Understanding Dravet Syndrome: The Unmet Need and Potential for Disease-Modification

Virtual Event for Investors & Analysts

December 9, 2024

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Agenda

TOPIC	PRESENTER
Introduction	**Edward M. Kaye, M.D.** Chief Executive Officer, Stoke Therapeutics
Natural History of Seizures and Developmental Deficits in Dravet Syndrome	**Joseph Sullivan, M.D., FAES** Professor of Neurology and Pediatrics and Director of the Pediatric Epilepsy Center of Excellence at the University of California San Francisco
Understanding Dravet Syndrome and its Impacts on Patients and Caregivers	**Veronica Hood, Ph.D.** Scientific Director, Dravet Syndrome Foundation **Mary Anne Meskis** Executive Director, Dravet Syndrome Foundation
Potential for Disease Modification in Dravet Syndrome	**Andreas Brunklaus, M.D.** Consultant Paediatric Neurologist, Royal Hospital for Children, Glasgow, UK; Honorary Professor, University of Glasgow, UK; Member of Dravet Syndrome UK's Medical Advisory Board
Q&A	**Barry Ticho, M.D., Ph.D., FACC** Chief Medical Officer, Stoke Therapeutics **Tommy Leggett** Chief Financial Officer, Stoke Therapeutics

OUR GOAL:

Restore protein expression by harnessing the body's potential with RNA medicine

Stoke's pipeline offers potential first-in-class disease modifying new medicines for diseases caused by protein insufficiency

Zorevunersen (STK-001) for Dravet syndrome

A severe genetic developmental epileptic encephalopathy

STK-002 for Autosomal Dominant Optic Atrophy (ADOA)

The most common inherited optic nerve disorder

Rett syndrome, SYNGAP1

Severe and rare genetic neurodevelopmental diseases

And beyond…

~6,500 additional genes with TANGO target signatures

Natural History of Seizures and Developmental Deficits in Dravet Syndrome

Joseph Sullivan, M.D.

Professor of Neurology and Pediatrics and Director of the Pediatric Epilepsy Center of Excellence at the University of California San Francisco

Dravet Syndrome: A Genetic Developmental & Epileptic Encephalopathy

85%
of cases caused by a **HAPLOINSUFFICIENCY** of the *SCN1A* gene

RESULTING in

50%
$Na_V1.1$ protein expression

1 out of 16,000
babies are born with Dravet syndrome

Up to 20%
of children and adolescents with Dravet syndrome die before adulthood, due to SUDEP[1], prolonged seizures, seizure-related accidents or infections

Seizures are not adequately controlled in **90%** of people with Dravet syndrome

~35,000
people affected in the U.S., Canada, Japan, Germany, France and the UK

Dravet syndrome is not concentrated in a particular geographic area or ethnic group

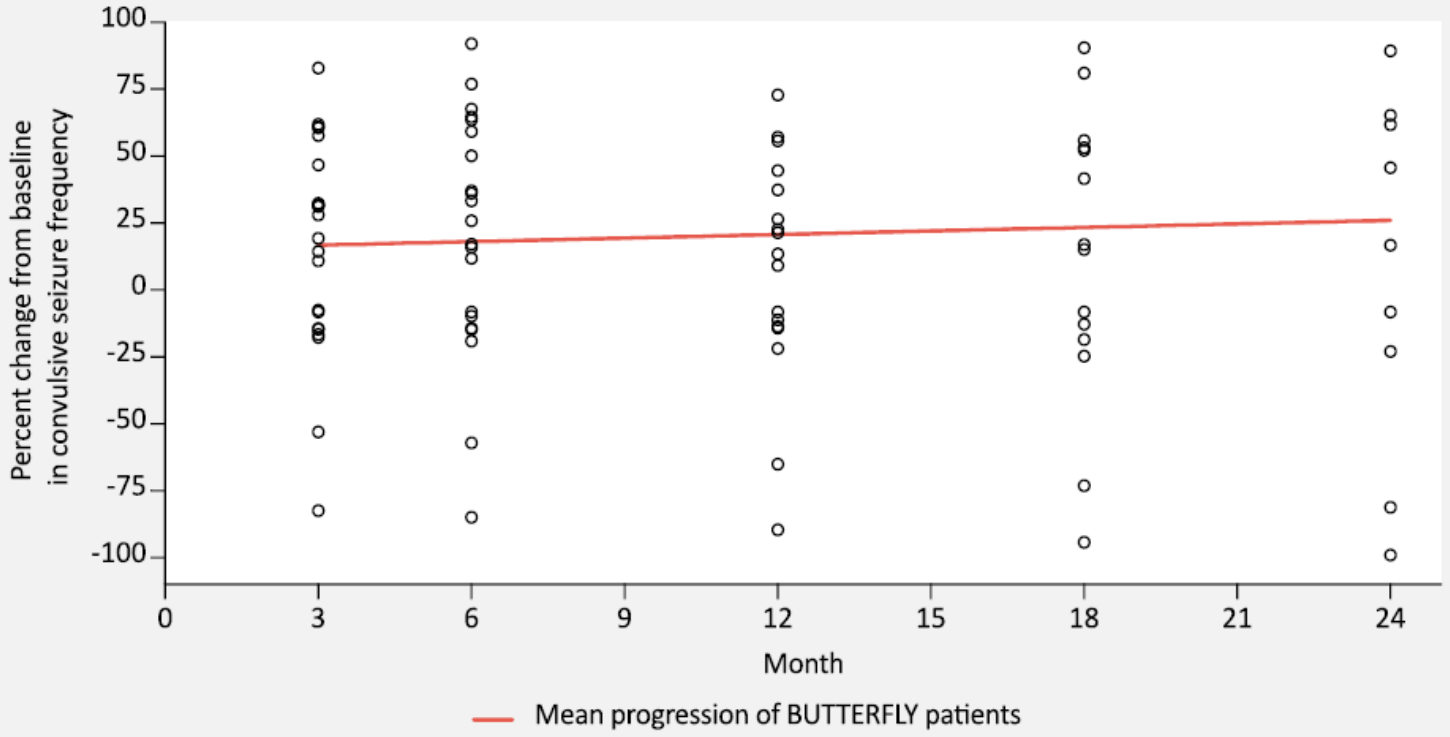
[1] Sudden Unexpected Death in Epilepsy

Sources: Symonds, J. et al., *Early childhood epilepsies: epidemiology, classification, aetiology, and socio-economic determinants. Brain,* 2021. *2018 Health Advances Report*; Djémié et al., *Molecular Genetics & Genomic Medicine,* 2016; Lagae et al., *Developmental Medicine & Child Neurology,* 2017; Wu, Y. et al., *Incidence of Dravet Syndrome in a US Population. Pediatrics,* 2015. Nabbout et al., *Orphanet Journal of Rare Diseases,* 2013

Natural History Data Show No Meaningful Improvement in Convulsive Seizure Frequency Despite Use of Standard Anti-Seizure Medicines

2-year observational data from the BUTTERFLY study of 2-18 year olds with Dravet syndrome

Change in Convulsive Seizure Frequency



Patients experienced a mean of **14.3 seizures** per 28 days despite receiving a mean of **3.5 ASMs** at baseline

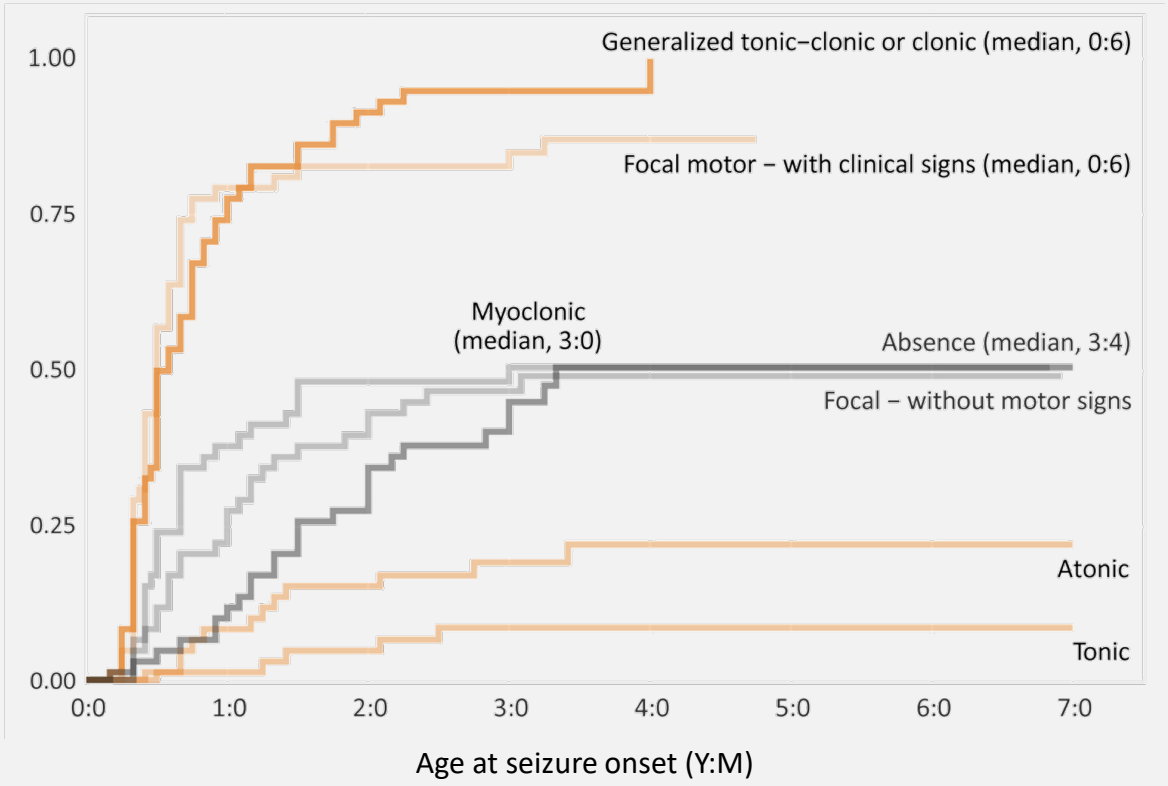
Most common ongoing anti-seizure medicines, n (%)	
Clobazam	25 (69.4%)
Fenfluramine	16 (44.4%)
Stiripentol	14 (38.9%)
Valproic Acid	14 (38.9%)
Cannabidiol	12 (33.3%)
Levetiracetam	8 (22.2%)

24-Month Analysis of BUTTERFLY: A Prospective, Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS), AES 2023

Seizure Frequency Increases with Age in Patients with DS <5 Years-old and Remains High Despite Use of Currently Available Anti-seizure Medicines

12-month observational data from the ENVISION natural history study

Seizure onset age by seizure type



Median of 3 ASMs at baseline

Patients with DS (N=58) aged 6 months to 5 years with a pathogenic or likely pathogenic SCN1A variant were enrolled. Median age (years:months) of seizure onset (for each seizure type) is displayed when 50% of participants experience onset. ASM, antiseizure medication; DS, Dravet syndrome; MCSF, monthly countable seizure frequency; SCN1A, sodium voltage-gated channel type 1 subunit alpha gene; Y:M, years:months. Perry MS et al. Epilepsia 2024; 65 (2): 322–337.

The Symptoms of Dravet Syndrome Extend Beyond Seizures[1]

- **Learning impairments**
- **Speech/communication impairments**
- **Appetite/eating disturbances**
- **Behavioral difficulties**
- **Sleep disturbances**
- **ASD and ADHD**
- **Motor impairments**
- **Psychiatric problems** (e.g. anxiety, psychosis)

Cognitive and behavioral impairments often have **early onset** from 2 years of age[2]

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; DS, Dravet syndrome.

1. Strzelczyk A, et al. Epilepsia Open 2023; 8 (4): 1256–1270. 2. Makiello P, et al. Epilepsia 2023; 64 (4): 1012–1020.

Cognitive Function Declines Compared to Peers as Patients with Dravet Syndrome Age

Change in developmental score over 10 years of follow-up in 61 patients with DS

Worsening impairment is observed in the **first 5 years of life**

Cognitive impairment in the initial study was assessed by clinicians using a Likert scale (where 1 = average; 2 = mild impairment; 3 = moderate impairment; 4 = severe impairment; and 5 = profound impairment). Developmental outcomes at follow-up were assessed by caregivers using a GAC score (where 80–100 = average range; 70–80 = mild; 60–70 = moderate; 50–60 = severe: and <60 = profound). DS, Dravet syndrome; GAC, General Adaptive Composite.

Feng T, *et al*. *Brain Commun* 2024; 6 (1): fcae004.

Vineland-3 Adaptive Behavior Scale Overview

Vineland-3 is commonly used to assess behavioral outcomes in Dravet syndrome

Domains	Subdomains (with examples)
Communication	• **Receptive** (Responds upon hearing name called) • **Expressive** (Says “Dada”, “Mama”, or caregiver name) • **Written** (Writes alphabet letters using correct orientation)
Motor Skills	• **Gross Motor** (Moves, scoots, or crawls across the floor) • **Fine Motor** (Picks up small objects with thumb and fingers)
Socialization	• **Interpersonal Relationships** (Tries to interact with others) • **Play and Leisure** (Responds when parent/caregiver is playful) • **Coping Skills** (Transitions easily from one activity to another)
Daily Living Skills	• **Personal** (Cooperates in dressing and undressing) • **Domestic** (Puts away books, toys, etc. when done) • **Community** (Talks with a familiar person using a phone)

How meaningful is a 2-point change (Never to Usually on Vineland-3)?

- Uses at least 3 basic gestures (for example, head nod for yes, head shake for no, reaching or pointing toward something desired, waving, clapping)
- Says at least 50 words (Described as a “Life-changing” impact by the caregiver)

- **Gross Motor**
  Walks 2 or more blocks without having to rest or needing physical support
- **Fine Motor**
  Pours liquid from one container to another with little or no spilling

Natural History Data: Despite Standard Anti-Seizure Medicines, Substantial Neurodevelopmental Gap Widens over Time

Regression analysis of adaptive behavior composite score for all Vineland-3 domains

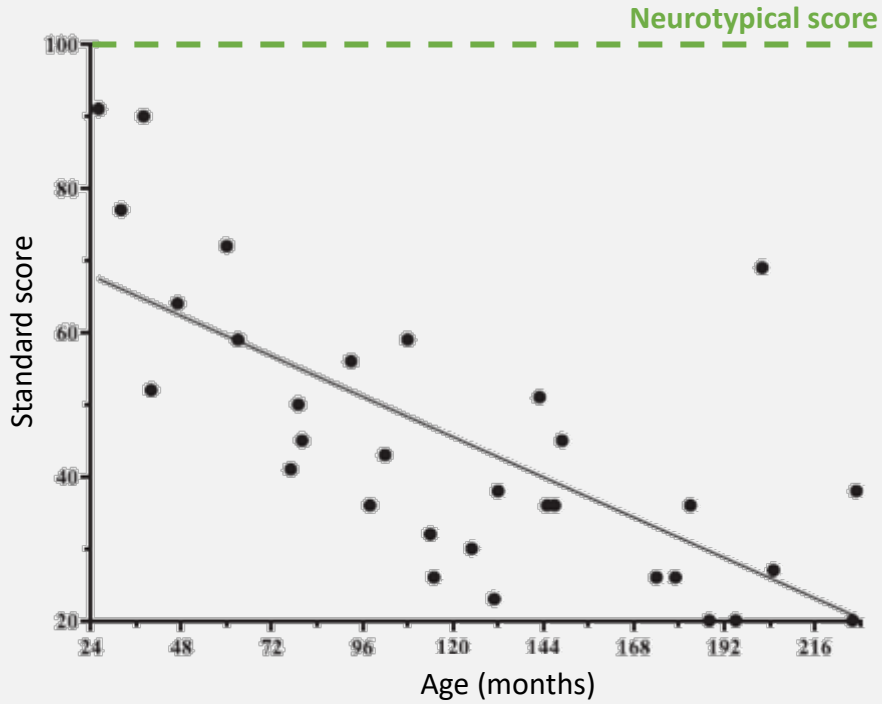


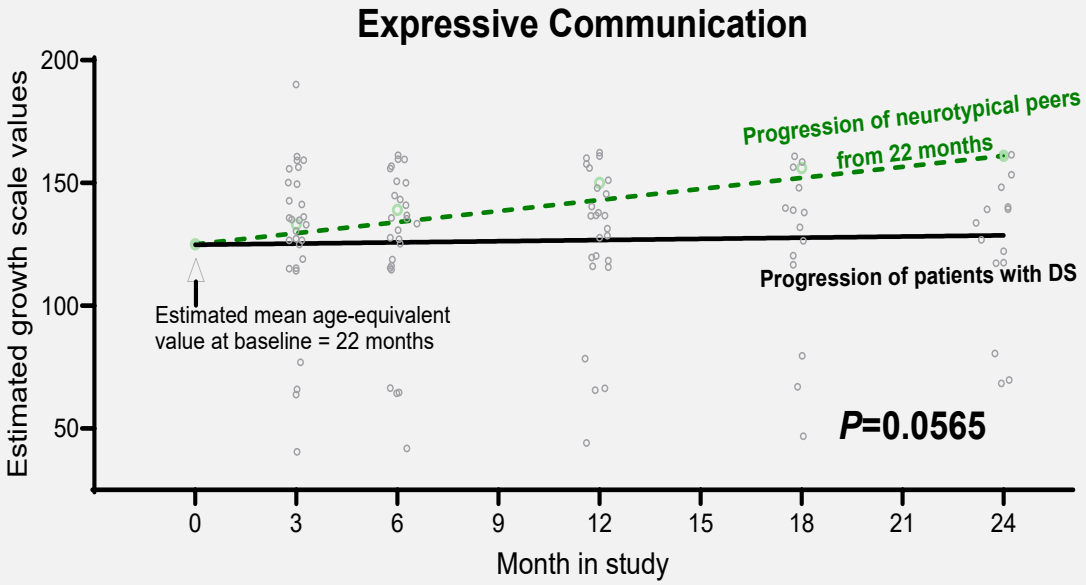
Fig. 1. Regression analysis of adaptive behavior composite score for individual patients with all VABS-III domains completed at baseline (n = 33/36). Regression analysis statistics: F(1,31) = 29.76; p ≤ 0.00001; r2 = 0.4898. The patients with scores of 91 and 90 were 2 years and 2 months and 3 years and 2 months old, respectively, at screening. The adaptive behavior composite score only includes the motor component for patients aged 2 years to 9 years and 11 months. The neurotypical score is 100 ± 15 SD. (Sullivan et al., 2022). VABS-III, Vineland Adaptive Behavior Scales – third edition. Sullivan J, Wirrell E, Knupp KG, et al. Epilepsy Behav 2022;137(Pt A):108955.

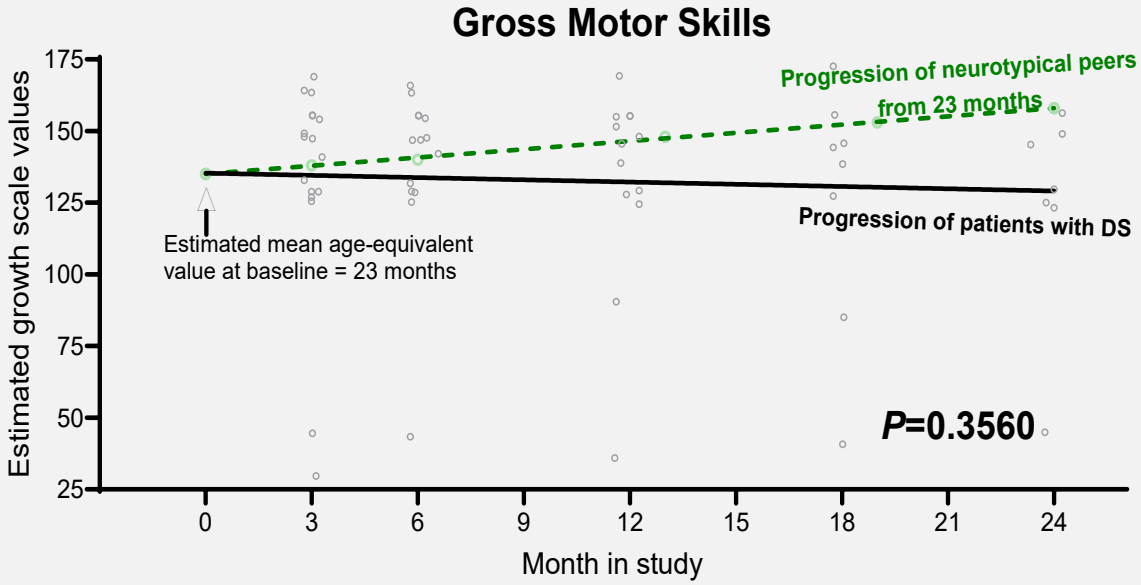
Adaptive Functioning and Neurodevelopment Plateau in Patients with Dravet syndrome [1–3]

Overall, adaptive functioning and neurodevelopment in patients with Dravet syndrome generally plateaued **with a widening developmental gap over time compared to neurotypical peers**

Vineland-3: Adaptive behavior in the Communication, Motor Skills, Socialization and Daily Living Skills domains

Disease progression modeling indicated no improvements in Expressive Communication, Personal Skills, Gross Motor, or Fine Motor through Month 24





DS, Dravet syndrome; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.

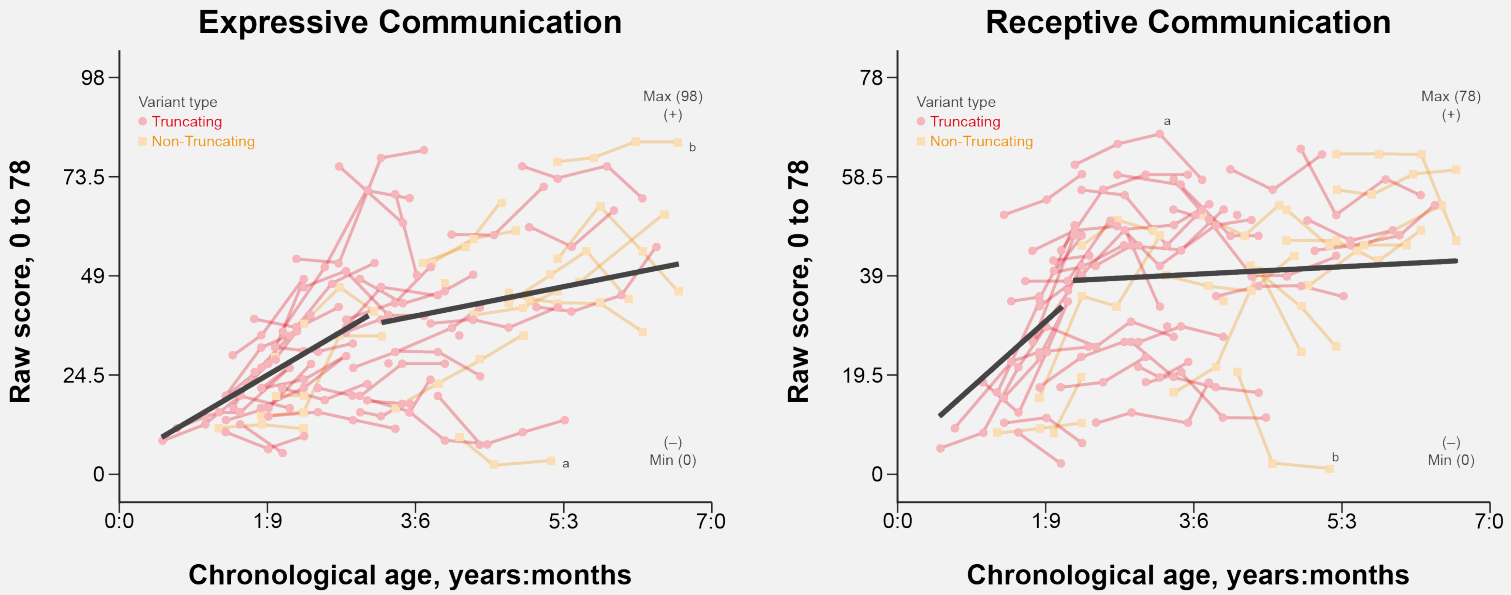
1. Sullivan J et al. Poster P788 Presented at EEC 2024; Rome, Italy, 7–11 September 2024. 2. Sullivan J, Wirrell E, Knupp KG, et al. Epilepsy Behav 2024;151:109604; 3. Sullivan J, Wirrell E, Knupp KG, et al. Epilepsy Behav 2022;137(Pt A):108955.

Language/Communication Delays are Independent of Seizure Burden and Persisted Despite use of Currently Available Anti-seizure Medicines

Observational data from the ENVISION natural history study

Gains in language/communication skills slowed or halted after 2 years of age

Trajectories for Vineland-3 subdomains



Median of 3 ASMs at baseline

[a]The lowest recorded score was 3 on a scale of 0 (minimum) to 98 (maximum) in a child at age 4:5 Y:M. [b]The highest score was 83 in a child at age 6:1 Y:M.
Pts, points; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition.
Perry MS, *et al*. *Epilepsia* 2024; 65 (2): 322–337.

Key Takeaways

Patients with Dravet sydrome experience a **wide range of symptoms in addition to seizures**, including learning impairments, behavioral difficulties, and speech/communication impairments[1]

Non-seizure symptoms typically have **early onset** and the developmental gap compared to neurotypical peers **widens over time**[2,3]

Non-seizure symptoms of DS highlight the **clinical need** for **disease-modifying therapies** that extend beyond seizure reduction

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; DS, Dravet syndrome.

1. Strzelczyk A, et al. Epilepsia Open 2023; 8 (4): 1256–1270. 2. Makiello P, et al. Epilepsia 2023; 64 (4): 1012–1020. 3. Feng T, et al. Brain Commun 2024; 6 (1): fcae004.

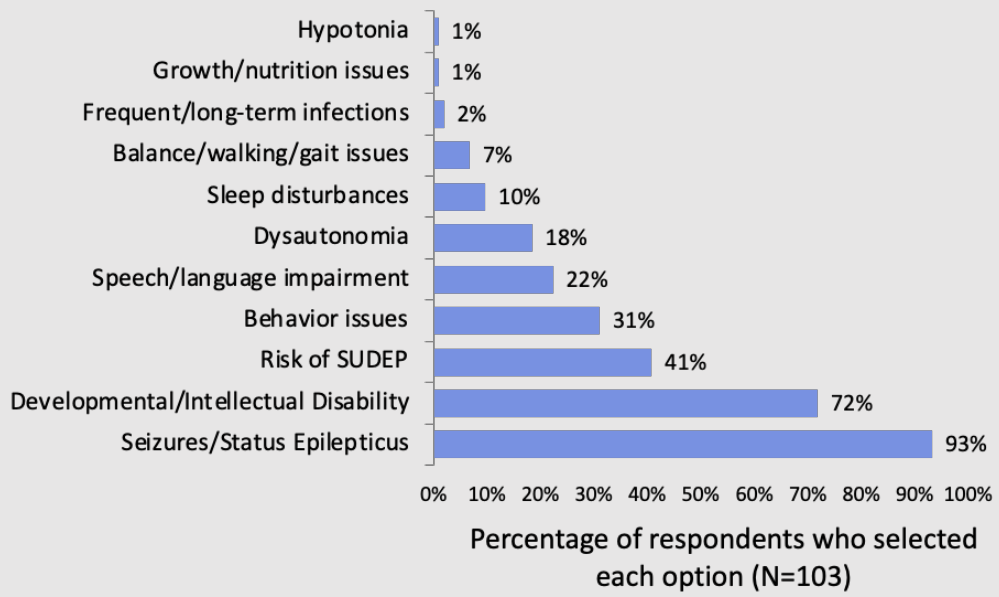
Understanding Dravet Syndrome and its Impacts on Patients and Caregivers

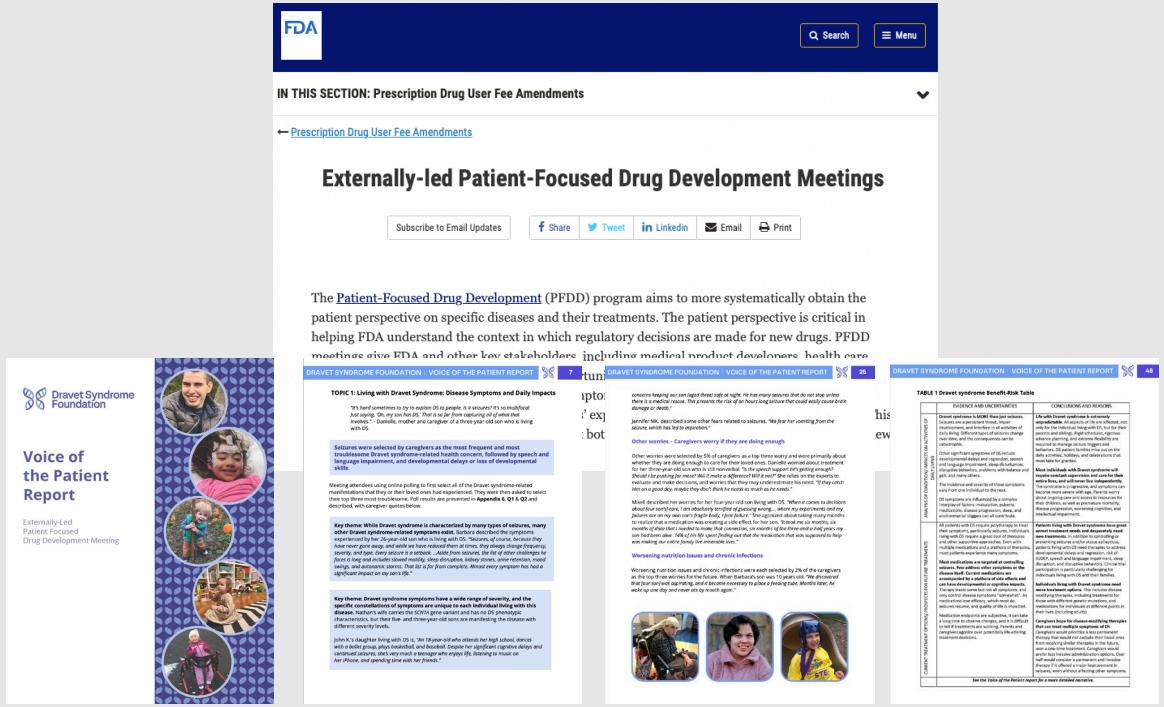
Veronica Hood, PhD, Scientific Director

Mary Anne Meskis, Executive Director

Dravet Syndrome Foundation

Treating Symptoms of DS: Caregiver Priorities Go Beyond Seizures





- Establishing treatment benefit for non-seizure outcomes in DS is challenging due to a paucity of DS-specific assessments
- While statistical methods to understand statistically meaningful changes in endpoints is very important, it is also clear that we need to know what change is meaningful to patients and families and this should help guide endpoint development
  - This view is outlined in the FDA Patient Focused Drug Development (PFDD) Guidance series

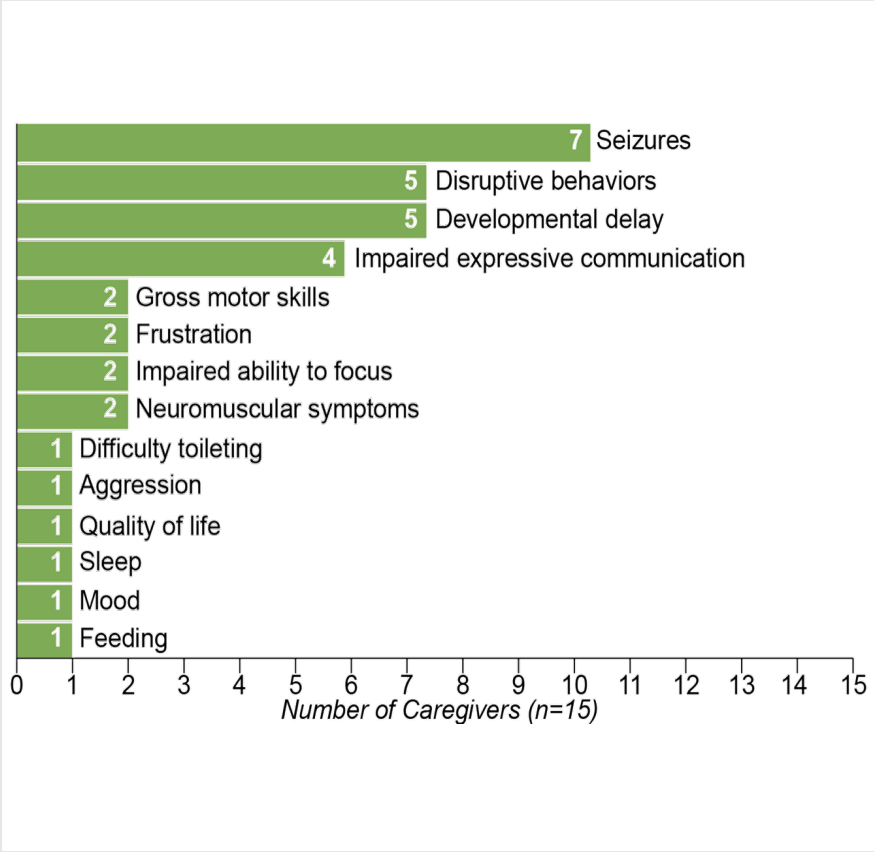
Assessing *Meaningful* Change

The Vineland Adaptive Behavior Scales-Third Edition (Vineland-3) is a clinician-administered, standardized assessment commonly used to assess behavioral outcomes in DS; however, meaningful change thresholds have not yet been established

- Caregivers ranked the Expressive and Receptive Communication subdomains as most important to change with treatment
- **Changes of 2–3 points in growth scale values** across subdomains were considered meaningful to at least 50% of caregivers

2 A 2-point growth scale value change in Expressive Communication (7/14), Gross Motor Skills (6/12), Interpersonal Relationships (9/14) and Coping Skills (8/13)

3 A 3-point growth scale value change in Receptive Communication (10/16), Fine Motor Skills (8/11), Play and Leisure (9/15) and Personal (6/11)



Footnotes: Calibri Regular italic 10pts (#7F7F7F)

Real-World Reflection on Meaningful Change

In developmental epilepsies where quality of life is so severely impacted, small impacts on domains outside of seizures actually have incredibly large impacts on day-to-day life

"The **biggest obstacle** she and the rest of family must overcome mostly involve **behavior and cognition** on a daily basis. Some are simple but can be exhausting to manage as time goes on." Her daughter requires a long time to formulate responses, does not accept assistance, and reacts poorly to sudden changes. "She will often **completely shut down**. ... She'll refuse to move and refuse to listen."

– Peiyi, Caregiver to 18-year old female with DS

"**Slowed mobility** impacts my son's ability to participate freely in activities and impacts how he feels day to day."

– Barbara, caregiver to 26-year old male with DS

"Because he is **unable to communicate verbally**, he uses rough physical interactions to communicate his needs. "[He gets] physical. He'll push me, he'll pull me." She expressed **worry over him injuring himself or her**

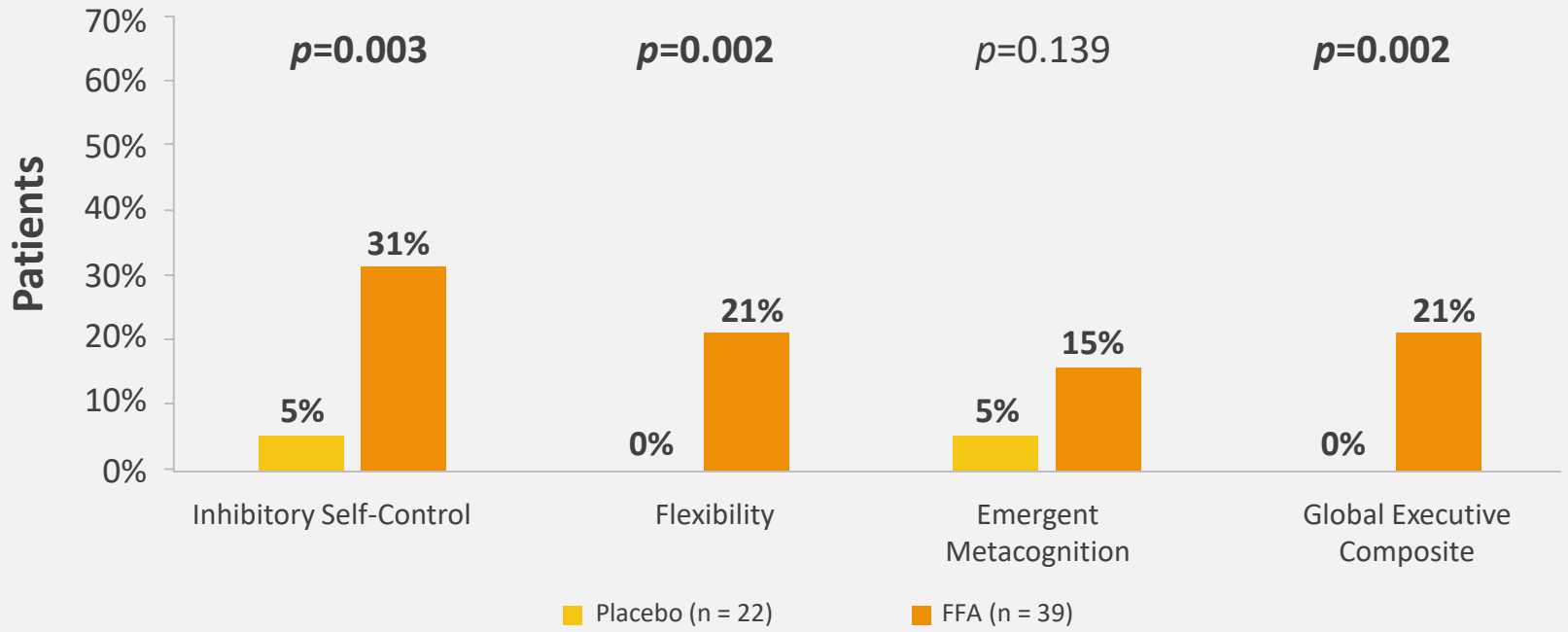
– Mandee, caregiver to 12-year old male with DS

Potential for Disease Modification in Dravet Syndrome

Andreas Brunklaus, M.D.
Consultant Paediatric Neurologist, Royal Hospital for Children, Glasgow, UK; Honorary Professor, University of Glasgow, UK;
Member of Dravet Syndrome UK's Medical Advisory Board

Post-hoc Analysis of Patients Treated with Fenfluramine Support Improvement in Non-seizure Outcomes, but the Neurodevelopmental Gap Observed in Natural History Studies Remains

Treatment with fenfluramine showed improvements in everyday Executive Function in children with Dravet syndrome



Percentage of preschool children with DS showing reliable, clinically meaningful improvement (RCI ≥ 90% certainty) in BRIEF®-P indexes/composite T-scores

Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: A critical period for early neurodevelopment. Bishop, Kim I. et al. Epilepsy & Behavior, Volume 138, 108994

Treatment Landscape for Dravet Syndrome is Moving Beyond Seizure Management to Address Unmet Needs

Multiple medicines[1] available for Seizure management

Bromide	Cannabinoid
Clobazam	Diazepam
Fenfluramine	Levetiracetam
Stiripentol	Topiramate
Valproate	Zonisamide

Currently no medicines available for Syndrome management

ASM, antiseizure medication; DS, Dravet syndrome; SOC, standard of care.

1. Lagae L, *et al. Dev Med Child Neurol 2018;* 60 (1): 63–72. Appendix S4. 2. Lagae L, *et al. Dev Med Child Neurol 2018;* 60 (1): 63–72.

Two Potential Disease-Modifying Therapies are Currently in Clinical Development for the Treatment of Dravet Syndrome

ETX101

- rAAV9 vector-delivered **gene regulation** therapy
- Designed to increase *SCN1A* expression through the delivery of an engineered transcription factor that regulates *SCN1A*
- Phase 1/2 ongoing

Zorevunersen

- **Antisense oligonucleotide** (ASO) therapy
- Designed to upregulate voltage-gated sodium channel $Na_V1.1$ by leveraging the wild-type copy of *SCN1A* to restore $Na_V1.1$ to physiological levels
- Phase 1/2a complete; OLEs ongoing; Phase 3 in planning

ETX101 and zorevunersen (STK-001) are in development and have not been approved by regulatory authorities for use.
ClinicalTrials.gov: NCT05419492. Available at: https://clinicaltrials.gov/study/NCT05419492.
ClinicalTrials.gov: NCT04442295. Available at: https://clinicaltrials.gov/study/NCT04442295.
ClinicalTrials.gov: NCT04740476. Available at: https://clinicaltrials.gov/study/NCT04740476. All websites accessed November 2024.

Parallel Phase 1/2a and OLE Studies of Zorevunersen Conducted in the US and UK for Patients with Dravet Syndrome Ages 2-18 Years Old

Patients were treated with zorevunersen on top of their existing anti-seizure drug regimen

	monarch	admiral
Design	Study location: US SAD: Up to 70 mg per dose* MAD: Up to 45 mg per dose*	Study location: UK MAD: Up to 70 mg per dose*
Enrollment	62 patients dosed	19 patients dosed
Primary endpoints	Safety and tolerability of single and multiple doses Characterize human PK and CSF drug exposure	
Secondary endpoints	Change in convulsive seizure frequency, overall clinical status, and QoL	
OLE studies	swallowtail Dosing ongoing in US 45 mg per dose every 4 months	Longwing Dosing ongoing in UK 45 mg per dose every 4 months

81 patients treated

Age at screening, years	
Median (range)	10.0 (2, 18)
Number of concomitant ASMs, n(%)	
≥3	69 (85.2%)
≥4	44 (54.3%)
Concomitant fenfluramine, n (%)	
Yes	40 (49.4%)
Baseline convulsive seizure frequency per 28 days (n=77†)	
Median (range)	17 (4.0, 2335.4)

Zorevunersen Generally Well-Tolerated in Studies to Date

Phase 1/2a studies (n=81)

- **30%** of patients experienced a study drug-related TEAE
  - Most common — CSF protein elevations (13.6%) and procedural vomiting (4.9%)
- **22%** of patients experienced a TESAE
  - All were unrelated to study drug except for 1 patient with SUSARs

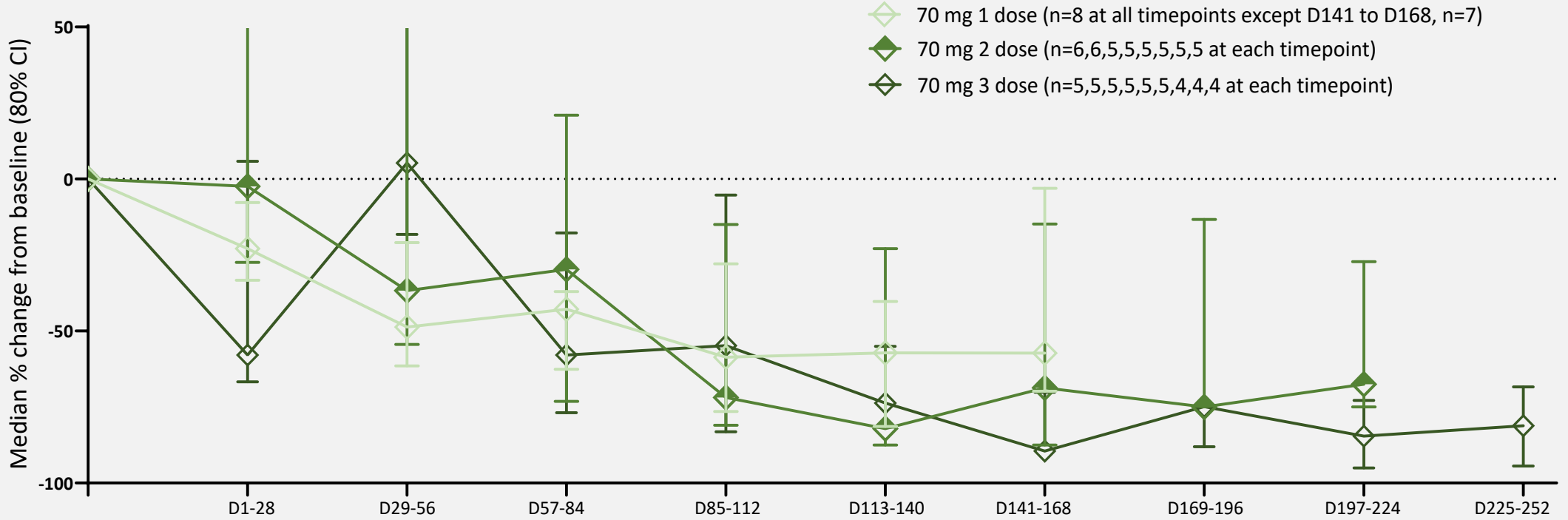
OLE studies (n=74)

- **79%** of patients had CSF protein elevations*
  - No clinical manifestations were observed in patients with elevated CSF protein
  - 1 patient discontinued treatment due to elevated CSF protein

Data cutoff was December 12, 2023, for MONARCH/ADMIRAL and June 28, 2024, for SWALLOWTAIL/LONGWING.
** >1 CSF protein value >50 mg/dL. Percentage based on 71/74 patients who had ≥1 post-baseline CSF protein value in Swallowtail or Longwing*
CSF, cerebrospinal fluid; OLE, open-label extension; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Ph1/2a Results: Initial 70mg Doses of Zorevunersen Demonstrated Substantial and Sustained Reductions in Convulsive Seizure Frequency

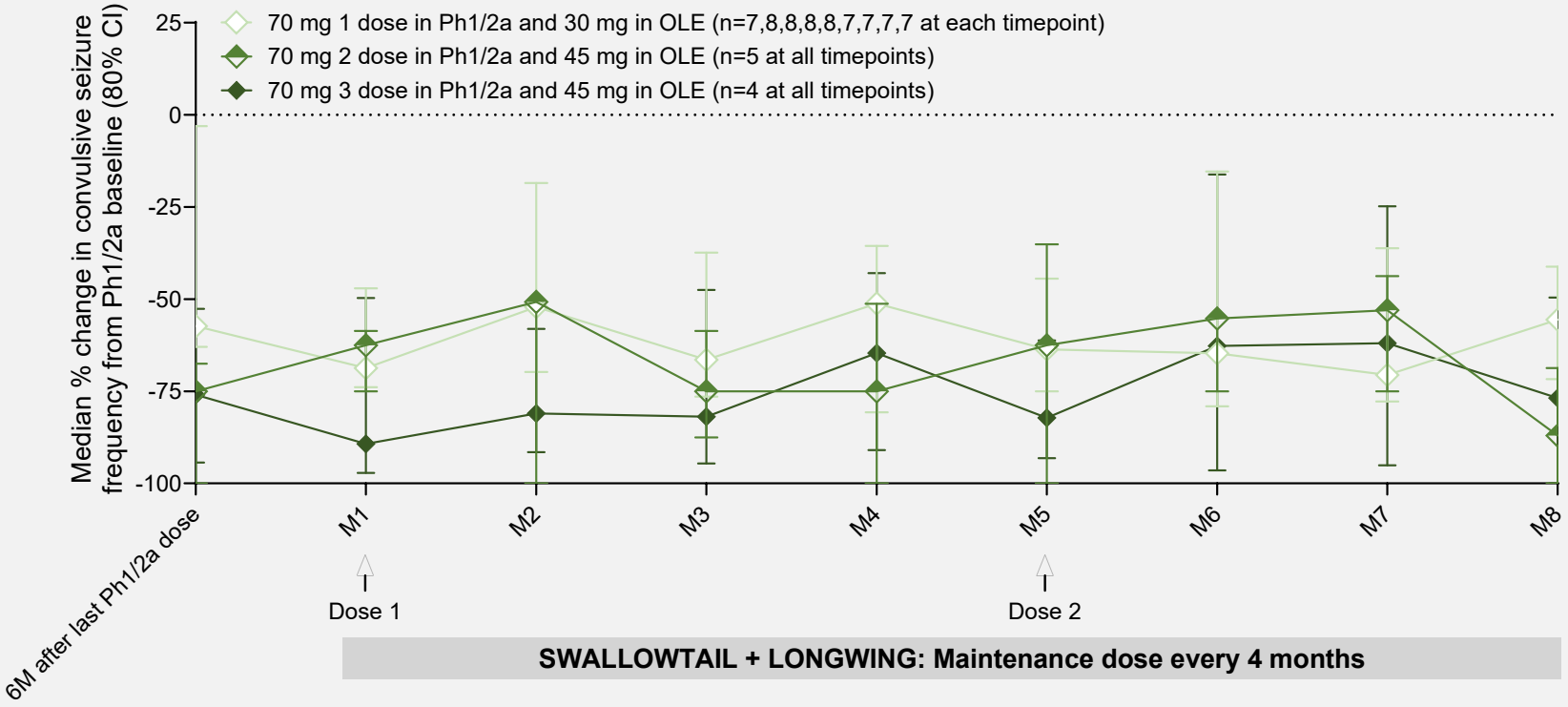
Median percent change in convulsive seizure frequency from baseline in Phase 1/2a studies



Phase 1/2 datacut: December,12 2023 (after End of Study).
Zorevunersen was administered on Days 1, 29 and 57 in MONARCH, and on Days 1, 57 and 85 in ADMIRAL. MONARCH study ended at Day 225 and ADMIRAL ended at Day 253. Patients were followed for 6 months after last dose of study drug. 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 1 patient in 70 mg 1 dose) and at time of ASM modification (1 patient in 70 mg 2 dose and 1 patient in 70 mg 3 dose).
ASM, antiseizure medication; CI, confidence interval; D, day.

OLE Results: Substantial and Durable Reductions in Convulsive Seizure Frequency Observed Among Patients Treated with Initial Doses of 70mg Followed by Maintenance Dosing in the OLEs

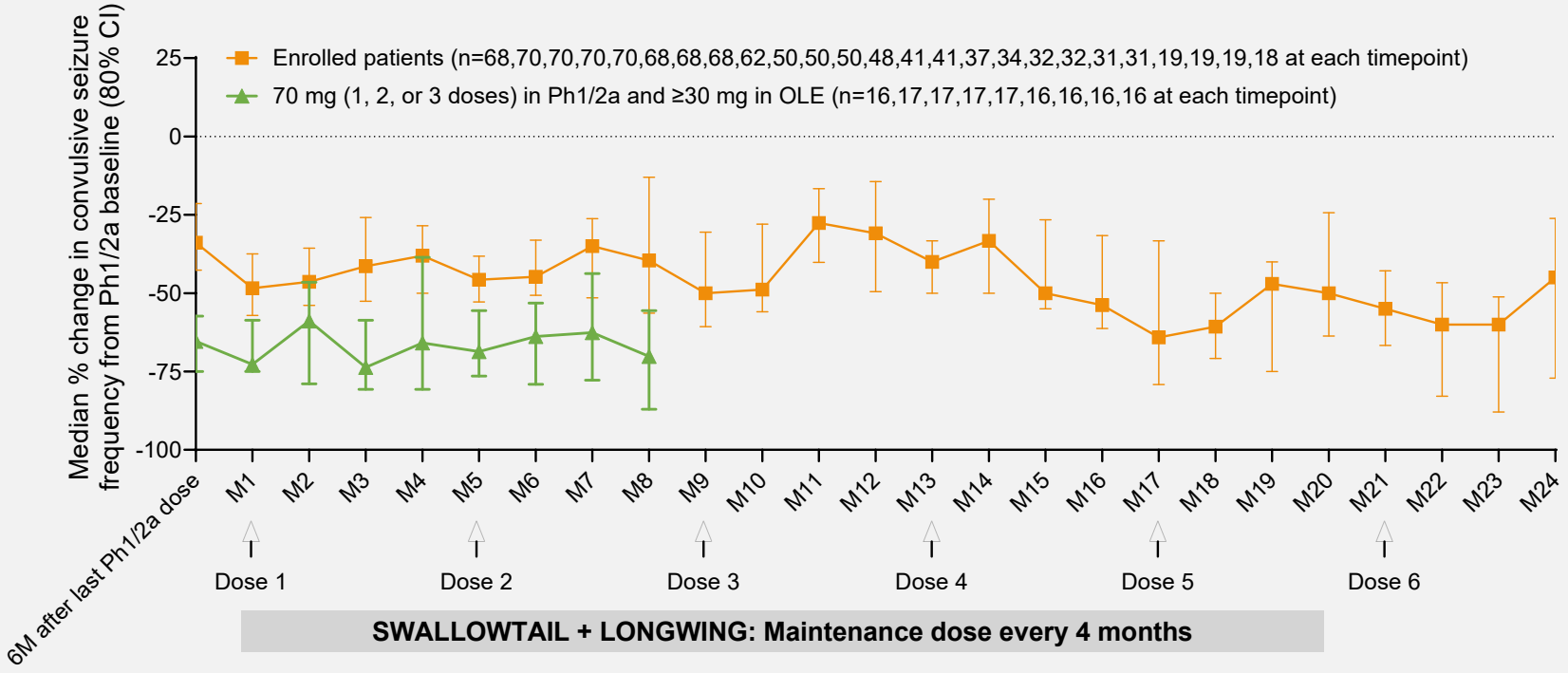
Median percent change in convulsive seizure frequency from Phase 1/2a baseline in the OLEs



Phase 1/2 datacut: December 12, 2023 (after End of Study); OLE datacut: 28 June 2024.
As of the data cut in the OLE, 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. No exclusion for ASM modification. Ph1/2a data excludes patients who did not enter the OLE.
ASM, antiseizure medication; CI, confidence interval; M, month; MAD, multiple ascending dose; OLE, open-label extension; Ph1/2a, Phase 1/2a; SAD, single ascending dose.

OLE Results: Substantial and Durable Reductions in Seizure Frequency Observed with Continued Treatment with Zorevunersen Through 2 Years

The most substantial effects were observed among patients treated with initial doses of 70mg followed by 45mg maintenance dosing in OLE

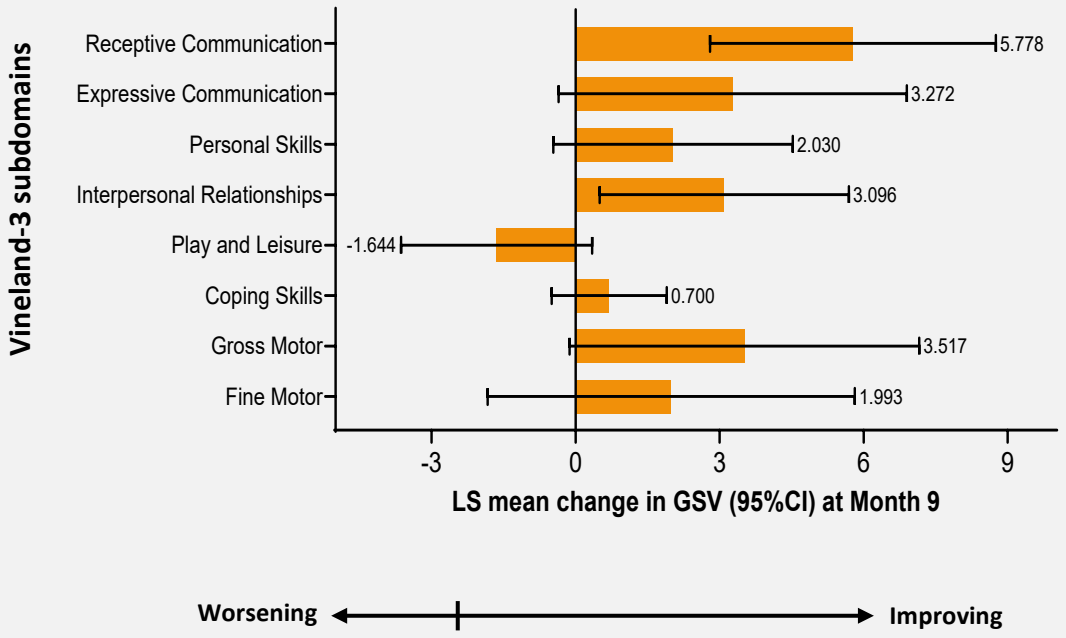


No exclusion for ASM modification. Ph1/2a data excludes patients who did not enter the OLE studies.
Ph1/2a data cut: December 12, 2023 (after End of Study); OLE data cut: June 28, 2024.
ASM, antiseizure medication; CI, confidence interval; M, month; OLE, open-label extension; Ph1/2a, Phase 1/2a

Patients Experienced Improvements in Cognition and Behavior Early in Treatment with Continuous Improvements in the OLE

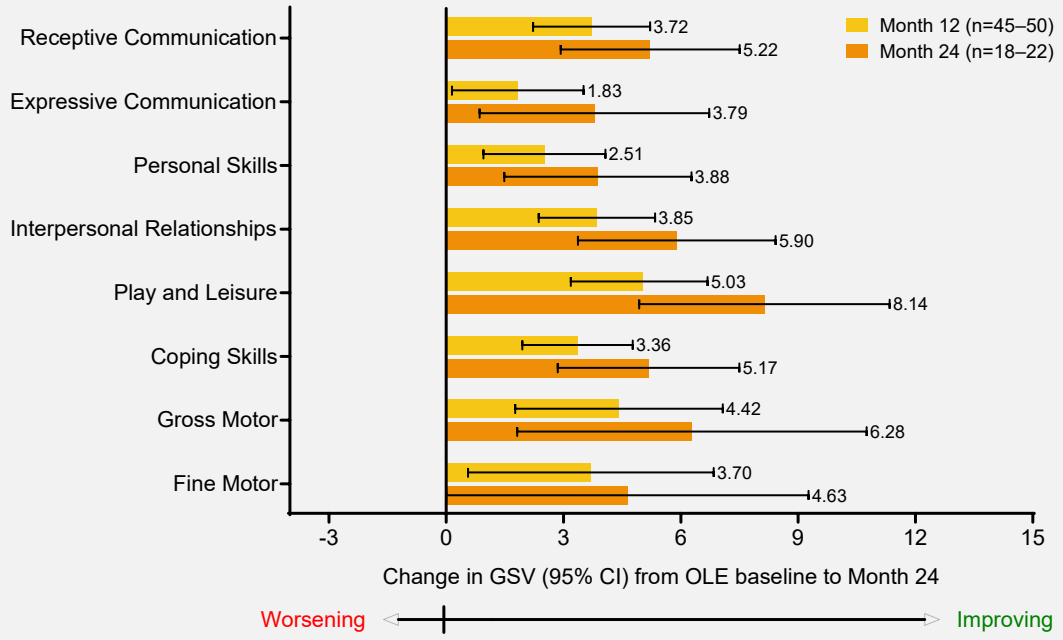
Phase 1/2a ADMIRAL Study

Improvement in adaptive behavior ~9 months after starting treatment with zorevunersen[1]



Open-Label Extension Studies SWALLOWTAIL & LONGWING

Continuous improvements in Vineland-3 subdomain growth scale values from OLE baseline[2]



1 Data from ADMIRAL (All Dose Cohorts) through Visit 2 (Month 4) in LONGWING from pre-treatment/naïve baseline analyzed with Machine Learning. ADMIRAL sample size: n=18 at screen and n=17 at Month 9. Data cutoff was December 12, 2023 for ADMIRAL.

2 Mixed-effects model for repeated measures constructed using data through Month 24 from enrolled patients in OLE studies. Data cutoff 28 June 2024.

Data Support Zorevunersen as Potentially the First Medicine to Treat the Underlying Cause of Dravet Syndrome

- Development in patients with DS **lags behind their neurotypical peers and the gap widens over time despite the use of best available ASMs**
- Small impacts on non-seizure symptoms have incredibly large impacts on the day-to-day life of patients and their caregivers
- **Substantial and durable reductions in convulsive seizure frequency through 2 years were observed in patients already receiving best available ASMs**, with the largest reductions in patients who received 70 mg initial doses in Phase 1/2a and 30 or 45 mg maintenance doses in the OLEs
- **Patients treated with zorevunersen experienced durable improvements in multiple measures of cognition and behavior, which continued to improve through 2 years** in **the OLEs** with ongoing maintenance dosing every 4 months
- Multiple maintenance doses of zorevunersen up to 45 mg were generally **well tolerated**

Data cutoff was December 12, 2023, for MONARCH/ADMIRAL and June 28, 2024, for SWALLOWTAIL/LONGWING.

Patient Past Medical History

12-year-old child with Dravet syndrome

- First seizure (generalized tonic clonic seizure from sleep) age 4 months
- Subsequent generalized tonic clonic and hemiclonic seizures triggered by fever and often prolonged with episodes of status epilepticus
- *De novo* pathogenic *SCN1A* missense variant identified
- Development normal prior to seizure onset
- Cognitive difficulties noticed around 2-3 years
- Baseline intellectual disability with IQ 55
- Baseline ASMs (at study entry): sodium valproate, clobazam, stiripentol, cannabidiol – despite treatment still having 4-5 seizures per month
- Enrolled in ADMIRAL study age 11 years
- Videos were captured at baseline and at 8 or 12 months after start of zorevunersen dosing

Each patient experience is unique and not representative of the patient population as a whole, nor is this patient's experience intended to depict what other patients may experience.

Zorevunersen is an investigational drug in clinical development and is not approved for marketing by the FDA or any other regulators

Handwriting

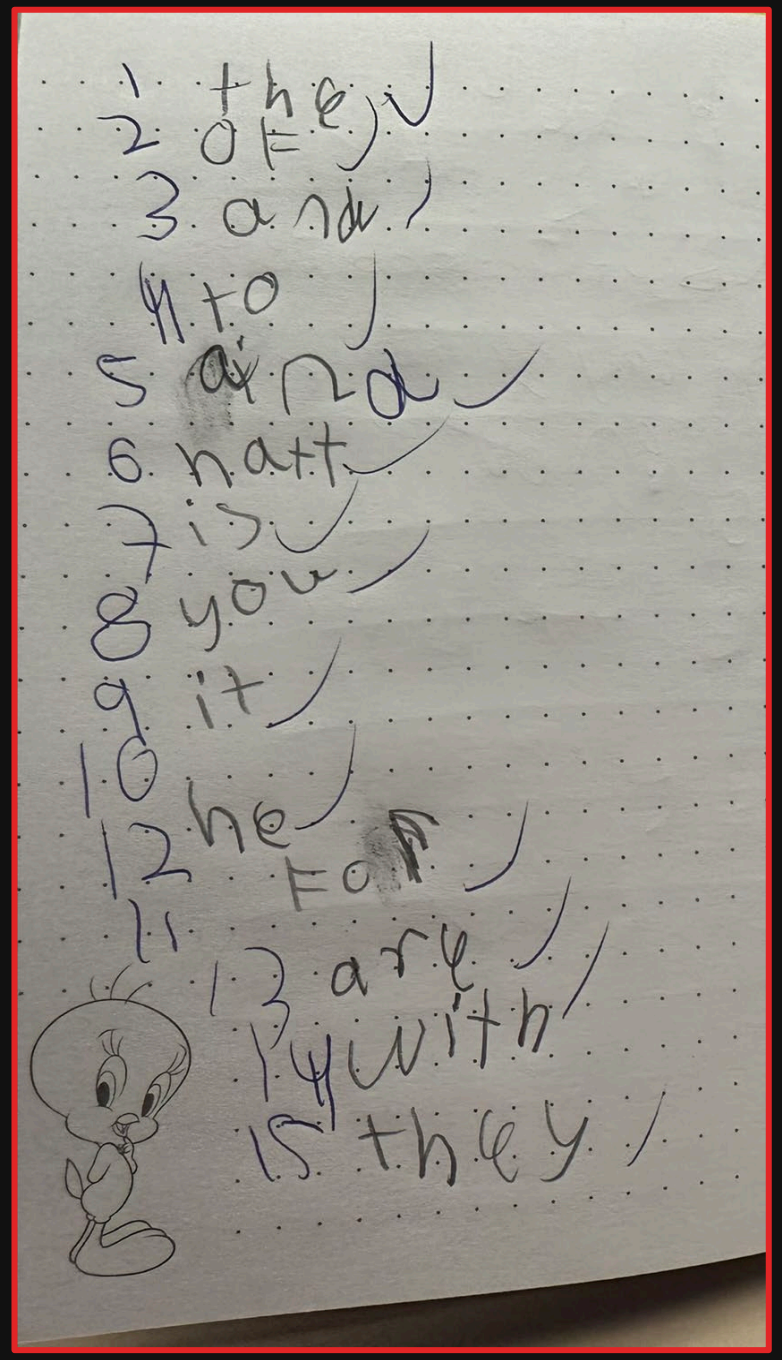
Before treatment with zorevunersen:

Uneven letters uneven and irregular spacing

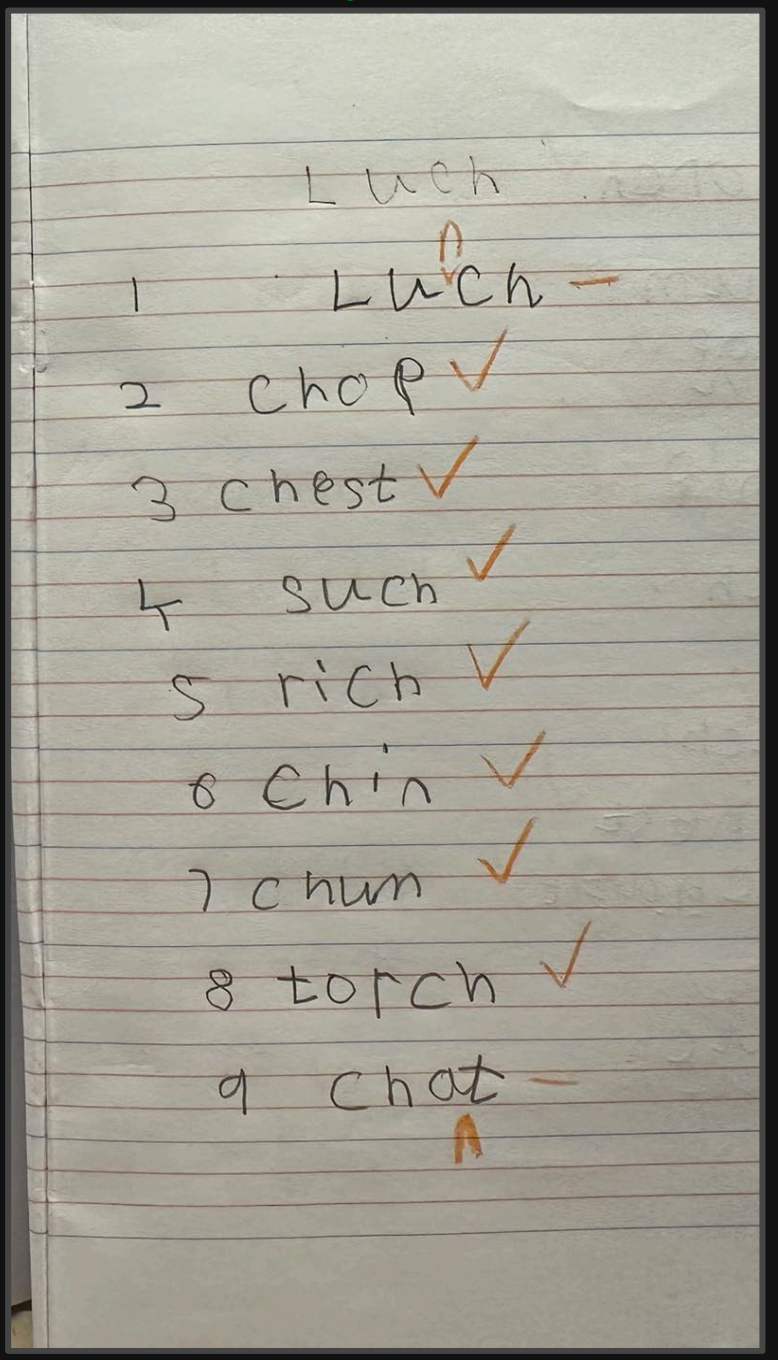
After ~9 months of treatment with zorevunersen:

Uniform letters and appropriate spacing

Before treatment – November 2022



ADMIRAL study – November 2023



Patient consent was provided by the patient family prior to video execution in connection with participation in the ADMIRAL/LONGWING studies. The ADMIRAL/LONGWING studies were sponsored and designed by Stoke Therapeutics. Post-production support from Porterhouse Medical US for these patient videos was also funded by Stoke Therapeutics. Zorevunersen is investigational and has not been approved by regulatory authorities for use.

Q&A Session

Edward M. Kaye, M.D.
Chief Executive Officer
Stoke Therapeutics

Joseph Sullivan, M.D., FAES
Professor of Neurology and Pediatrics and Director of the Pediatric Epilepsy Center of Excellence at the University of California San Francisco

Andreas Brunklaus, M.D.
Consultant Paediatric Neurologist, Royal Hospital for Children, Glasgow, UK; Honorary Professor, University of Glasgow, UK; Member of Dravet Syndrome UK's Medical Advisory Board

Barry Ticho, M.D., PhD, FACC
Chief Medical Officer
Stoke Therapeutics

Tommy Leggett
Chief Financial Officer
Stoke Therapeutics

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