Zorevunersen Regulatory Alignment & Phase 3 Plans

Virtual Event for Investors & Analysts

January 7, 2025

Agenda

CEO Opening Remarks

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

The Potential for Disease Modification in the Treatment of Dravet Syndrome: Clinical Data and Phase 3 Plan

Barry Ticho, M.D., Ph.D., FACC, Chief Medical Officer
Kimberly Parkerson, M.D., Ph.D., SVP, Head of Neurology Clinical Development

Zorevunersen Commercial Opportunity

Jason Hoitt, Chief Commercial Officer

Q&A

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This presentation discusses product candidates, including zorevunersen, that have not yet been approved for marketing by the U.S. Food and Drug Administration or any other regulatory agency.

Opening Remarks

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

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 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 add'l genes with TANGO target signatures

STOKE THERAPEUTICS

Compelling Clinical Data and Key Stakeholder Engagement Underscore the Potential for Zorevunersen

Clinical Data

Substantial and durable reductions in **seizure frequency** and continuing improvements across **multiple measures of cognition and behavior** are evidence of disease modification

Breakthrough Therapy Designation

Indicates that zorevunersen may demonstrate **substantial improvement over available therapy**

The Right Team

An **experienced team** that is ready to take zorevunersen into Phase 3

KEY TAKEAWAYS

First-ever Phase 3 study of a potential disease-modifying medicine for **Dravet syndrome**

Disease modification would represent a **major step forward in the treatment** of Dravet syndrome – fundamental shift in the treatment

**Breakthrough Therapy Designation is not the same as drug approval. Zorevunersen is an investigational drug candidate.*

FDA Breakthrough Puts Zorevunersen on an Efficient Path

	Breakthrough Therapy Designation (BTD)
Qualifying Criteria	A drug that is intended to treat a serious condition AND **preliminary clinical evidence indicates that the drug may demonstrate substantial improvement** on a clinically significant endpoint(s) over available therapies
Status	Granted December 2, 2024
Benefits	**All Fast Track Designations** **Intensive Guidance:** Frequent interactions with FDA to support efficient development **Organizational Commitment:** Involvement of Senior FDA staff in the review process **Rolling Review:** Submit portions of the marketing application as they are completed **Eligible for Priority Review:** Faster NDA review time vs standard applications

EMPEROR Phase 3 protocol has been submitted to FDA

STOKE THERAPEUTICS

**Breakthrough Therapy Designation is not the same as drug approval. Zorevunersen is an investigational drug candidate.*

Zorevunersen Clinical Data

Barry Ticho, M.D., Ph.D.
Chief Medical Officer

Current Treatments For Dravet Aim to Reduce Seizures Leaving a Significant Gap in Treatment of the Syndrome

MULTIPLE MEDICINES available for Seizure Management

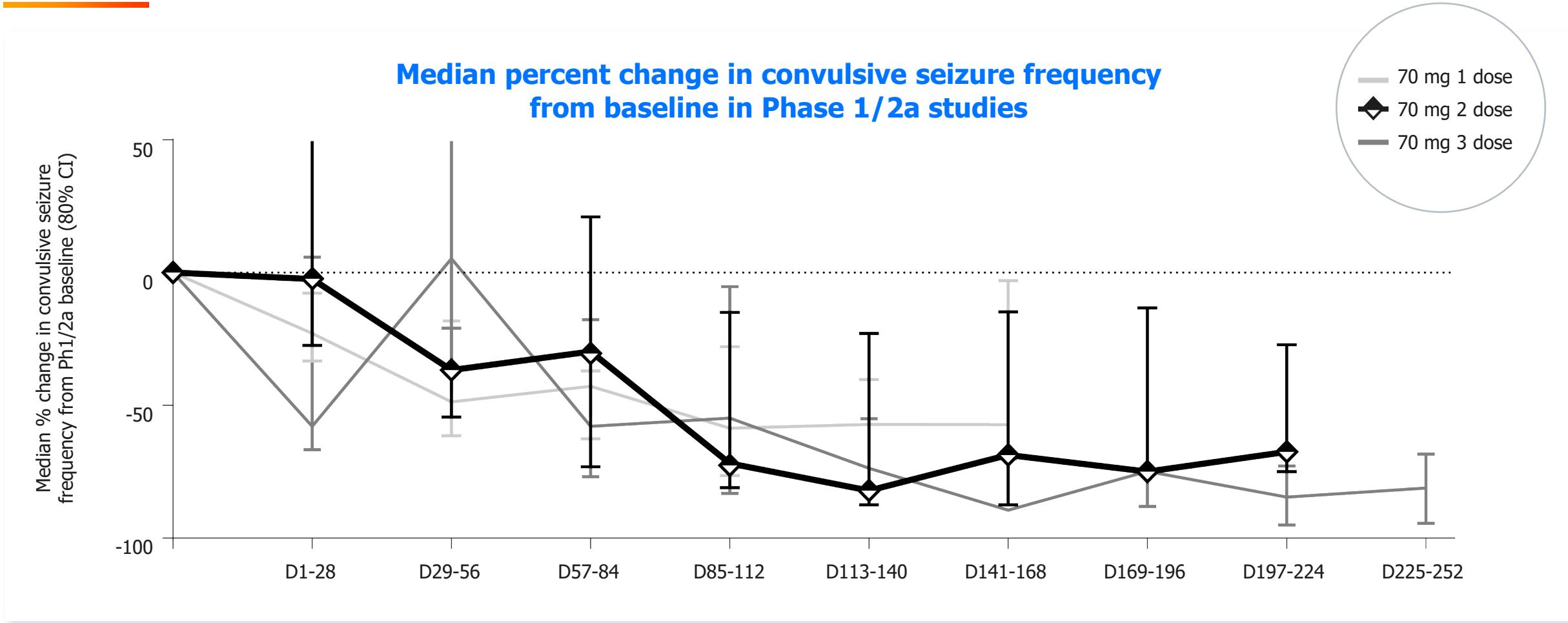
- Bromide
- Cannabinoid
- Clobazam
- Diazepam
- Fenfluramine
- Levetiracetam
- Stiripentol
- Topiramate
- Valproate
- Zonisamide

Currently **NO MEDICINES** available for Syndrome Management

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

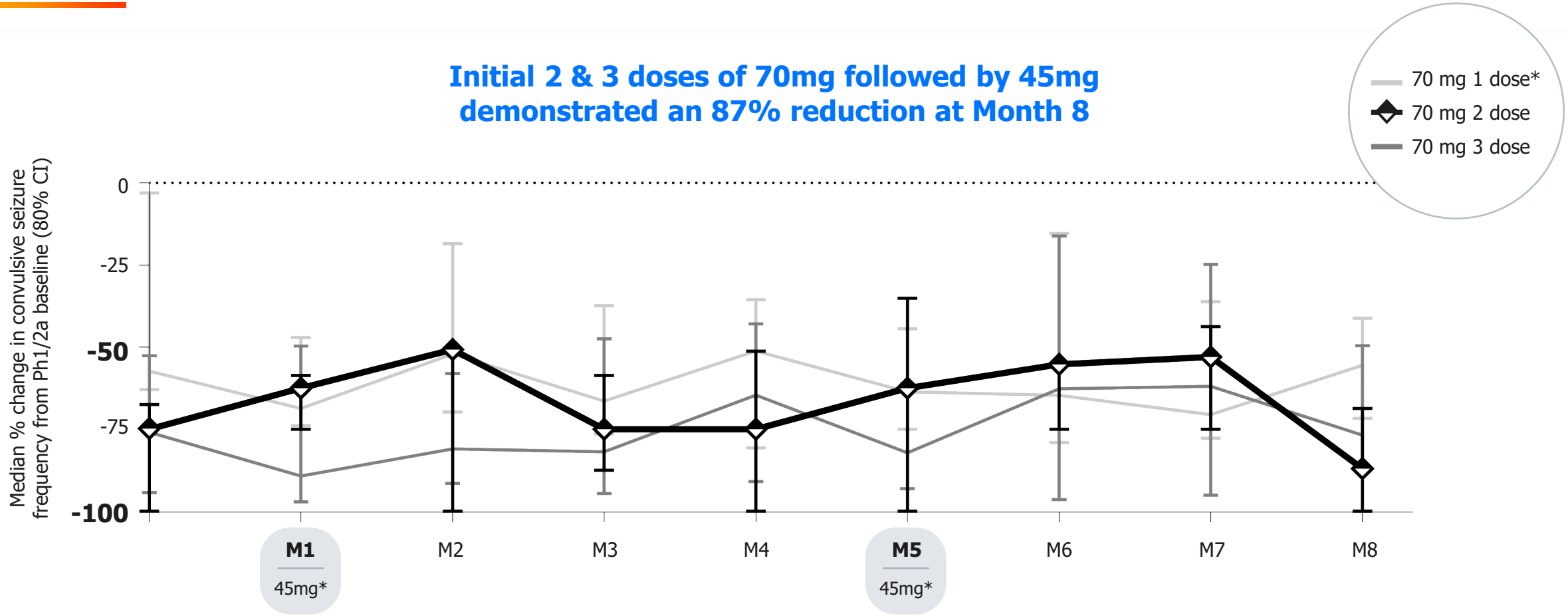
1. Lagae L, et al. Dev Med Child Neurol 2018; 60 (1): 63–72. Appendix S4. 2. Lagae L, et al. Dev Med Child Neurol 2018; 60 (1): 63–72.

Initial 70mg Doses of Zorevunersen Demonstrated Substantial and Sustained Reductions in Convulsive Seizure Frequency



Ongoing Treatment Demonstrated Substantial and Durable Reductions in Convulsive Seizure Frequency

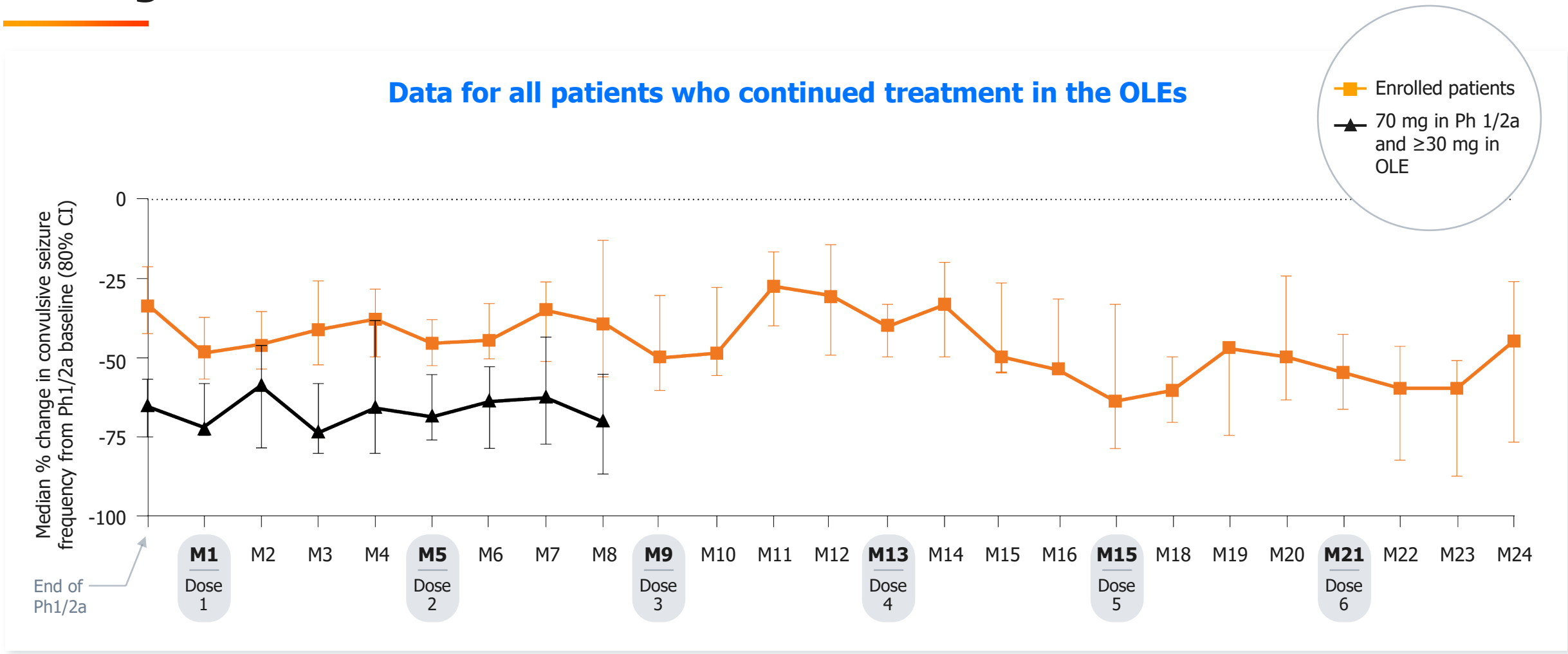
Initial 2 & 3 doses of 70mg followed by 45mg demonstrated an 87% reduction at Month 8



Patients from the single dose 70mg cohort received 30mg doses at M1 and M5.

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. AES 2024

Durable, Substantial Reductions in Seizures On Top of SOC Observed Through Two Years of Treatment with Zorevunersen



Orange: Enrolled Patients (n=70 M1 and 17 at M24 based on study progression)

Black: 70mg Cohorts from Ph1/2a who received ≥30 mg in OLE (n=16 – 17 at each timepoint)

Ph1/2a End of Study results.; OLE data cut: June 28, 2024.

Sullivan, J et al. 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 (poster). American Epilepsy Society Annual Meeting, December 6-10, 2024 (Los Angeles, USA).

Zorevunersen Generally Well-Tolerated Across Studies

Phase 1/2a studies

(n=81)

TEAEs

- **30% of patients** experienced a study drug-related TEAE
- Most common: **CSF protein elevations** (13.6%) and **procedural vomiting** (4.9%)

TESAEs

- **22% of patients** experienced a TESAE
- All were **unrelated to study drug** except for 1 patient with SUSARs

OLE studies

(n=74)

Findings consistent with Ph1/2, with the exception of a higher incidence of CSF protein elevation

- **79% (56/71*)** of patients in the OLEs had at least 1 CSF protein value >50 mg/dL
- **No clinical manifestations** have been observed in these patients
- One patient discontinued treatment due to elevated CSF protein levels

To date,

>600 doses of zorevunersen†

have been administered; 3 years of treatment in some patients

End of Phase 1/2a study data. Datacut June 28, 2024, for OLEs.

**71/74 patients had ≥1 post-baseline CSF protein value in the OLEs*

†Number of doses to date includes doses administered after the June 28, 2024, safety datacut for the OLEs.

CSF, cerebrospinal fluid; OLE, open-label extension; SUSAR, suspected unexpected serious adverse reaction; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

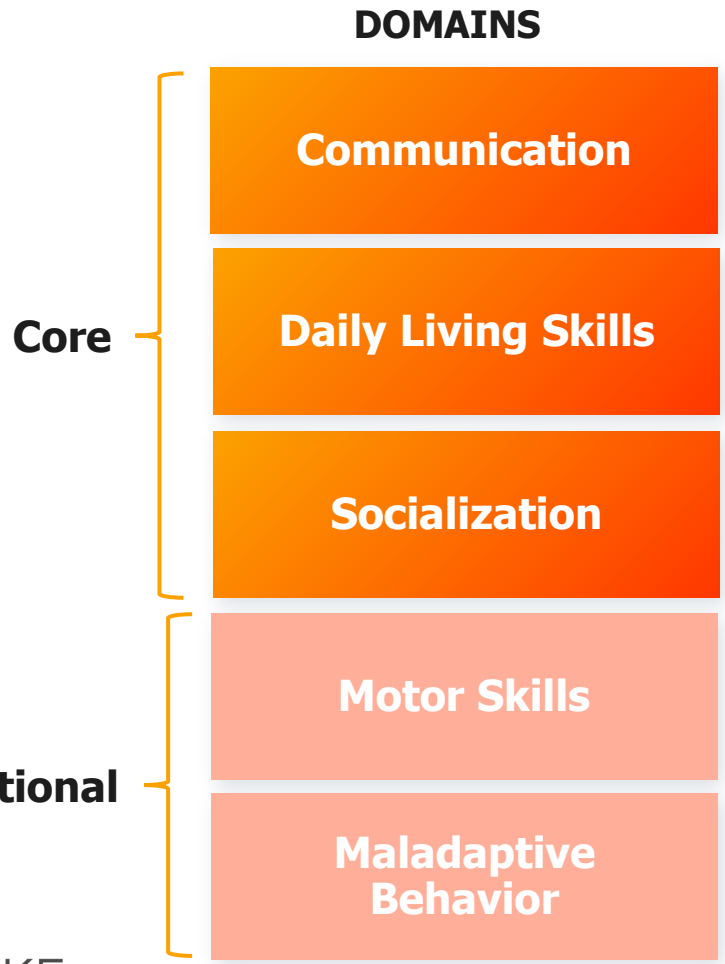
STOKE THERAPEUTICS

Potential for Disease Modification

Kimberly Parkerson, M.D., Ph.D.
Head of Neurology Clinical Development

Vineland-3 is Commonly Used to Assess Cognitive & Developmental Outcomes

Vineland-3 Adaptive Behavior Scales – Overview



SUBDOMAINS (examples of tasks)

Receptive — Responds upon hearing name called
Expressive — Says "Dada", "Mama", or caregiver name
Written — Writes alphabet letters using correct orientation

Personal — Cooperates in dressing and undressing
Domestic — Puts away books, toys, etc. when done
Community — Talks with a familiar person using a phone

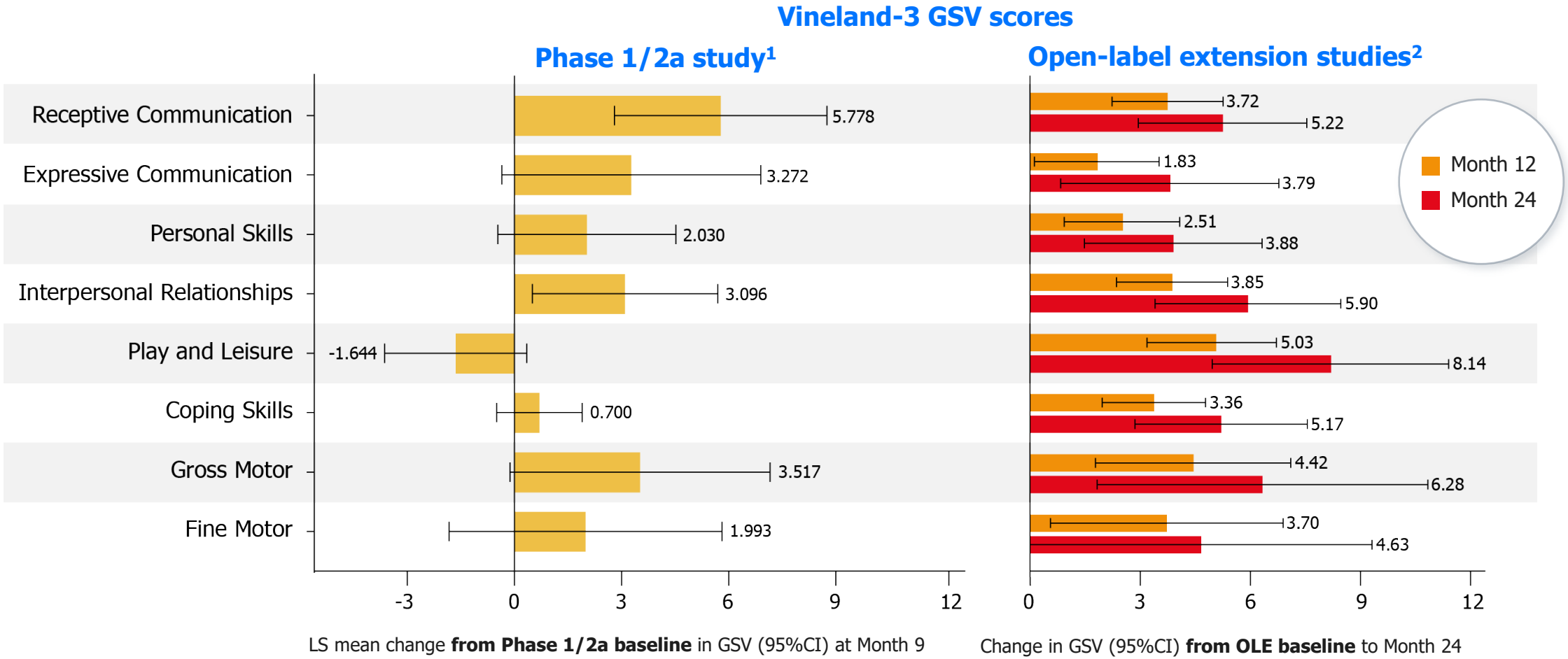
Interpersonal Relationships — Tries to interact with others
Play and Leisure — Responds when parent/caregiver is playful
Coping Skills — Transitions easily from one activity to another

Gross Motor — Moves, scoots, or crawls across the floor
Fine Motor — Picks up small objects with thumb and fingers

Internalizing— Experiences extreme anxiety or lacks energy or interest
Externalizing — Has temper tantrums or is overly active or restless
Critical Items — Engages in repetitive behaviors or self-harm

STOKE THERAPEUTICS

Improvements in Cognition and Behavior Within 9 Months Continuing Improvements Throughout the OLEs



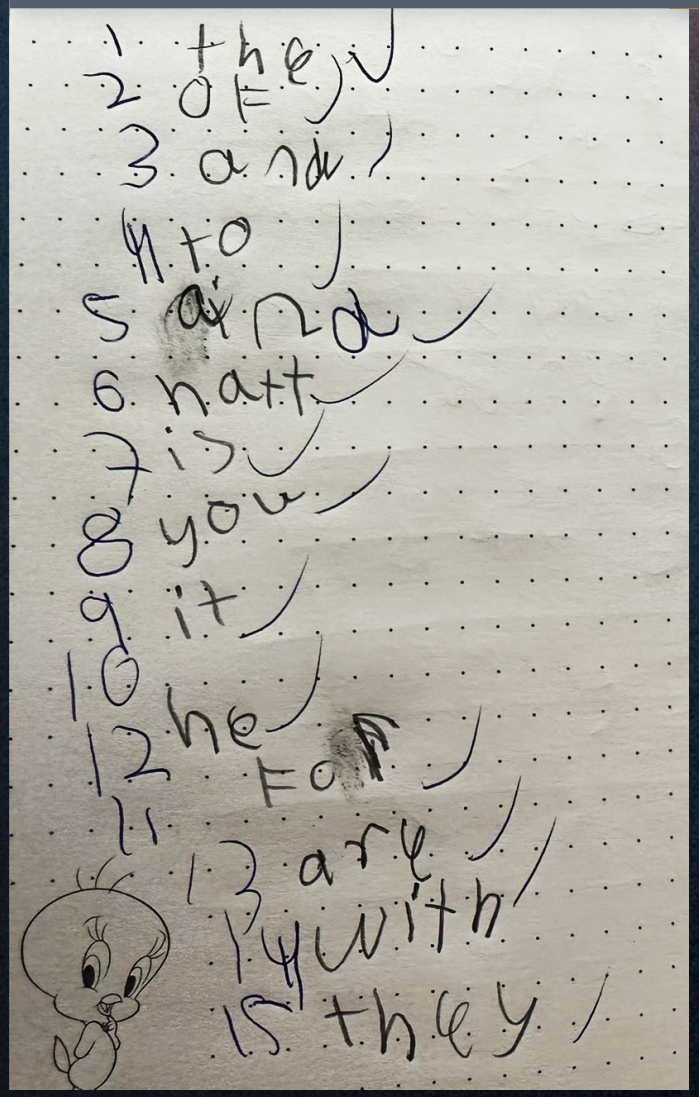
[1] *Machine learning model constructed using data from EOS Ph1/2a ADMIRAL (all dose cohorts) and data through Month 4 visit in LONGWING OLE (as of Nov. 2023)*

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

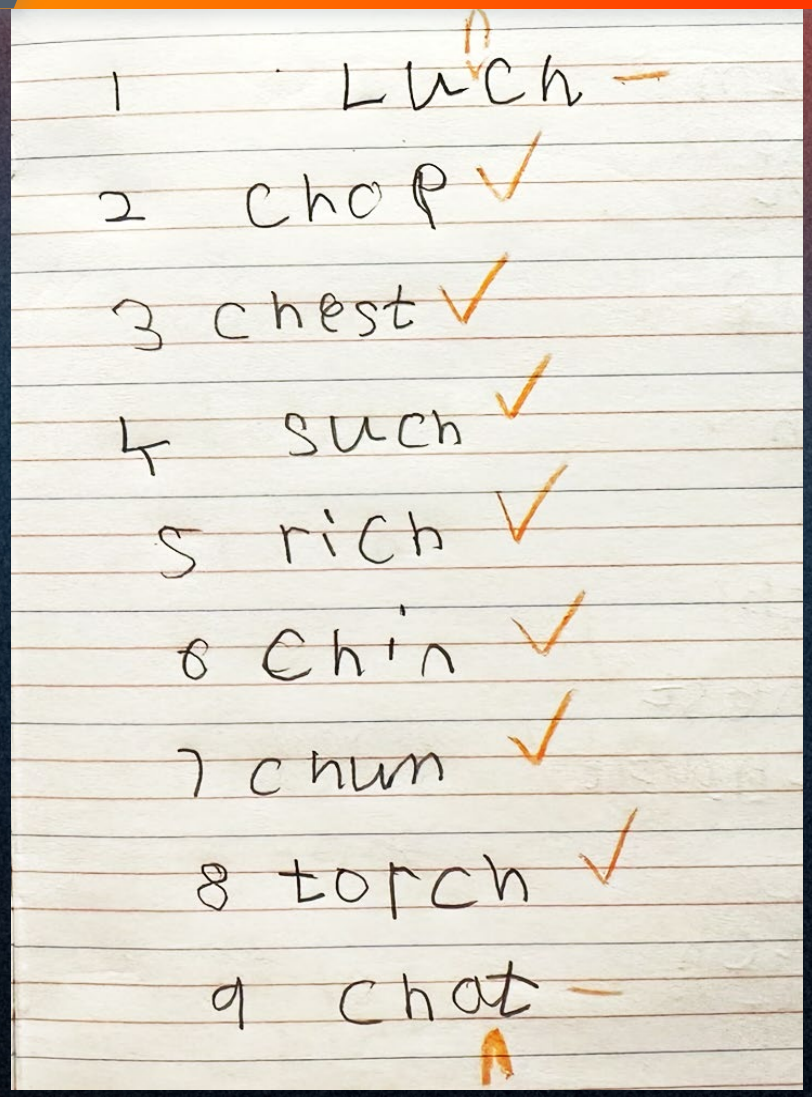
Handwriting from a 12 year-old before and after treatment with zorevunersen*

Each patient experience is unique and not representative of the patient population as a whole. This patient's experience is not intended to depict what other patients may experience.

BEFORE Treatment
November 2022



AFTER 9mo of Treatment
November 2023



Images captured during the Phase 1/2a ADMIRAL study independently by the investigator.
Brunklaus A, et al, British Paediatric Neurology Association Conference (scheduled January 9, 2025).
**Zorevunersen is an investigational drug candidate and has not been approved for marketing by the FDA or any other regulatory authorities.*

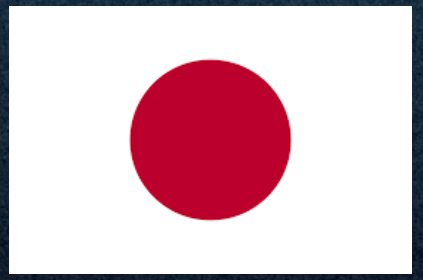
Strong Regulatory Alignment

FDA

EMA

Global Alignment FOR EMPEROR Phase 3 Protocol

PMDA

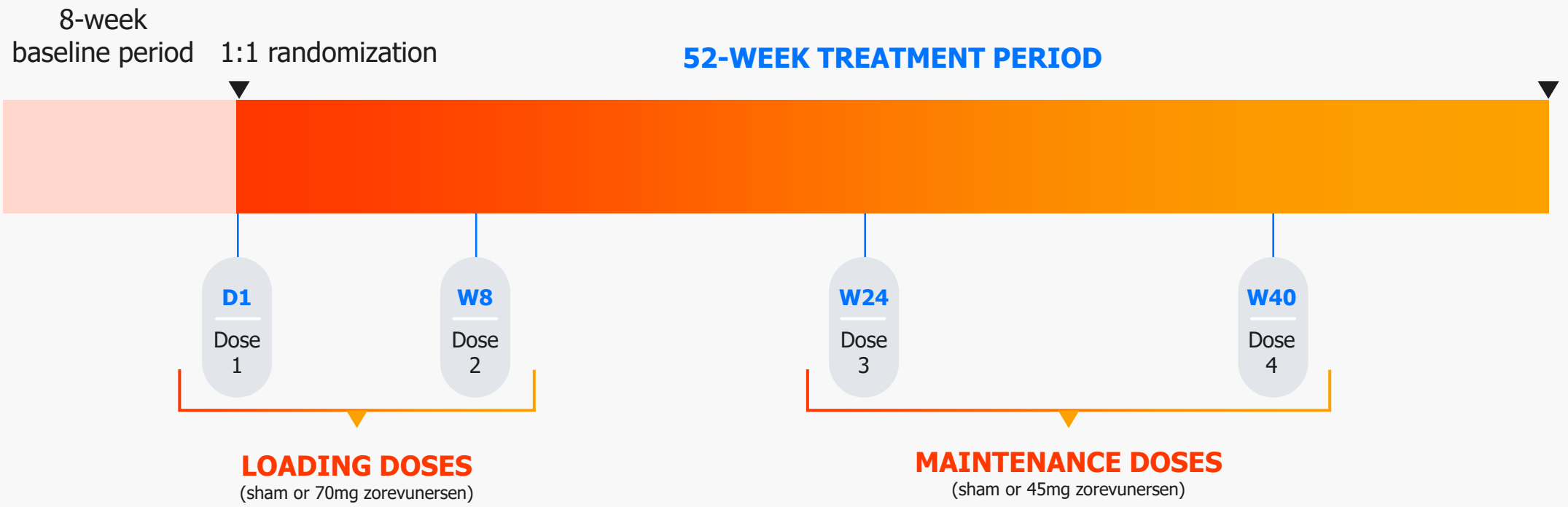


Regulatory discussions ongoing

Emperor Clinical Study Design

First Phase 3 study of a potential disease-modifying medicine for Dravet syndrome

TOTAL STUDY DURATION: 60 WEEKS



EMPEROR Phase 3 Study Overview

Planned Study Parameters

Primary endpoint

Seizures

Percent change from baseline in major motor seizure frequency in patients receiving zorevunersen as compared to sham

Key secondaries

Durability of effect on major motor seizure frequency

Improvements in behavior & cognition measured by Vineland-3 subdomains

Other Endpoints

Safety, CGI-C, CaGI-C, BSID-IV, and others

Study Design: Sham-controlled, 1:1 randomization

Dosing Regimen: 2x70mg + 2x45mg

Study Start: Mid-2025

Population: 2 to <18 years with a confirmed variant in the *SCN1A* gene not associated with gain of function

Number of Patients Randomized: ~150

Sites: ~60 across the US, UK, EU and Japan

Treatment Duration: 52 weeks

Data Anticipated: YE 2027

STOKE THERAPEUTICS

Regulatory discussions ongoing

Operational Optimization

Strategies to Drive Efficiency for Emperor Start-Up and Implementation

Speed

- Rapid-start sites identified
- Returning Ph1/2a sites
- Streamlined document submissions to sites
- Pre-screening process to expedite enrollment

Efficiency and Quality

- Site visits to ensure quality and compliance
- Pursue as many centralized IRB sites as possible
- Electronic informed consent

Caregiver and Site Support

- Clinical Trial Educators
- Travel concierge service
- Global patient advocacy education and engagement

HCP Collaboration

- Personalized support for site staff
- Regional study referral programs

STOKE THERAPEUTICS

Commercial Opportunity

Jason Hoitt
Chief Commercial Officer

Zorevunersen is Positioned to Change the Treatment of Dravet Syndrome, Representing Blockbuster Potential

SIGNIFICANT NEED

Current treatments focus on reducing seizure frequency. There is nothing available to treat the entire syndrome.

CLINICAL DATA

Substantial and durable reductions in seizures and continuing improvements in cognition and behavior on top of standard of care anti-seizure medicines.

STAKEHOLDER SUPPORT

HCPs and caregivers have had an overwhelming positive reaction to the zorevunersen profile as a disease-modifying medicine.

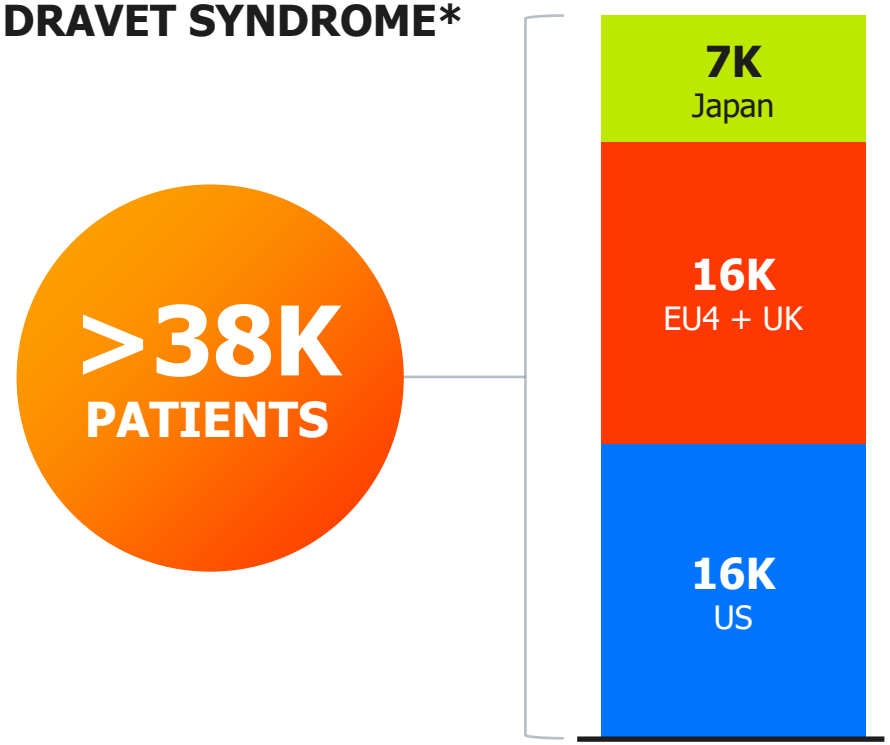
> **The option of a treatment, such as zorevunersen**, that could not only potentially reduce or eliminate seizures, as well as offer some level of disease reversal, would **represent a profound breakthrough for individuals living with Dravet syndrome**. It could change Dravet syndrome from a profoundly life-altering and debilitating condition into a more manageable challenge, providing the **opportunity for patients to live a more fulfilling and independent life**.
>
> **Mary Anne Meskis,** Executive Director, Dravet Syndrome Foundation

STOKE THERAPEUTICS

Substantial Patient Population

More than 38K patients with Dravet syndrome across 7 major markets

PREVALENCE OF DRAVET SYNDROME*



SIGNIFICANT UNMET NEED DESPITE ANTI-SEIZURE MEDICINES

No disease modifying medicines are currently available

Seizures are inadequately controlled in 90% of patients

- **Mean 14.3 seizures per 28 days** while receiving an average of 3.5 ASMs at baseline

Developmental delays and cognitive impairment are persistent and cannot be treated today

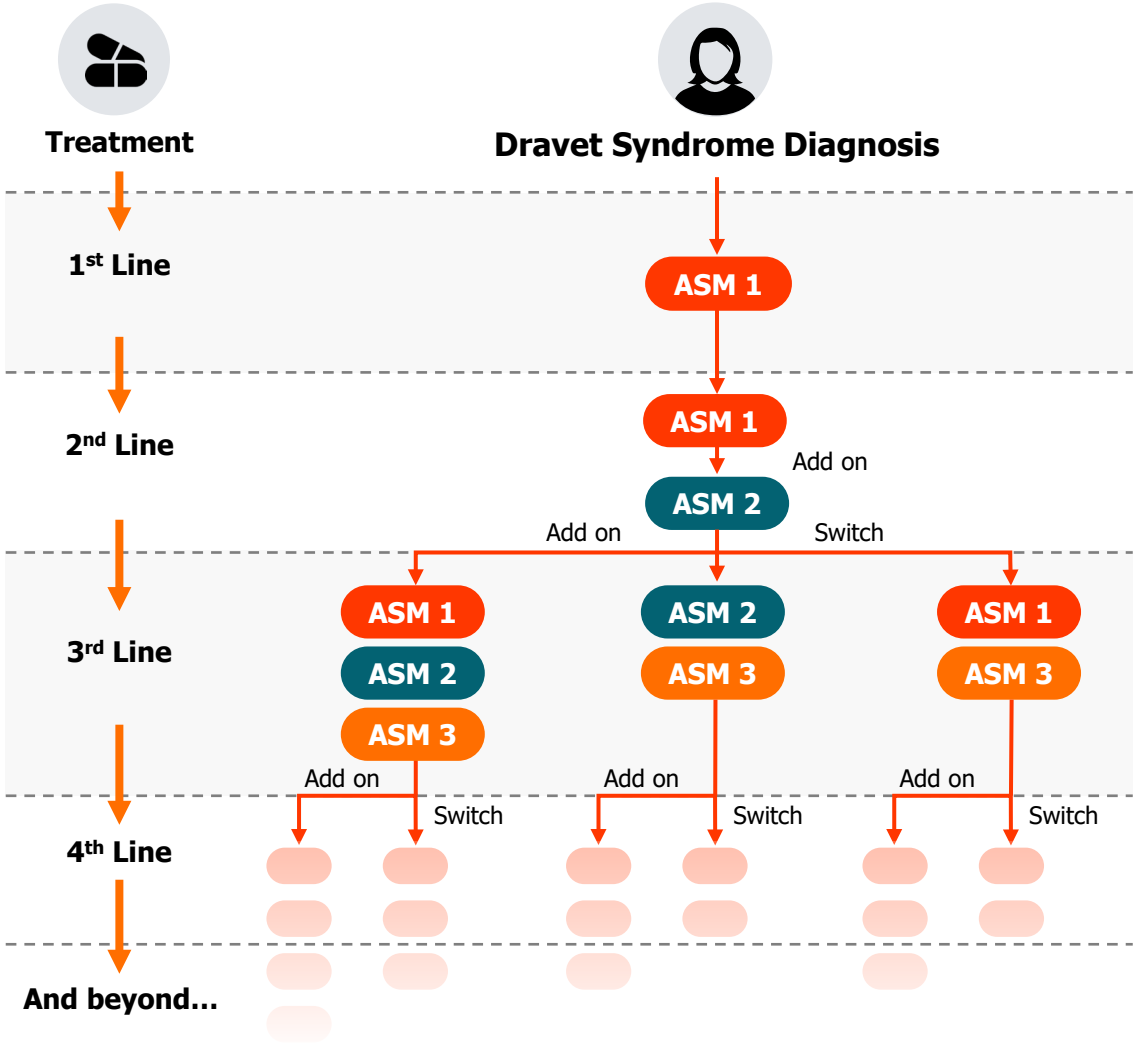
- Patients with Dravet syndrome **fall further and further behind** their neurotypical peers

**Numbers may not add up due to rounding. EU4: Germany, France, Italy and Spain; ASMs: anti-seizure medications*

Wu. Pediatrics. 2015; UN World Population Prospects 2022; World Bank Open Data 2021; WHO Life Tables 2019; Physician Interviews; ClearView Analysis. Sullivan, J. et al., 24-Month Analysis of BUTTERFLY. AES 2023. Lagae et al., Developmental Medicine & Child Neurology, 2017; 2018 Health Advances Report; Dravet Syndrome Foundation Voice of the Patient Report

Once Diagnosed, the Current Treatment Paradigm is Burdensome and Ineffective

Most patients are on ≥3 anti-seizure medicines



CLINICIAN PERSPECTIVES ON CURRENT TREATMENT OPTIONS

"We have 20–25 ASMs but there is no magic pill. We **need something that addresses the root cause**."

"A lot of these patients end up being **sedated around the clock** between the meds and the disease."

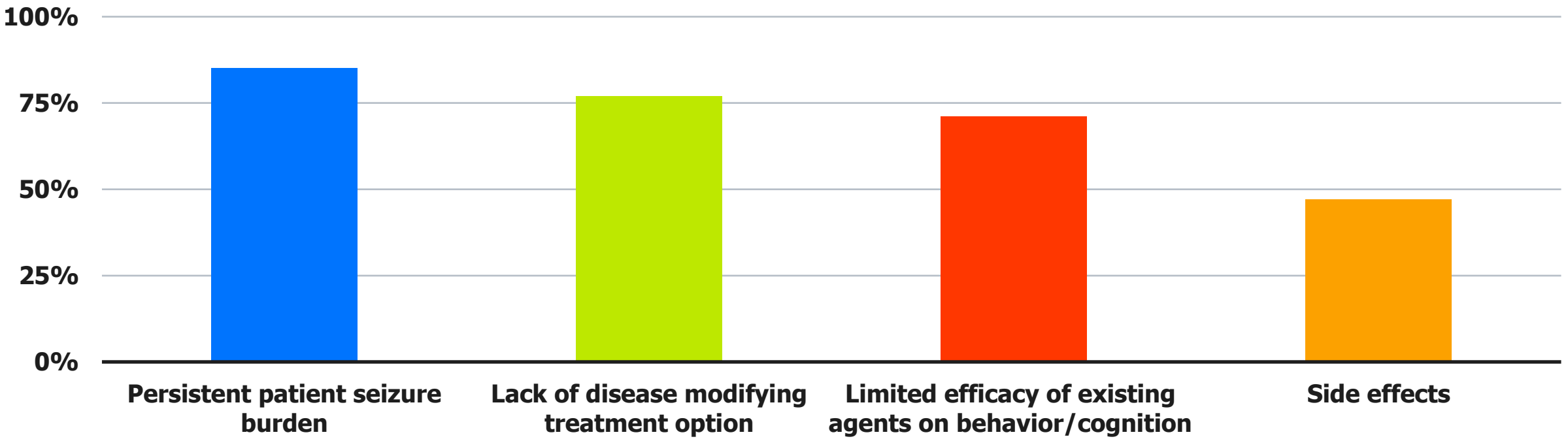
"We need to improve **seizure** control given patients can **still experience 20 seizures in a week while on many medications**."

Adapted from Wirrell et al. International consensus on diagnosis and management of Dravet syndrome. May 2022.
Comments extracted from company sponsored interviews using a Product X profile based on MONARCH and ADMIRAL study results.

Approximately 90% of HCPs See a Significant Unmet Need for Patients with Dravet Syndrome

Most pressing unmet needs identified by HCPs*

Percent of respondents



*Based on Stoke quantitative market research with 135 HCP participants who treat Dravet syndrome in the US and EU in 2024.

Support for a Disease Modifying Therapy for Dravet Syndrome

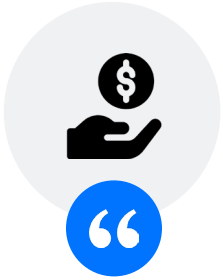
Caregivers & Advocates

My excitement for this product is a 10 out of 7. This gives me hope that there is something that can help my child.

HCPs

No SOC has shown meaningful impact on cognitive improvement. The MOA leads me to believe this will be effective in both reducing seizures and improving cognition and behavior.

Payers



I am happy with the seizure reduction because it is on top of what we consider to be best in class. Behavioral and cognitive benefit is also a helpful endpoint.

ZOREVUNERSEN HAS BLOCKBUSTER POTENTIAL

Based on Company sponsored interviews using a Product X profile based on MONARCH and ADMIRAL study results.
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Closing Remarks

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

Q&A