended at Day 224 and ADMIRAL ended at Day 252.

CI, confidence interval; MAD, multiple ascending dose; SOC, standard of care.

Substantial and sustained reductions in seizure frequency were observed with single or multiple doses of 70 mg zorevunersen

Reductions in seizure frequency were observed in patients for up to 6 months after the last 70 mg zorevunersen dose on top of SOC medications

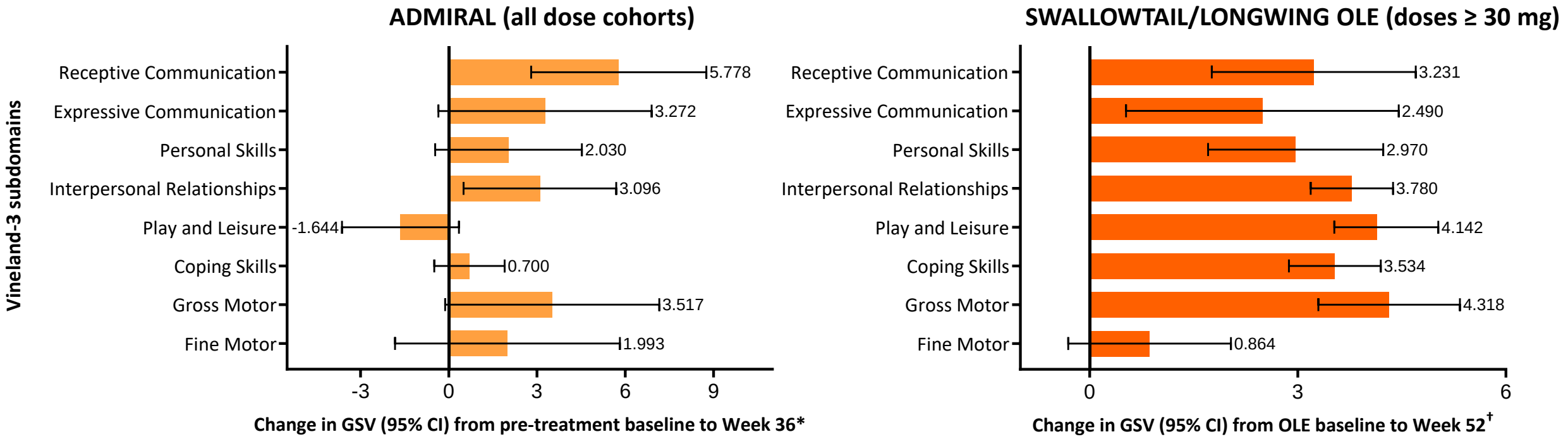




**70 mg MAD cohort data are from the UK ADMIRAL study.*
CI, confidence interval; MAD, multiple ascending dose; SAD, single ascending dose; SOC, standard of care; UK, United Kingdom.

Improvements in cognition and behavior were observed within the 1st year of treatment in the Phase 1/2 ADMIRAL study and continued with ongoing treatment in the OLEs

Improvements are in stark contrast to natural history data



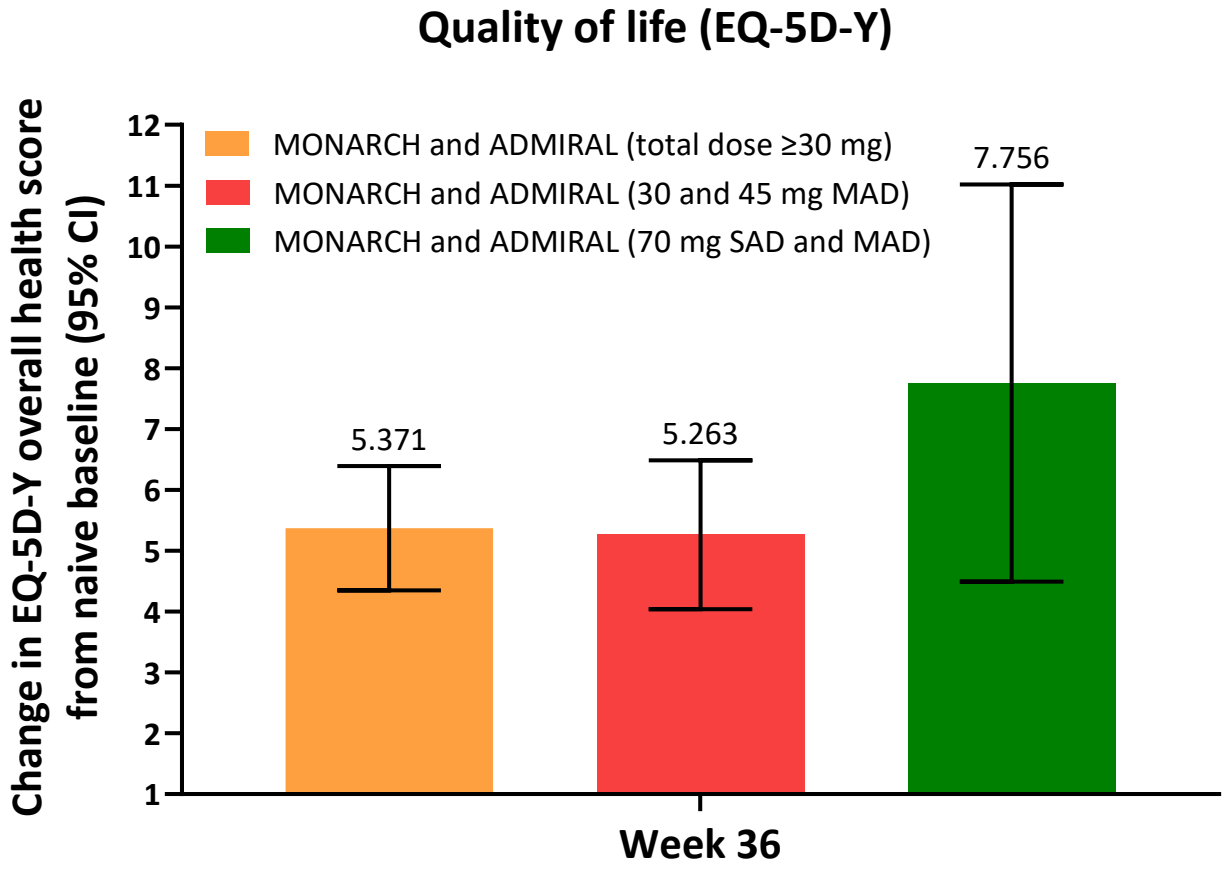
*Data cutoff December 12, 2023, for ADMIRAL and November 1, 2023, for SWALLOWTAIL/LONGWING. *Data from ADMIRAL (all dose cohorts – 30 mg, 45 mg, and 70 mg MAD) through Visit 2 (Week 16) in LONGWING from pre-treatment/naïve baseline analyzed with machine learning. ADMIRAL sample size: n=18 at screen and n=17 at Week 36.*

†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; Vineland-3, Vineland Adaptive Behavior Scale, Third Edition.

Data indicated improvements in overall clinical status and quality of life within 36 weeks after treatment with zorevunersen

Predicted rate of improvement was greater for patients treated with single and multiple doses of 70 mg zorevunersen



- Additionally, marked improvements in **overall clinical status** were observed by **caregivers** and **clinicians** on CaGI-C and CGI-C scales

Mixed-effects model for repeated measures with a first-order autoregressive covariance structure constructed with data from MONARCH and ADMIRAL through Visit 2 (Week 16) in SWALLOWTAIL and LONGWING from pre-treatment/naïve baseline. EQ-5D-Y sample size: n=64 at screen and n=43 at Week 32/Week 36. CaGI-C, caregiver global impression of change; CGI-C, clinical global impression of change; CI, confidence interval; EQ, EuroQol; EQ-5D-Y, EuroQol 5-dimension questionnaire youth; MAD, multiple ascending dose; SAD, single ascending dose; VAS, visual analogue scale.

Conclusions

- Results from MONARCH/ADMIRAL Phase 1/2a studies suggest the potential of zorevunersen as the **first disease-modifying medicine for Dravet syndrome**
- Zorevunersen resulted in **seizure reduction and improvements in cognition and behavior, overall clinical status, and quality of life**
- Treatment with single and multiple doses of up to 70 mg zorevunersen was generally **well-tolerated**
- Phase 1/2a data support a **potential 70 mg loading dose regimen** in a registrational study

SOC, standard of care.

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