

# Stoke Therapeutics

NASDAQ: STOK

November 2024

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This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: the advantages that may be achieved with TANGO: the ability of zorevunersen (STK-001) to treat the underlying causes of Dravet syndrome and reduce seizures or show improvements in behavior or cognition at the indicated dosing levels or at all; the timing and expected progress of clinical trials, data readouts, regulatory decisions and other presentations for zorevunersen and STK-002; the timing of regulatory interactions or the outcomes thereof; our future operating results, financial position and cash runway; and our expectations, plans, aspirations and goals, including those related to the goals of our collaboration with Acadia. Statements including words such as "anticipate," "plan," "will," "continue," "expect," "ongoing," or "potential" and statements in the future tense are forward-looking statements. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they prove incorrect or do not fully materialize, could cause our results to differ materially from those expressed or implied by such forward-looking statements, including, but not limited to, risks and uncertainties related to: our ability to advance, obtain regulatory approval of, and ultimately commercialize our product candidates, including zorevunersen; the timing of data readouts and interim and final results of preclinical and clinical trials; positive results in a clinical trial may not be replicated in subsequent trials or successes in early stage clinical trials may not be predictive of results in later stage trials; our ability to fund development activities and achieve development goals; our ability to protect our intellectual property; global business, political and macroeconomic conditions, including inflation, interest rate volatility, cybersecurity events, uncertainty with respect to the federal budget, instability in the global banking system and volatile market conditions, and global events, including public health crises, and ongoing geopolitical conflicts, such as the conflicts in Ukraine and the Middle East; and other risks and uncertainties described under the heading "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2023, our quarterly reports on Form 10-Q and the other documentation we file from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this presentation, and we undertake no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

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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 and progressive genetic epilepsy

**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

## Advantages of Stoke's Approach vs. Other Genetic Approaches



Selectively boosts expression  
only in tissues where the  
protein is normally expressed



No observed unwanted  
off-target genetic effects



Utility across small and large  
gene targets and mutations



Does not  
alter DNA

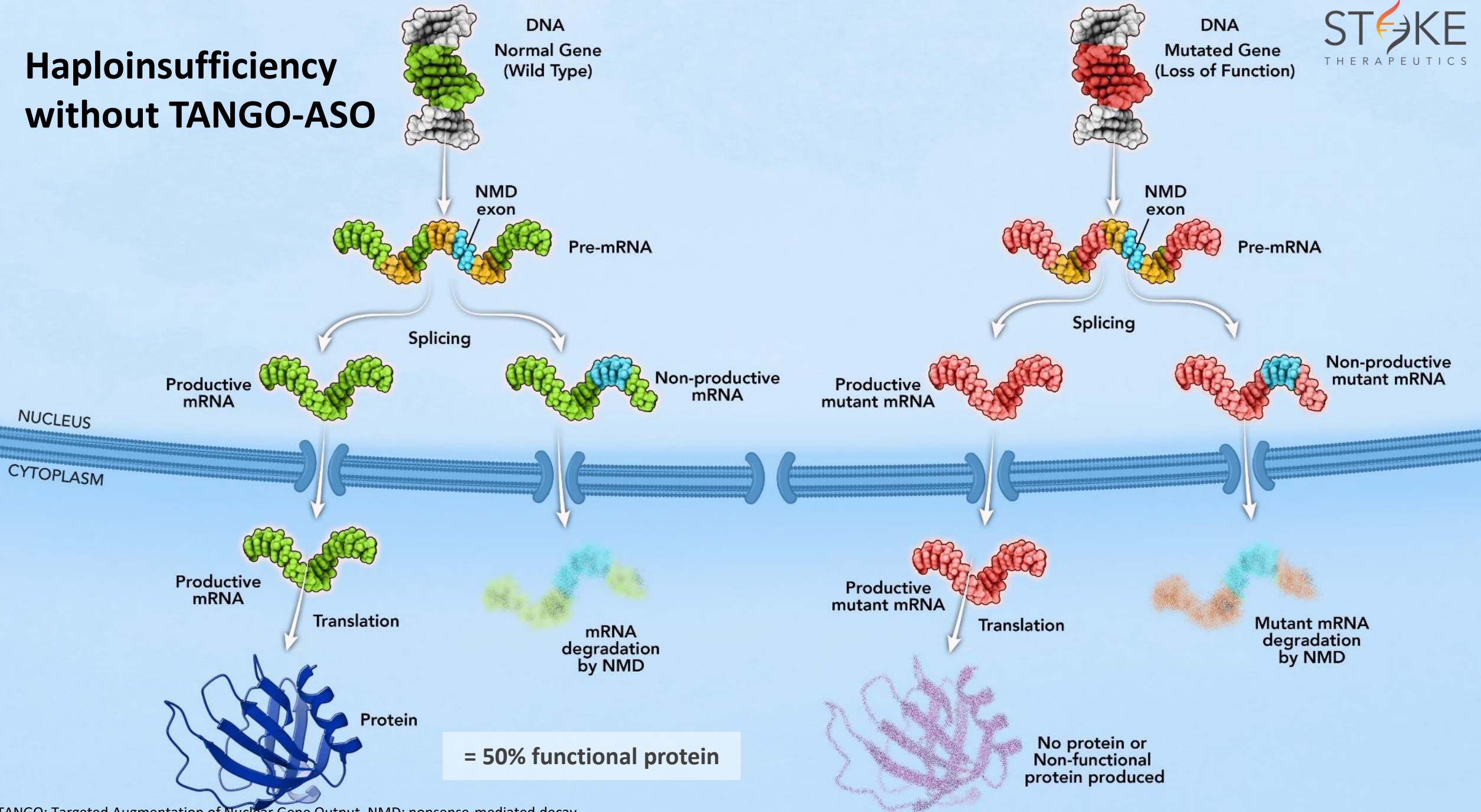


Ability to control dose level  
and duration



Simple and scalable  
manufacturing

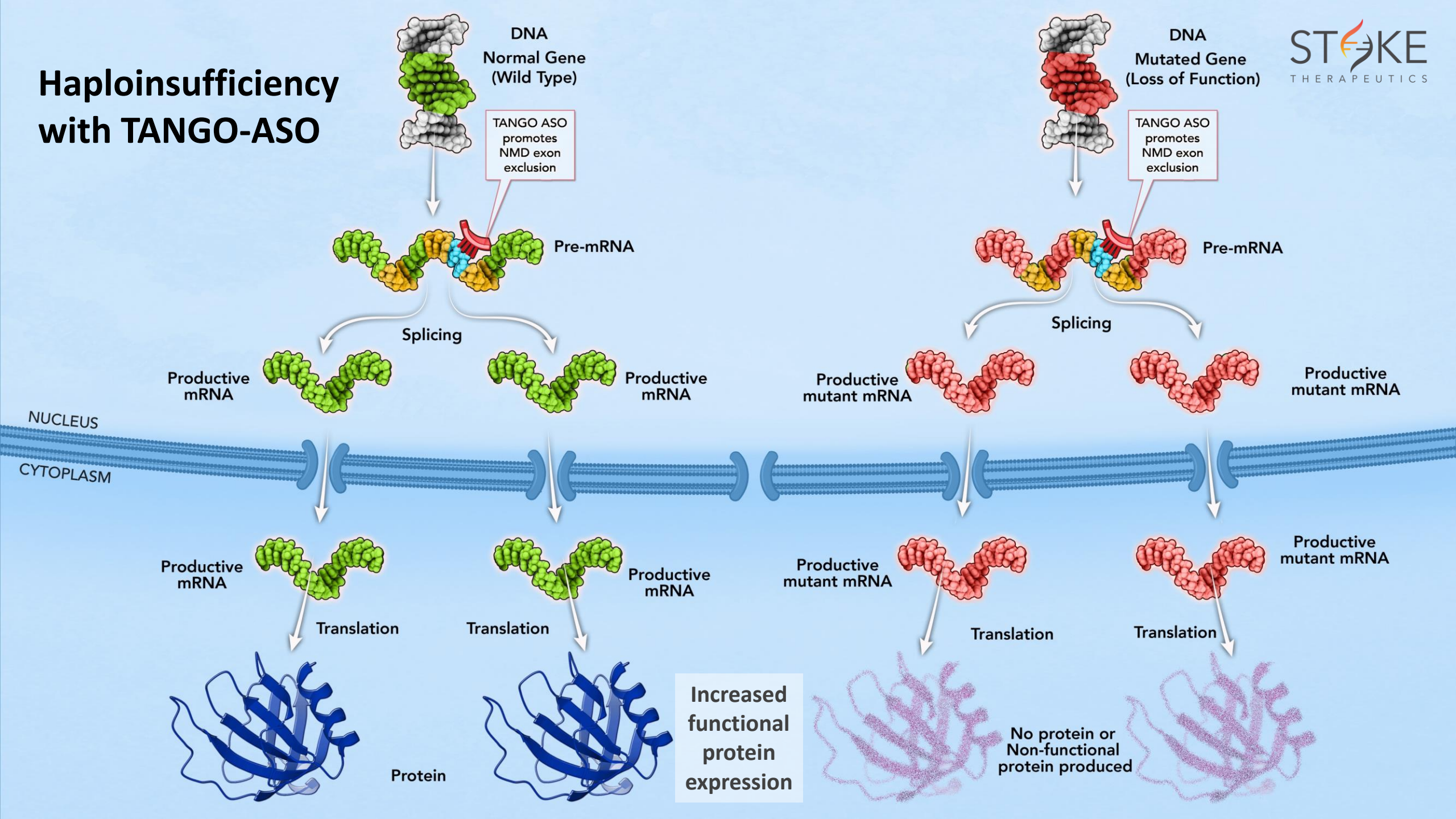
# Haploinsufficiency without TANGO-ASO



= 50% functional protein

No protein or Non-functional protein produced

# Haploinsufficiency with TANGO-ASO



# Dravet Syndrome: A Severe, Progressive Genetic Epilepsy

**85%**

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

RESULTING in

**50%**

Na<sub>v</sub>1.1 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<sup>1</sup>, prolonged seizures, seizure-related accidents or infections

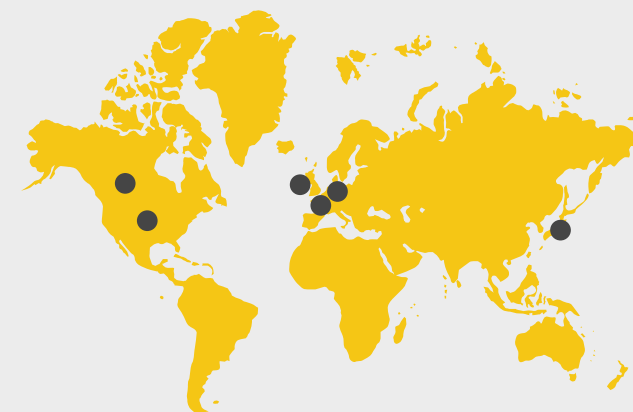


Seizures are not adequately controlled in

**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*

<sup>1</sup> 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

# The Effects of Dravet Go Beyond “Just Seizures”



## Intellectual Disability & Developmental Delays

*“Over time, we have seen **slow, steady decline** in all areas, from speech, to mobility, endurance, loss of energy, tolerance for stimulation, stamina, etc.”*



## Language & Speech Disturbances

*“At age 19, [our son] stopped talking, seemingly **losing his capacity for speech** overnight. Most days he is silent, and though he can understand simple conversation he is largely **unable to express himself.**”*



## Movement & Balance

*“We're disappointed when [our son's] physical activity is limited and the short walk or visit that we plan with his grandmothers must now be changed to a longer **wheelchair ride.**”*

## Sleep Abnormalities

*“Every single night, he has **seizures in his sleep.** In addition to all of the other comorbidities of DS, he's **robbed of the basic human necessity** of getting a good night's sleep. This impacts our entire family, as it is hard to function on **so little sleep day after day.**”*



# Zorevunersen is on Track to be the First Disease-Modifying Medicine to Treat the Underlying Cause of Dravet Syndrome

Multiple medicines available for

## Seizure management

*Despite these treatments, seizures are not adequately controlled in 90% of patients with Dravet syndrome*

### Available medicines used to control seizures:

- Acetazolamide
- Benzodiazepines
- Brivaracetam
- Cannabidiol
- Carbamazepine
- Clobazam
- Ethosuximide
- Felbamate
- Fenfluramine
- Lamotrigine
- Levetiracetam
- Mesuximide
- Oxcarbazepine
- Phenytoin
- Rufinamide
- Stiripentol
- Topiramate
- Valproate products
- Zonisamide

No medicines currently available for

## Dravet syndrome management

### zorevunersen

**The first potential disease-modifying approach to address the genetic cause of Dravet syndrome**

# Landmark New Data Support the Potential for Zorevunersen to be The First Medicine to Treat the Underlying Cause of Dravet Syndrome

Reductions in seizures and improvements in cognition and behavior that support the potential for disease modification

Phase 1/2a Study Data: 70mg doses demonstrated **substantial & sustained** reductions in convulsive seizure frequency of:

**85% at  
3 months**

(n=10)

&

**74% at  
6 months**

(n=9)

on top of the best available anti-seizure medicines



**OLE Studies (30mg, 45mg):**

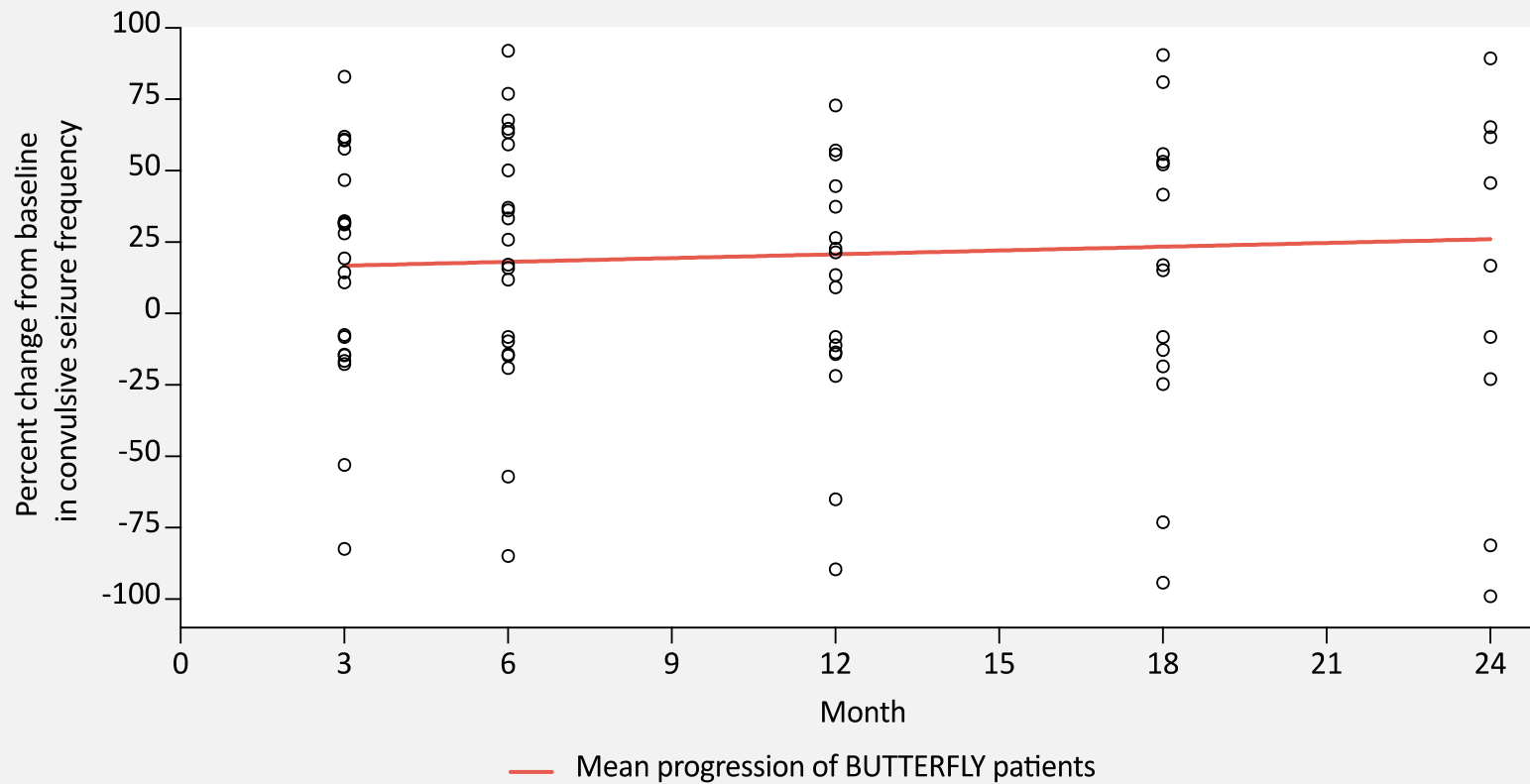
Durable **reductions in seizures** and meaningful **improvements in multiple measures of cognition & behavior** over 12 months



**Safety:** Single & multiple doses up to 70mg were generally well-tolerated

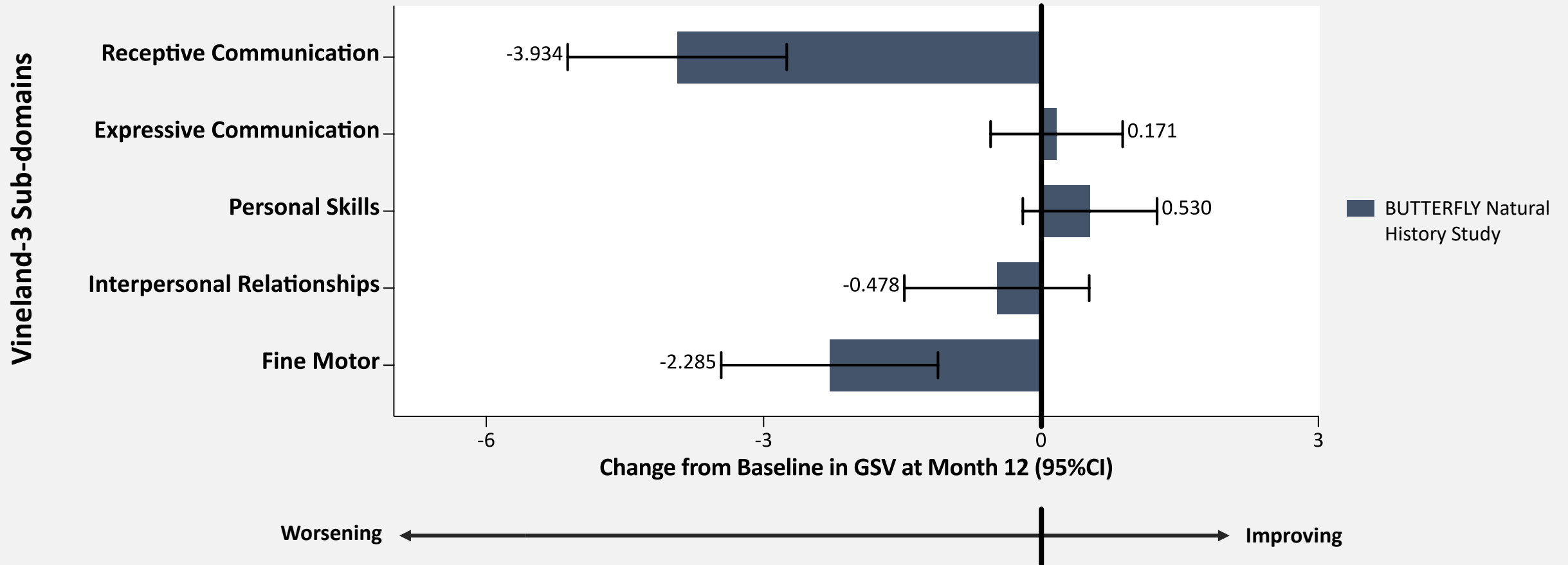
# Natural History Data: Despite Standard Anti-Seizure Medicines, No Meaningful Improvement in Convulsive Seizure Frequency

**Change in Convulsive Seizure Frequency**

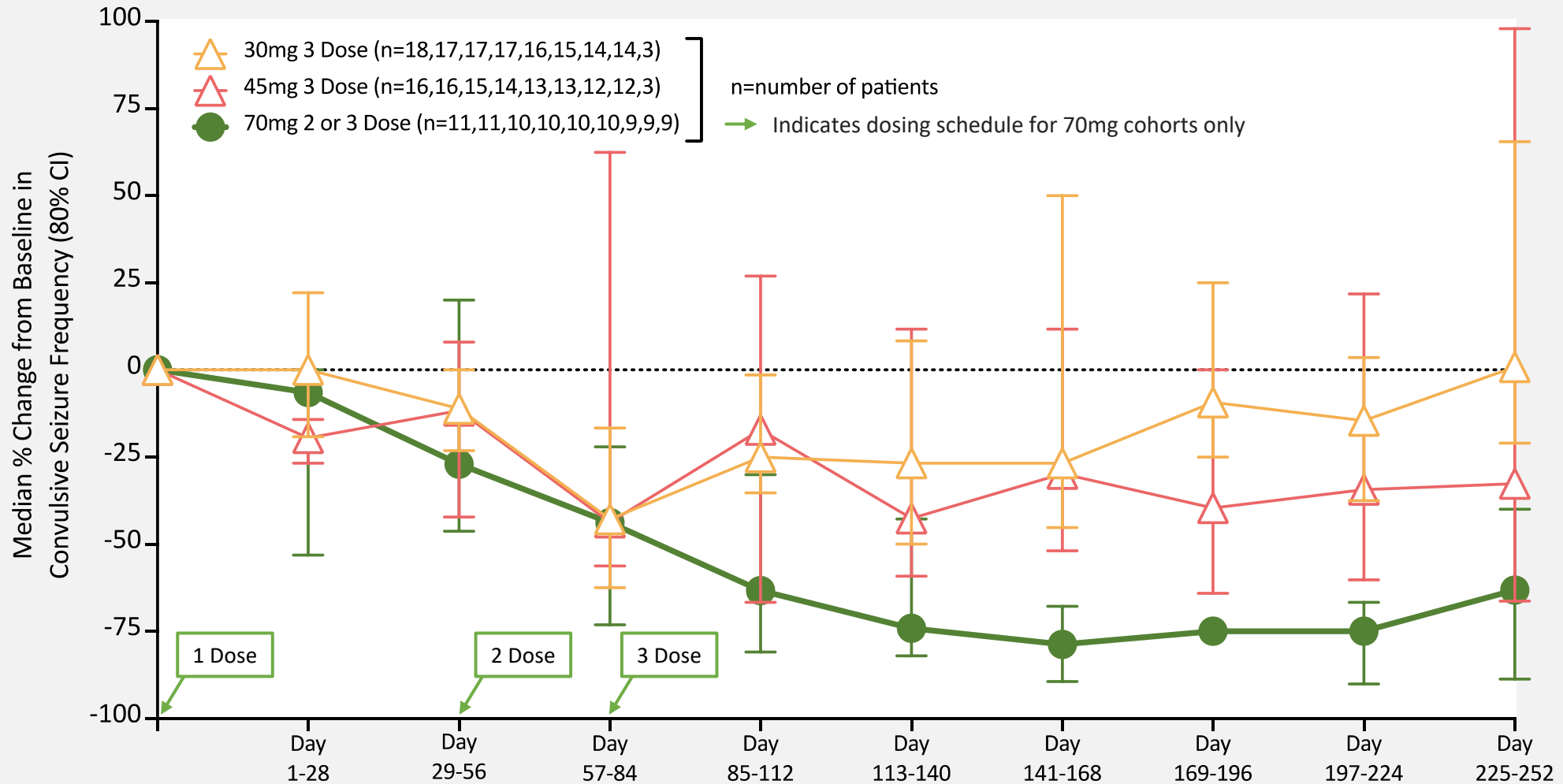


Patients were treated with the best available anti-seizure medicines	
Median baseline convulsive seizure frequency per 28 days (95% CI), n=26	
10.0 (5.50, 15.5)	
Most common ongoing anti-seizure medicines, n (%)	
Clobazam	25 (69.4%)
Fenfluramine	16 (44.4%)
Stiripentol	14 (38.9%)
Valproic Acid	14 (38.9%)
Cannabidiol	12 (33.3%)
Levetiracetam	8 (22.2%)

# Natural History Data: Despite Best Available Anti-Seizure Medicines, No Improvement in Cognition and Behavior

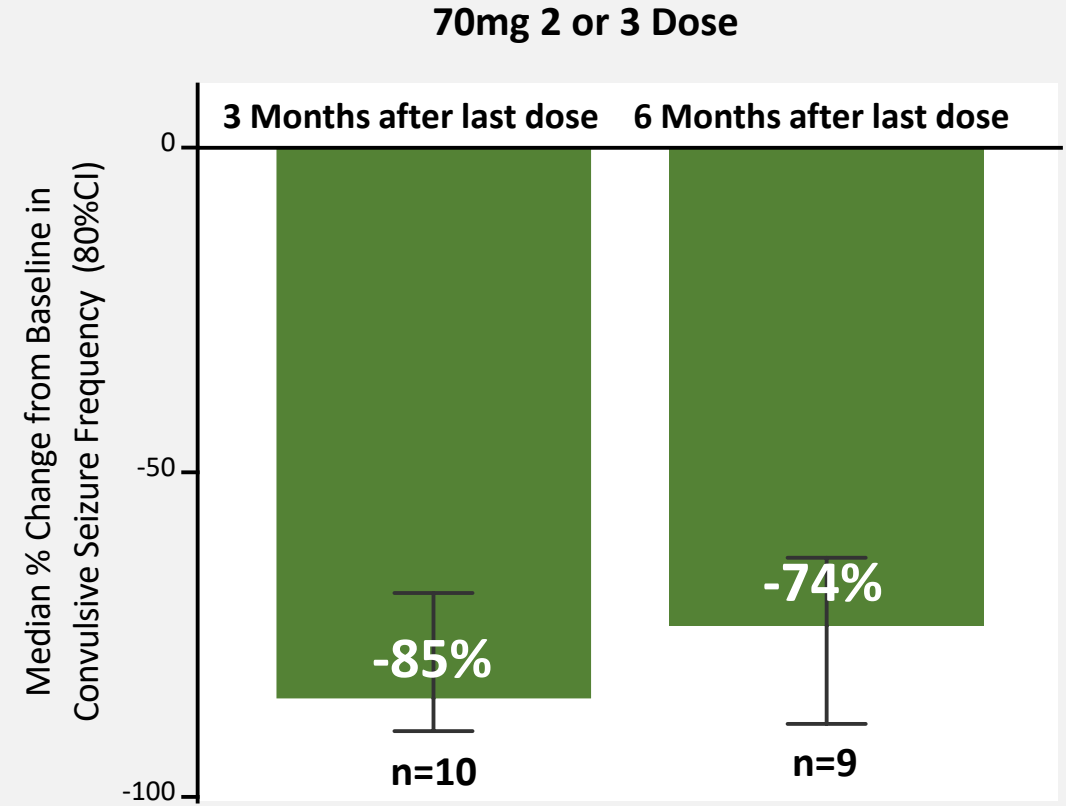
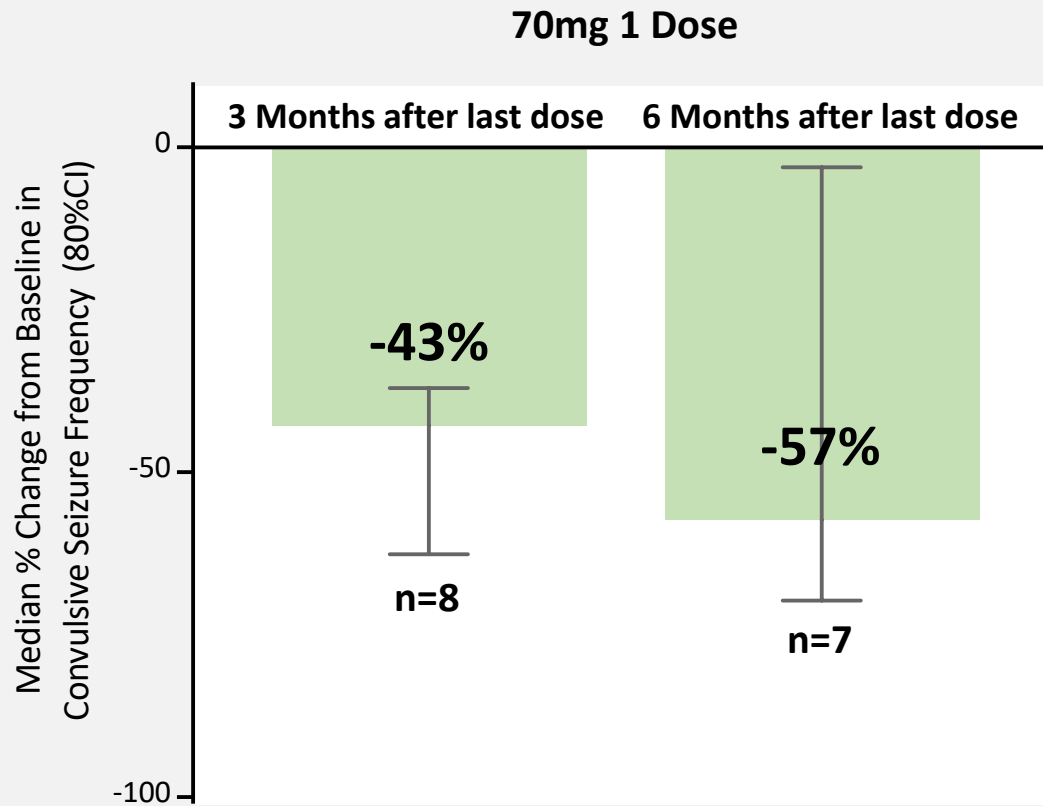


# 70mg Doses of Zorevunersen Demonstrated the Most Substantial Reductions in Seizure Frequency on Top of Standard of Care Medicines



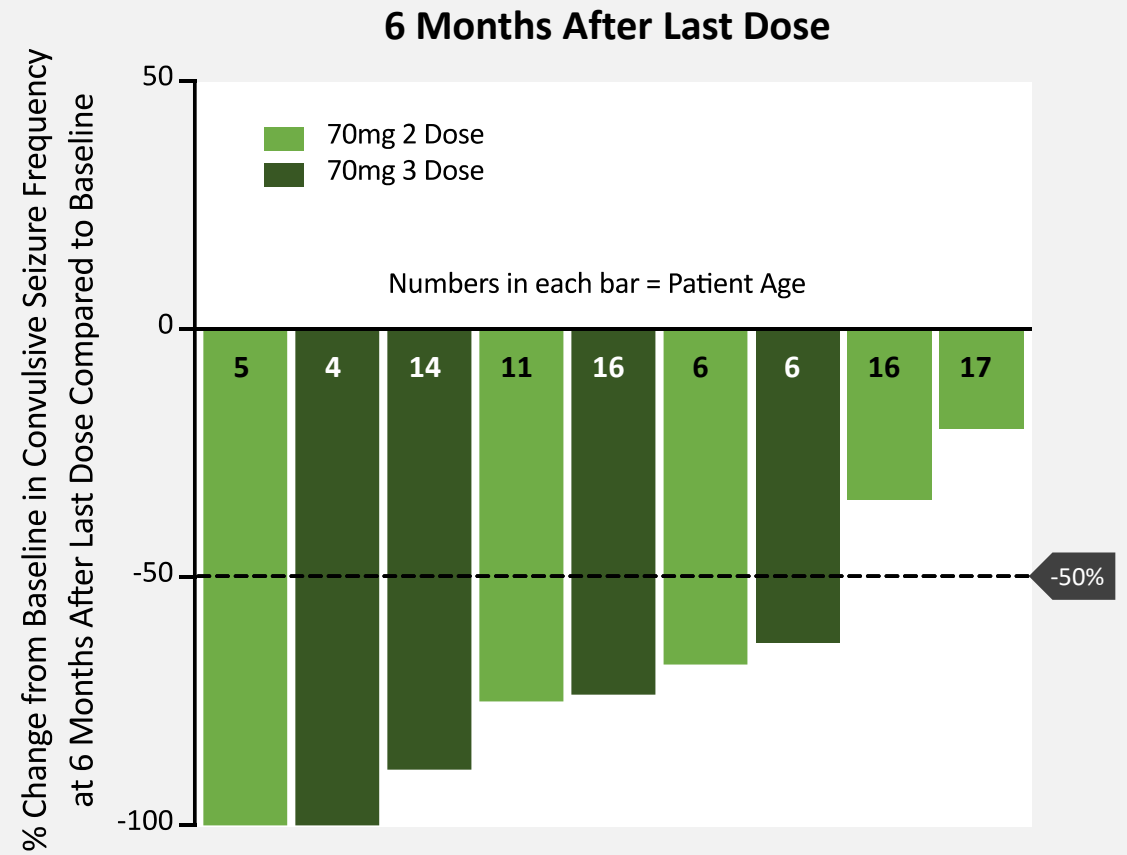
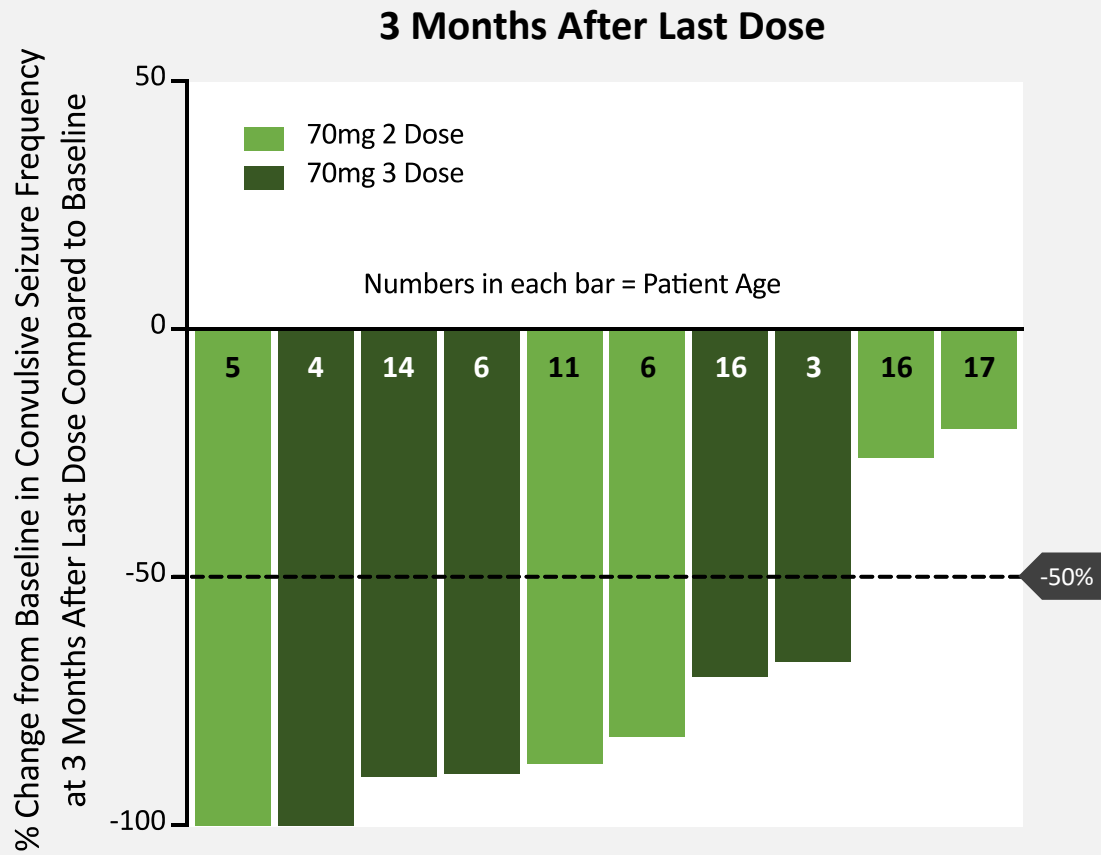
# Substantial and Sustained Reductions in Seizure Frequency with 1, 2 or 3 Doses of Zorevunersen (70mg)

Benefits observed across highly refractory patients already taking best available anti-seizure medicines



# ~80% of Patients Treated with 2 or 3 Doses of Zorevunersen (70mg) Experienced >50% Reduction in Seizures

A 50% responder rate is an important measure of efficacy



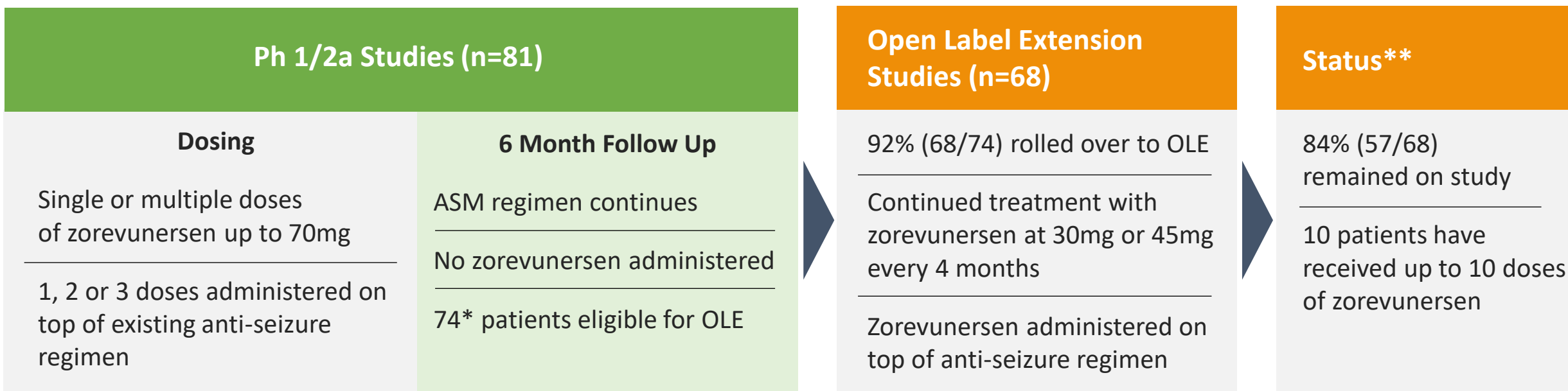
Note: 3 months after last dose refers to D113 to D140 (2 dose MAD) and D141 to D168 (3 dose MAD) and 6 months after last dose refers to D197 to D224 (2 dose MAD) and D225 to D252 (3 dose MAD)  
2 and 3 dose data is from UK ADMIRAL study

# Phase 1/2a Data Support a Potential 70mg Loading Dose Regimen in a Phase 3 Registrational Study

The most substantial reductions in seizures observed with 2 and 3 doses of 70mg

- 85% at 3 months and 74% at 6 months post last dose
- ~80% of patients experienced >50% reduction in convulsive seizure frequency

## Patient Progression Through Studies



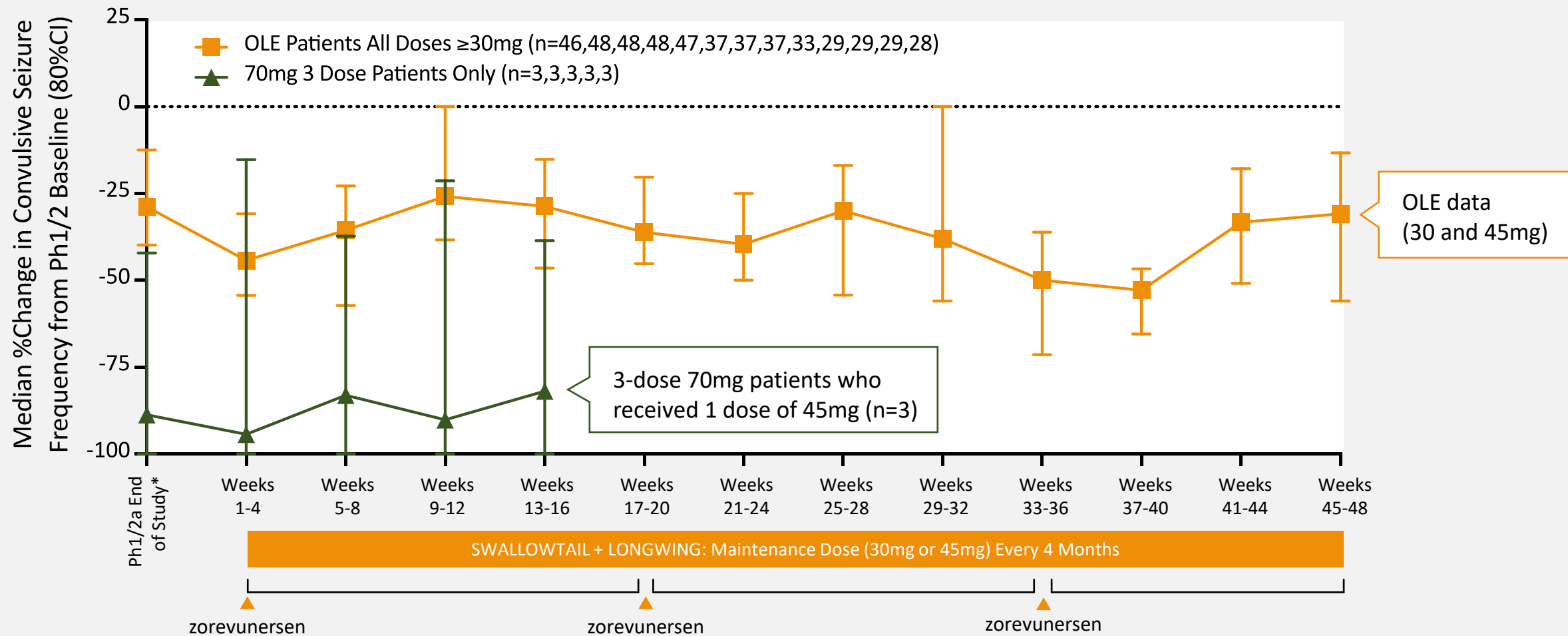
\*6 additional patients had not yet completed Phase 1/2a at the time of the OLE data cut.

\*\*Data cutoff dates: Phase 1/2a Studies 12DEC2023; OLE Studies 01NOV2023



# Durable Reductions in Seizure Frequency Observed with Continued Treatment with Zorevunersen in OLE Studies

OLE seizure analysis included patients that received  $\geq 30\text{mg}$  in Phase 1/2a studies

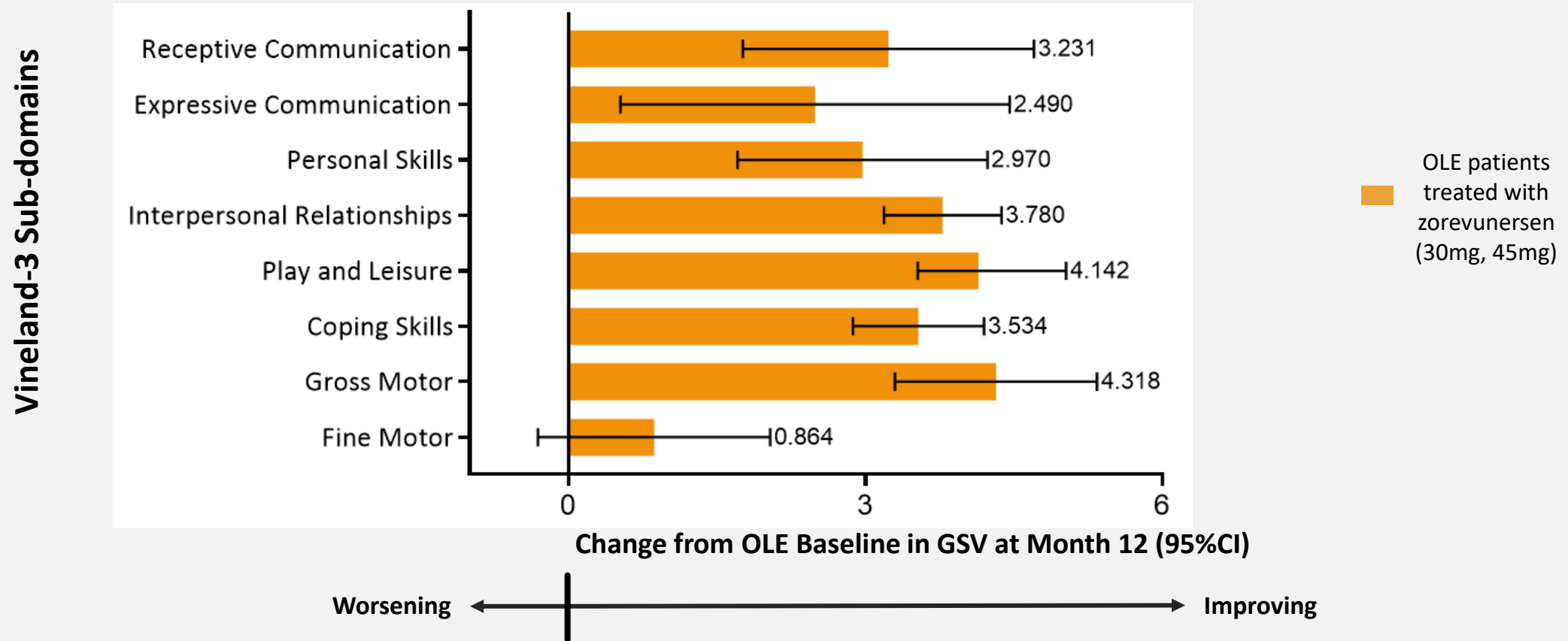


\*End of Study = 24 Weeks After Last Dose in Phase 1/2 Study.

Note: Of the 81 total patients in the Phase 1/2a studies, 15 patients from the 70mg cohort had not been evaluated in the OLE at the data cut and 18 patients received  $< 30\text{mg}$  or did not roll over into the OLE, resulting in 48 patients in the OLE seizure analysis shown above.

# Meaningful Improvements in Cognition and Behavior Over 12 Months with Continued Treatment with Zorevunersen (30mg, 45mg)

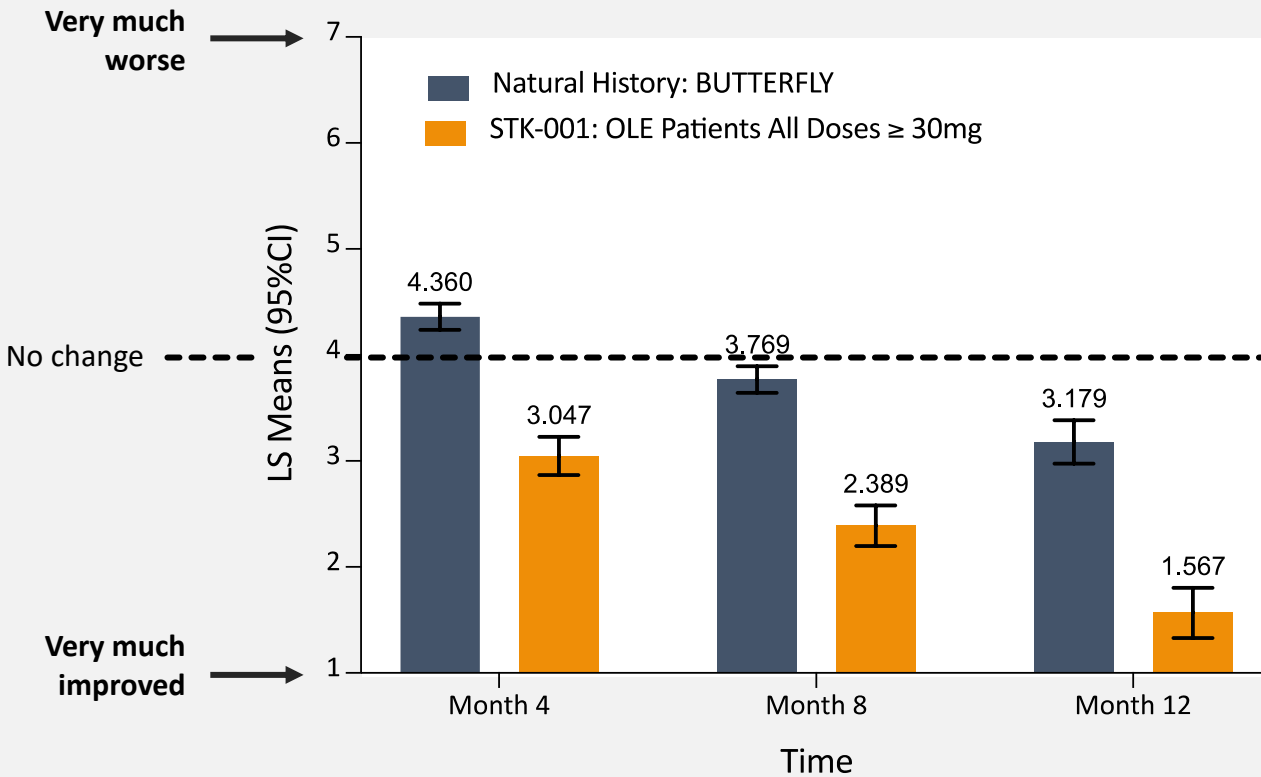
Improvements are in stark contrast to natural history study data



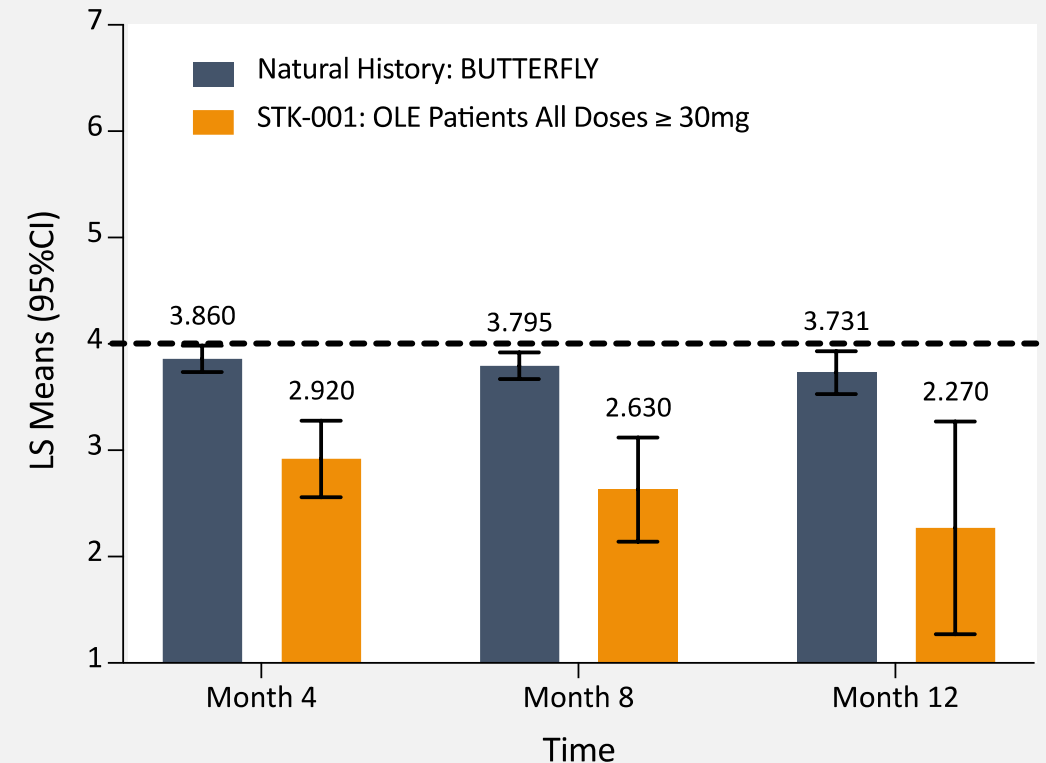
# Meaningful Improvements in Overall Condition Over 12 Months with STROKE THERAPEUTICS Continued Treatment with Zorevunersen (30mg, 45mg)

Consistency across clinician and caregiver assessments of improvements observed in the OLEs

Clinical Global Impression of Change (CGI-C)



Caregiver Global Impression of Change (CaGI-C)



Note: Analysis based on a mixed-effects model for repeated measures (MMRM). Data from BUTTERFLY through Month 24 from start of study analyzed with machine learning. Due to differences between trials, cross-study comparisons may provide limited information on the efficacy or safety of a drug.

# Single & Multiple Doses Up To 70mg Were Generally Well-Tolerated

No new safety findings related to study drug

## Phase 1/2a Studies (n=81)

**30%** had a TEAE related to study drug. CSF protein elevations and procedural vomiting were the most common

**22%** had a TESAE. These events were assessed as unrelated to study drug except for the previously reported case of one patient who experienced SUSARs

## OLE Studies (n=68)

**74%** had CSF protein elevations\*. No clinical manifestations have been observed in patients with elevated CSF protein levels. 1 patient discontinued treatment due to elevated CSF protein

\* >1 CSF protein value >50mg/dL

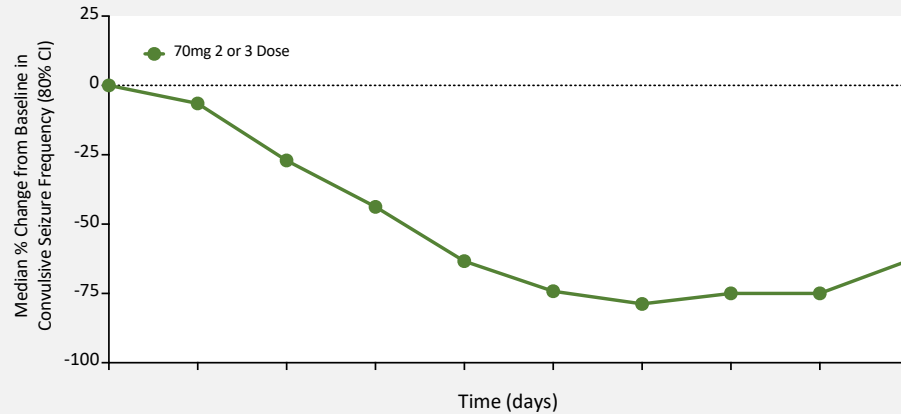
TEAE: treatment-emergent adverse event.

TESAE: treatment-emergent serious adverse event

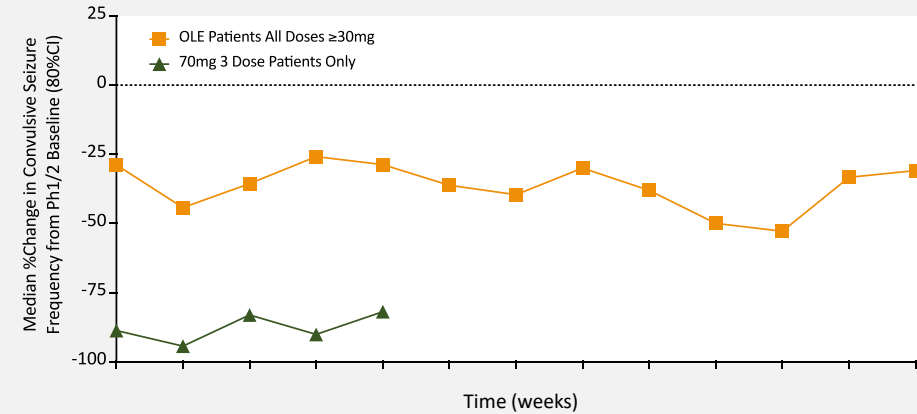
SUSARs: Suspected Unexpected Serious Adverse Reactions

# Landmark New Data Support the Potential for Zorevunersen to be the First Medicine to Treat the Underlying Cause of Dravet Syndrome

**Phase 1/2a (2 and 3 doses of 70mg):**  
**Substantial & sustained** reductions in seizure frequency

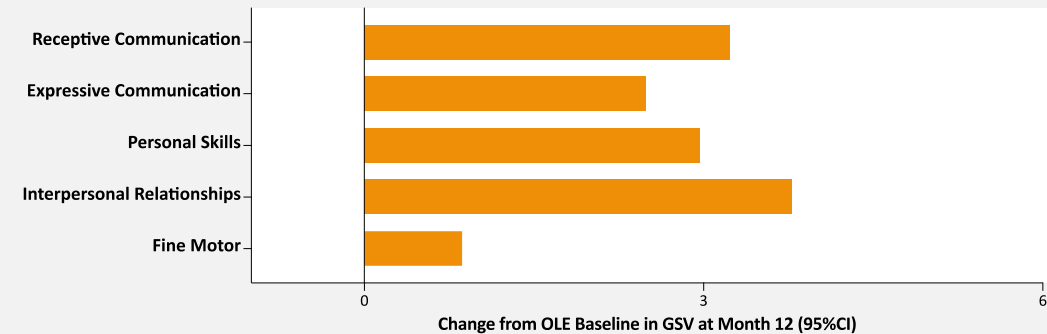


**Open-Label Extensions (30mg, 45mg):**  
**Durable** reductions in seizures with dosing every 4 months



**Next Steps:** Meet with regulatory agencies to discuss Phase 3 registrational study of 70mg followed by 45mg

**OLE (30mg, 45mg): Meaningful improvements**  
in multiple measures of **cognition & behavior** over 12 months



# Autosomal Dominant Optic Atrophy (ADOA): A Severe, Progressive Optic Nerve Disorder

**65-90%**

of cases caused by mutations in one allele of the *OPA1* gene, most of which lead to a **HAPLOINSUFFICIENCY**



RESULTING in



**50%**

*OPA1* protein expression and disease manifestation

**1 out of 30,000**

people are affected globally with a higher incidence of ~1 out of 10,000 in Denmark due to a founder effect



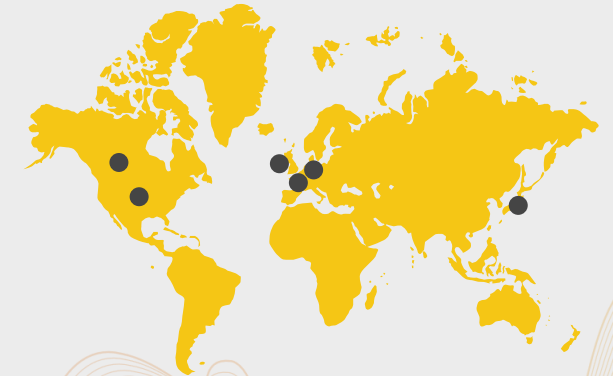
Up to

**46%**

of patients are registered legally blind

**~18,000**

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



**>400**

Different *OPA1* mutations reported in ADOA patients

**80%**

of patients are symptomatic by age 10

# No Approved Disease-Modifying Therapies for ADOA

## Healthy Vision



## Simulation of Optic Neuropathy



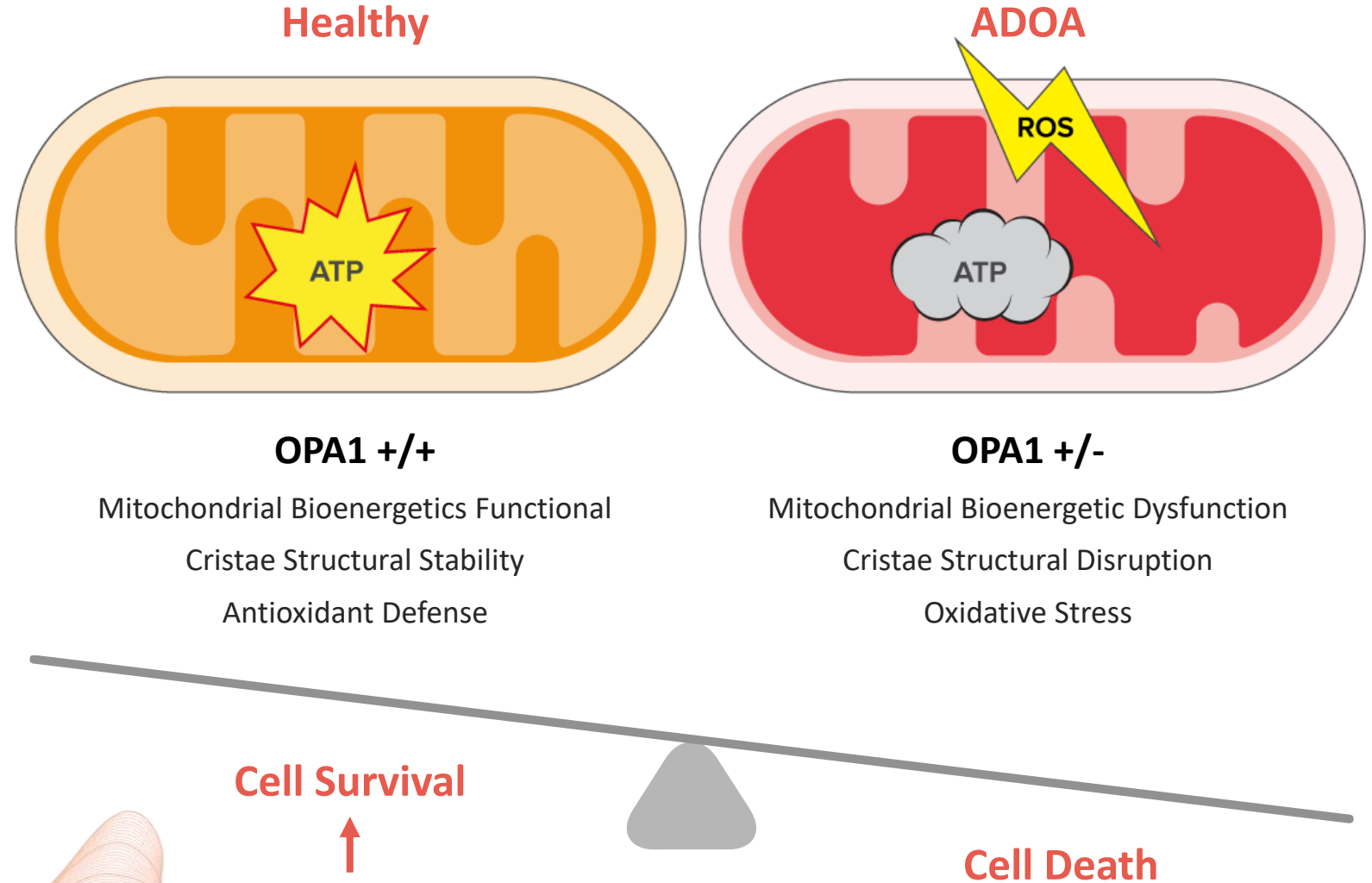
- Most common inherited optic nerve disorder
- Leads to central field defects and reduced color vision in both eyes
- Severity can vary; rate of vision loss difficult to predict
- Supportive services and low-vision aids are offered for patients



Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013; Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol*, 2016  
Image of child sourced from ICR, Ophthalmology Center Barcelona. Accessed Jan. 8, 2021 from <https://icrcat.com/en/eye-conditions/leber-hereditary-optic-neuropathy/>  
Credit: Lhon Eye Society Sweden. Image shown depicts Leber Hereditary Optic Neuropathy, which presents visual effects similar to ADOA.

# OPA1 is Critical for Normal Mitochondrial Function and Cellular Metabolism

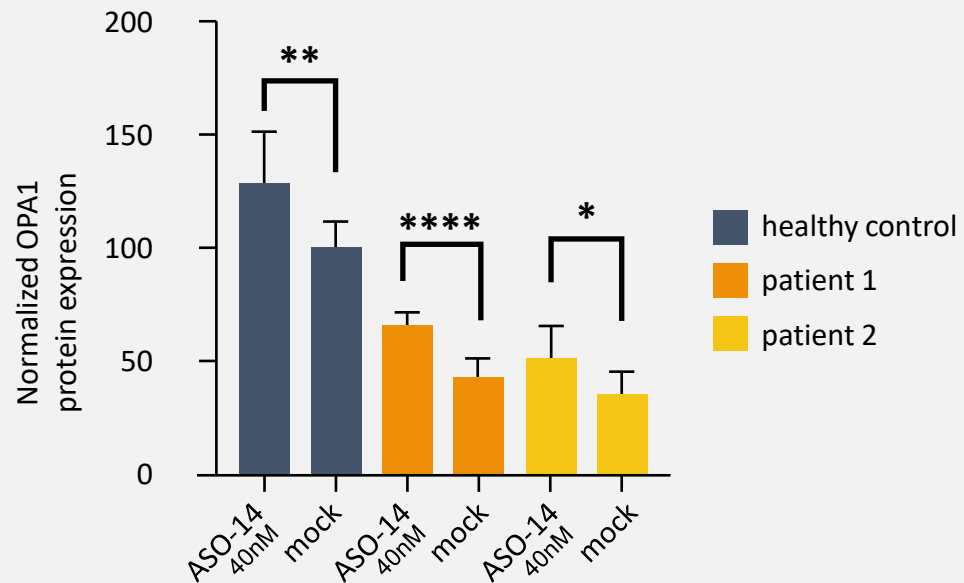
- Retinal ganglion cells have very high energy (ATP) requirements
- Impaired mitochondrial function leads to cell death
- OPA1 is critical for mitochondrial function and energy production



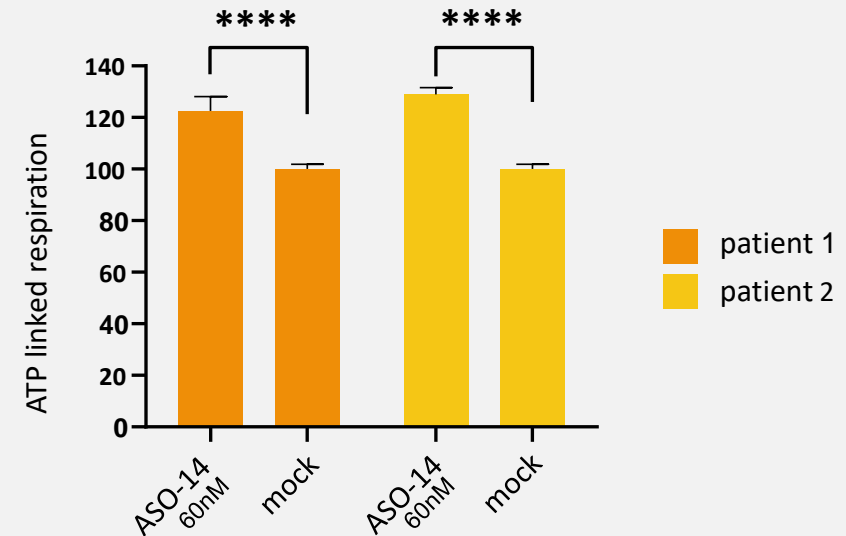


# TANGO ASO Increases OPA1 Protein and ATP Linked Mitochondrial Respiration in ADOA Patient Cells

ASO treatment increased OPA1 protein levels in OPA1 deficient ADOA patient cells



ASO treatment increased ATP linked respiration in OPA1 deficient ADOA patient cells

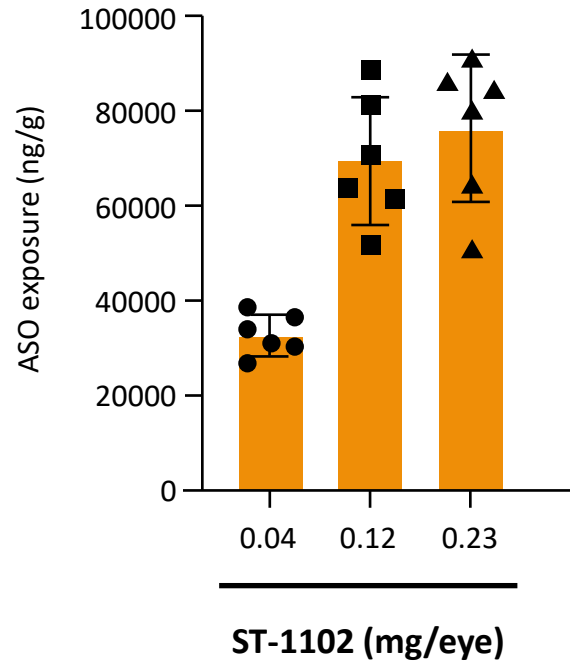


Source (left graph): Stoke data

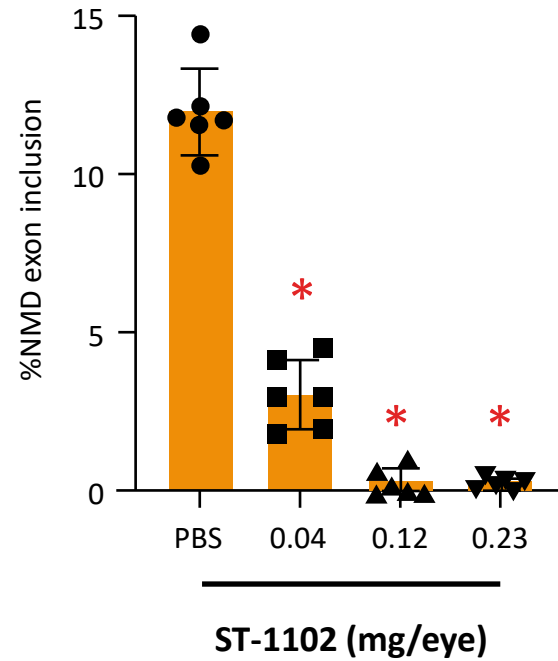
Source (right graph): Venkatesh A, et al. Antisense Oligonucleotide STK-002 Increases OPA1 in Retina and Improves Mitochondrial Function in Autosomal Dominant Optic Atrophy Cells. Nucleic Acid Therapeutics, September, 2024.

# TANGO ASO Demonstrates Dose-Dependent OPA1 Protein Increases in Rabbit Retina

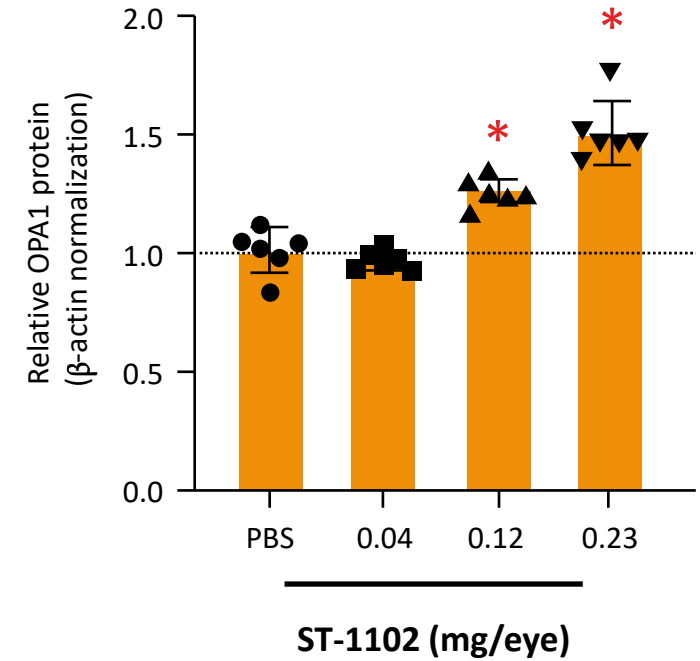
ASO exposure in retina  
Day 29



Target engagement  
Day 29



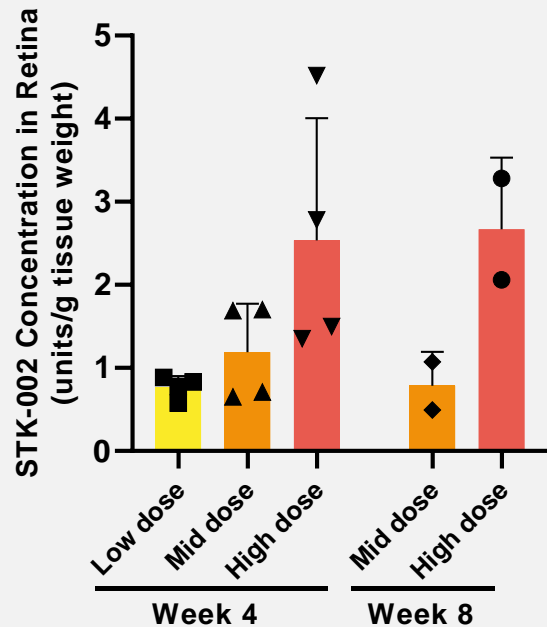
OPA1 protein  
Day 29



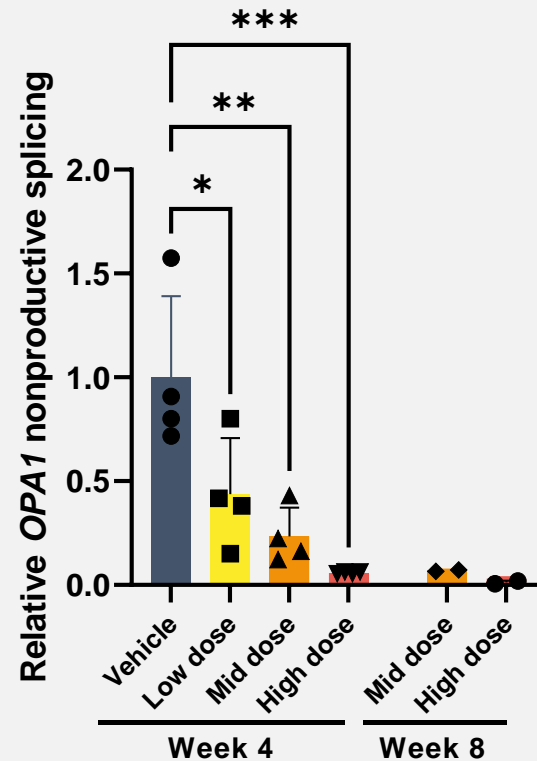
\* $P < 0.0005$  by one-way ANOVA compared to PBS group

# Dose-Related Target Engagement and OPA1 Protein Upregulation in Retinal Tissue of NHPs following IVT Administration of STK-002

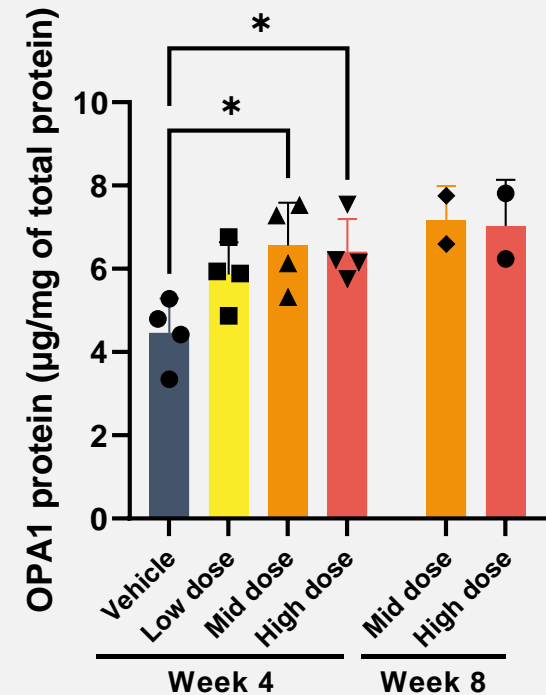
STK-002 exposure



Target engagement



OPA1 protein



NHP: Non-human primates

IVT: Intravitreal

Source: Venkatesh A, et al. Antisense Oligonucleotide STK-002 Increases OPA1 in Retina and Improves Mitochondrial Function in Autosomal Dominant Optic Atrophy Cells.

Nucleic Acid Therapeutics, September, 2024.

# Our Pipeline of First-in-Class Disease-Modifying Potential Medicines

PROGRAM	TARGET	DISCOVERY & PRECLINICAL	PHASE 1/2	PHASE 3	PARTNER
<b>Central Nervous System</b>					
Dravet Syndrome	SCN1A	zorevunersen (STK-001)			100% Stoke Global
SYNGAP1	SYNGAP1				Stoke: Acadia 50:50
Rett Syndrome	MECP2				Acadia Worldwide License
Undisclosed	Undisclosed				Acadia Worldwide License
<b>Ophthalmology</b>					
ADOA	OPA1	STK-002			100% Stoke Global

# Rett Syndrome: A Severe, Debilitating Neurological Disorder

~33%

of cases caused  
by hypomorphic  
mutations of the *MECP2*  
gene<sup>1</sup>

RESULTING in

Partial loss of  
function of the  
MeCP2 protein



**1** out of **10,000** to **15,000** females are born with Rett syndrome<sup>2</sup>

Period of rapid  
decline typically  
begins between

**6 to 18**  
months<sup>4</sup>

Symptoms include<sup>3</sup>:

- **Loss of purposeful hand use**
- **Involuntary hand movements such as handwringing**
- **Loss of speech**
- **Loss of mobility or gait disturbances**



**60-80%** of patients have **epilepsy**<sup>4</sup>

Note: All seizure types have been reported in Rett syndrome. Complex partial and generalized tonic-clonic are the most common  
Sources: <sup>1</sup> RettBase (<http://mecp2.chw.edu.au/>); GnomAD (<https://gnomad.broadinstitute.org/>); NOMAD; <sup>2</sup> National Institutes of Health – National Institute of Neurological Disorders and Stroke; <sup>3</sup> International Rett Syndrome Foundation; <sup>4</sup> Operta et al., Brain Behav 2019

# SYNGAP1: A Severe Intellectual Disability / Developmental and Epileptic Encephalopathy (ID/DEE)

>80%

of cases caused by a  
**HAPLOINSUFFICIENCY**  
of the *SYNGAP1* gene<sup>1</sup>

RESULTING in

50%

SynGAP protein  
expression



**1-2** out of **100,000** children are born with SYNGAP1-ID/DEE



**1-2%**

of all **intellectual disability**  
cases<sup>2</sup>

**100%**

of patients have **developmental delay**  
or **intellectual disability**<sup>3</sup>



**84%**

of patients have  
**generalized epilepsy**<sup>3</sup>

**~50%**

of patients have **autism and other**  
**behavioral abnormalities**<sup>3</sup>

# 2024 Summary of Priorities



## Advance Zorevunersen for Dravet Syndrome toward a Phase 3 Registrational Study

- ✓ Q1 Data Readout
- Discussions with FDA and global regulatory agencies continue to progress; Company to provide an update on Phase 3 registrational plans by year-end

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**\$269.2M in Cash, Cash Equivalents, and Marketable Securities as of 9/30/24**



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