Stoke Therapeutics

NASDAQ: STOK

September 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 produce candidates; 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

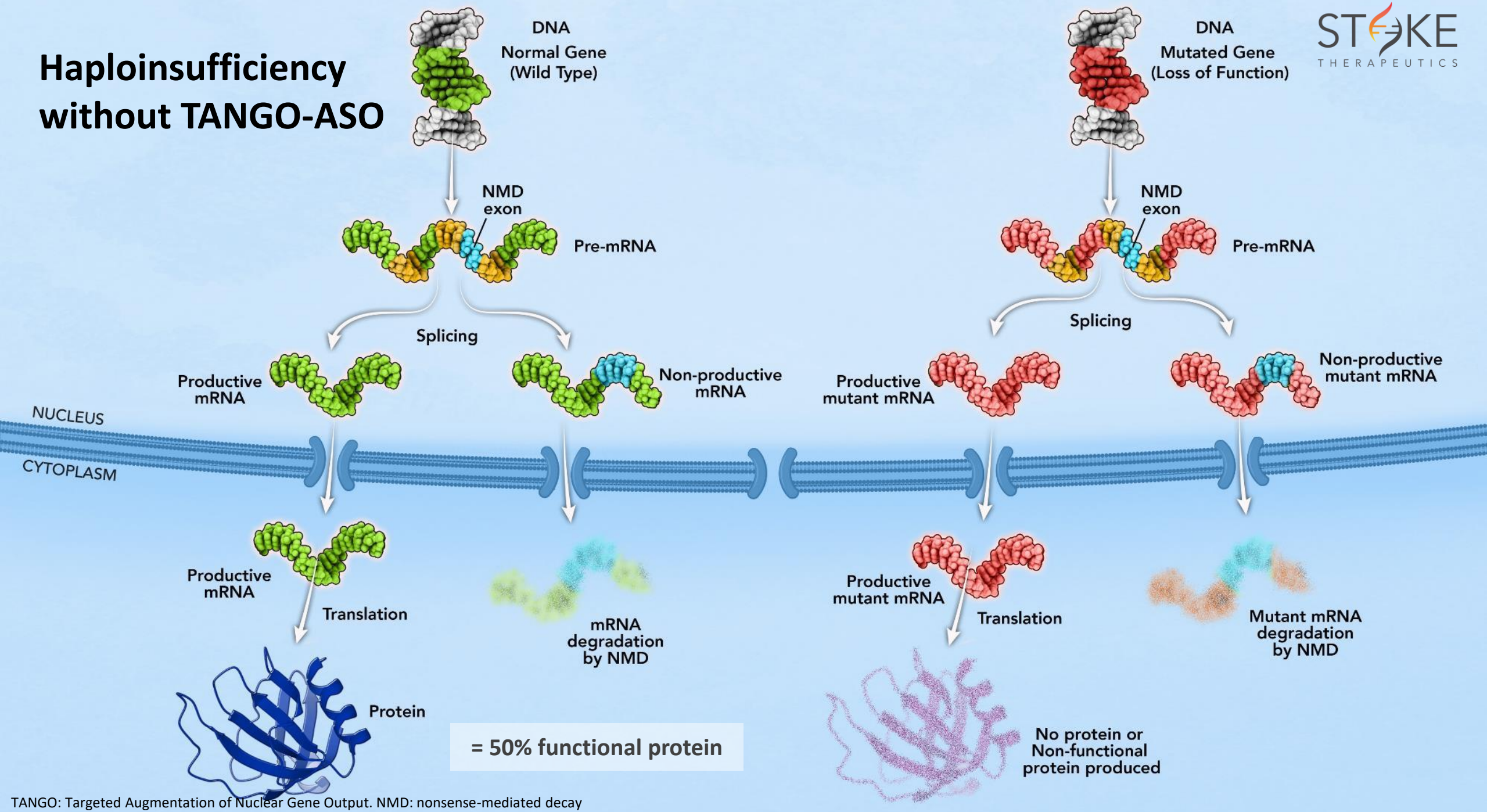
Utility across small and large gene targets and mutations

Does not alter DNA

Ability to control dose level and duration

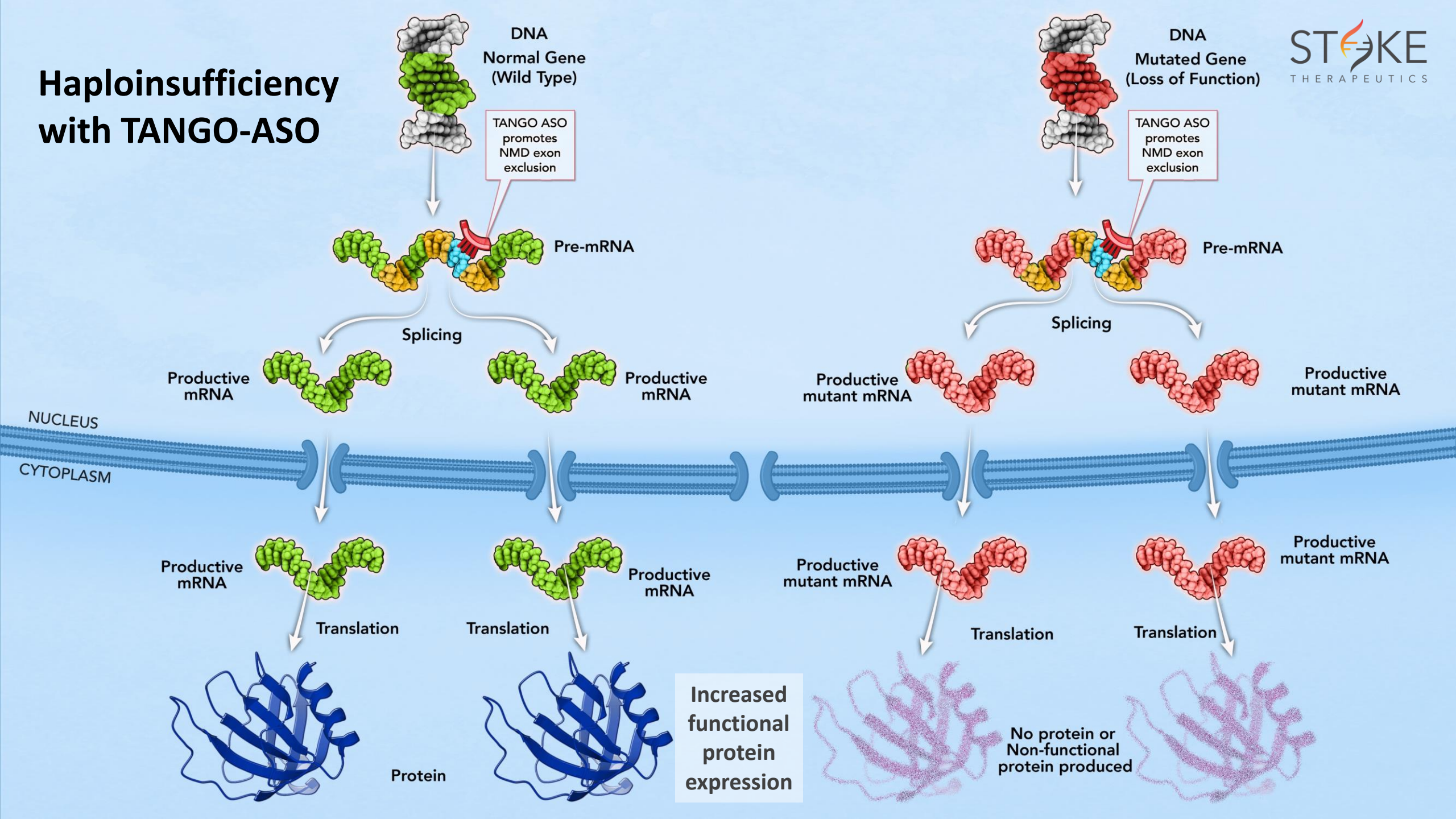
Simple and scalable manufacturing

Haploinsufficiency without TANGO-ASO



TANGO: Targeted Augmentation of Nuclear Gene Output. NMD: nonsense-mediated decay

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%
$Na_V1.1$ 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

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.”*

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**.”*

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**.”*

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**."*

Source: Voice of the Patient Report Published by the Dravet Syndrome Foundation, May 2022

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

Source: Lagae et al., Developmental Medicine & Child Neurology, 2017

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)

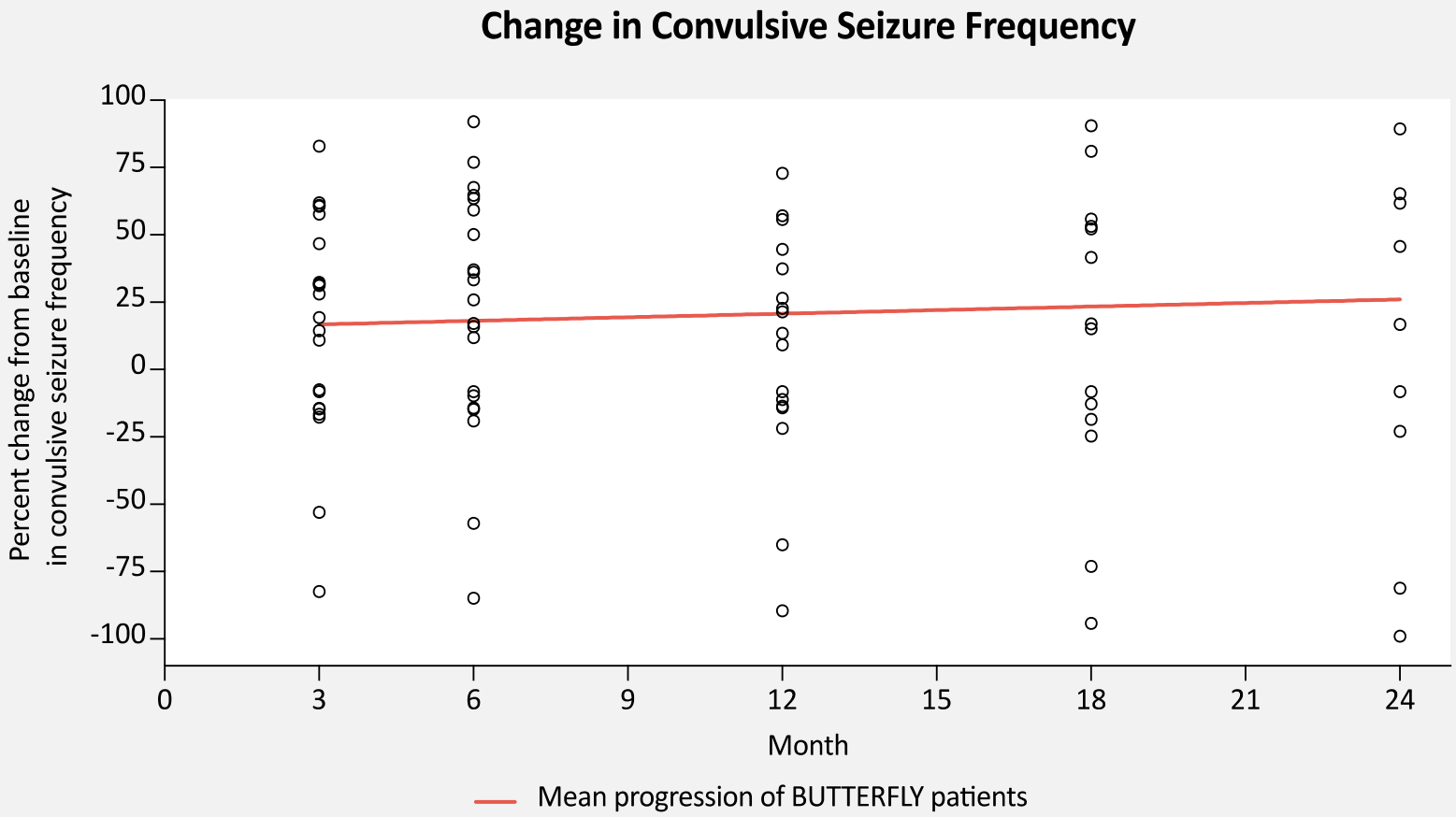
on top of the best available anti-seizure medicines

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

OLE: Open-Label Extension Study

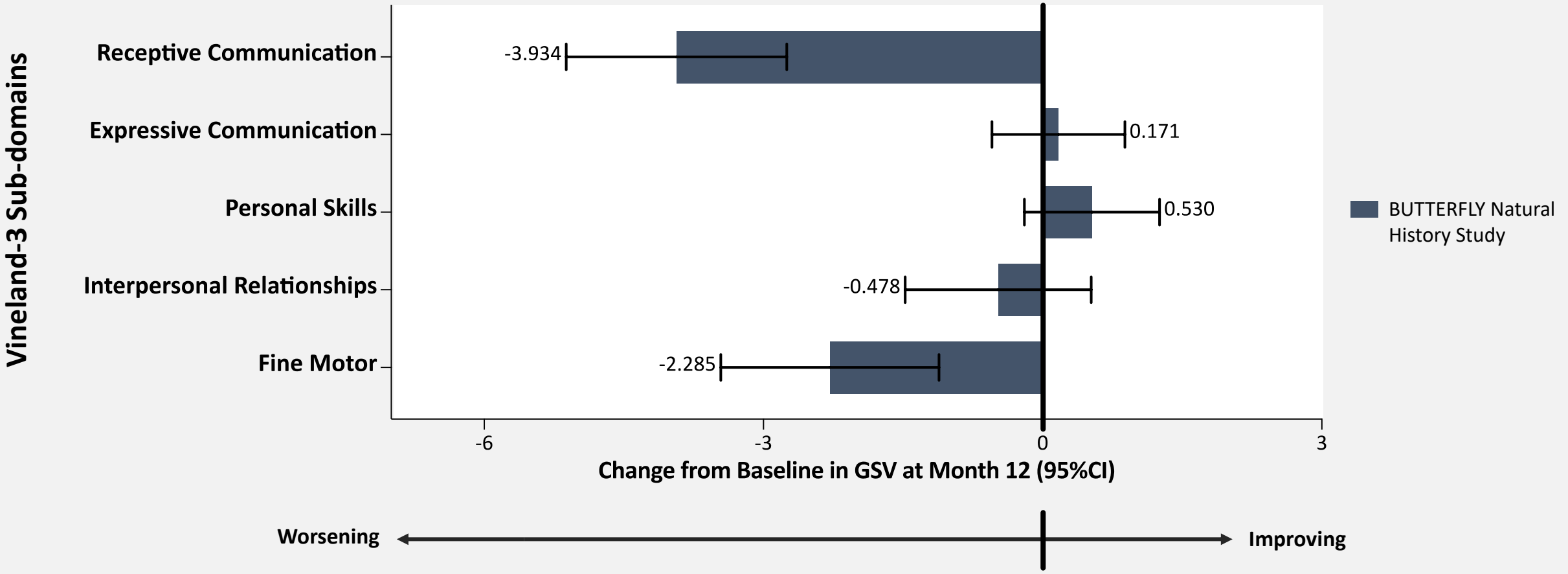
Natural History Data: Despite Standard Anti-Seizure Medicines, No Meaningful Improvement in Convulsive Seizure Frequency



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%)

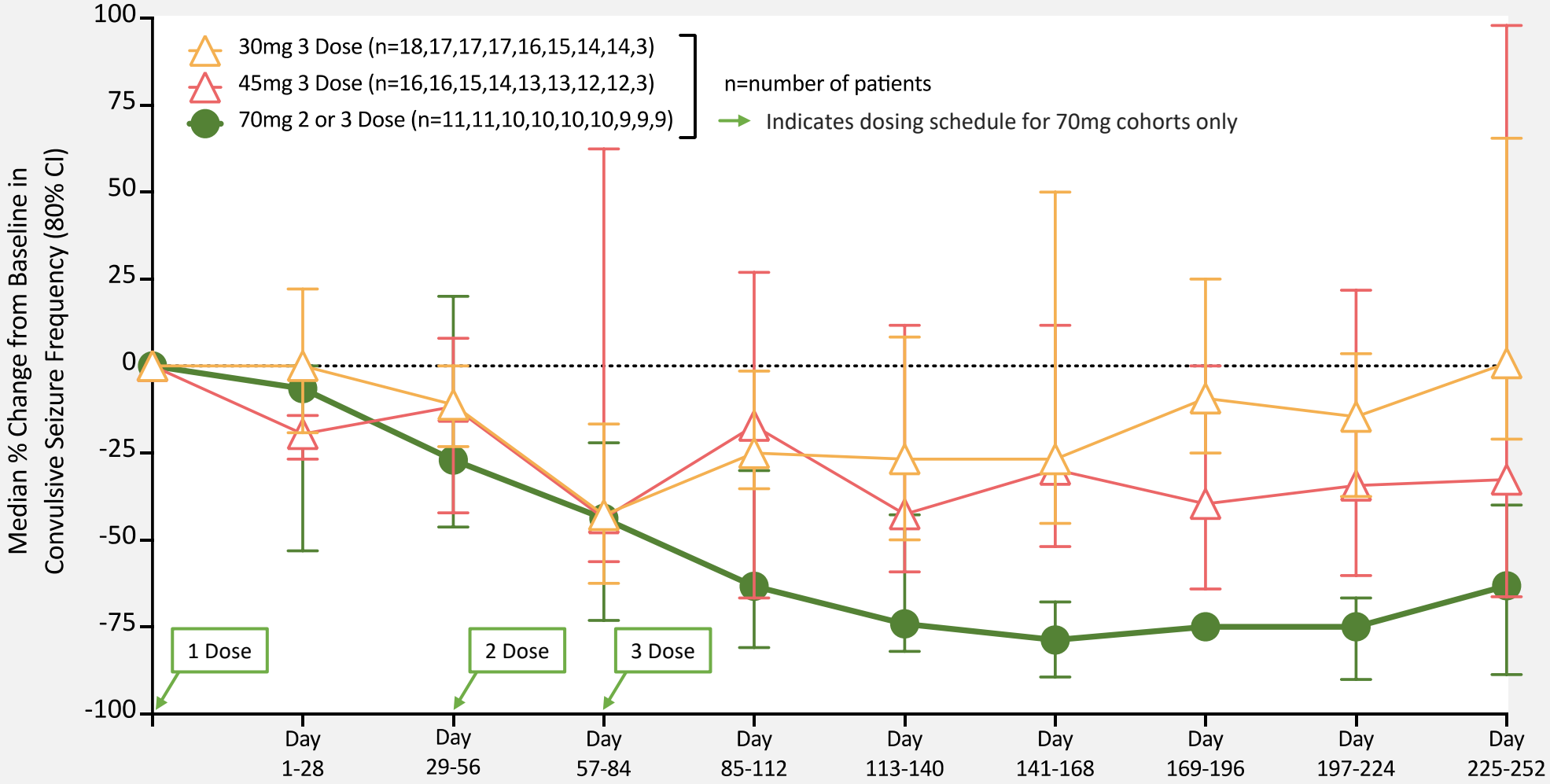
Source: 24-Month Analysis of BUTTERFLY: A Prospective, Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS), AES 2023.

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



Note: Analysis based on data from BUTTERFLY through Month 24 analyzed with Machine Learning.
Vineland-3: The Vineland Adaptive Behavior Scales, Third Edition. GSV = Growth Scale Value.

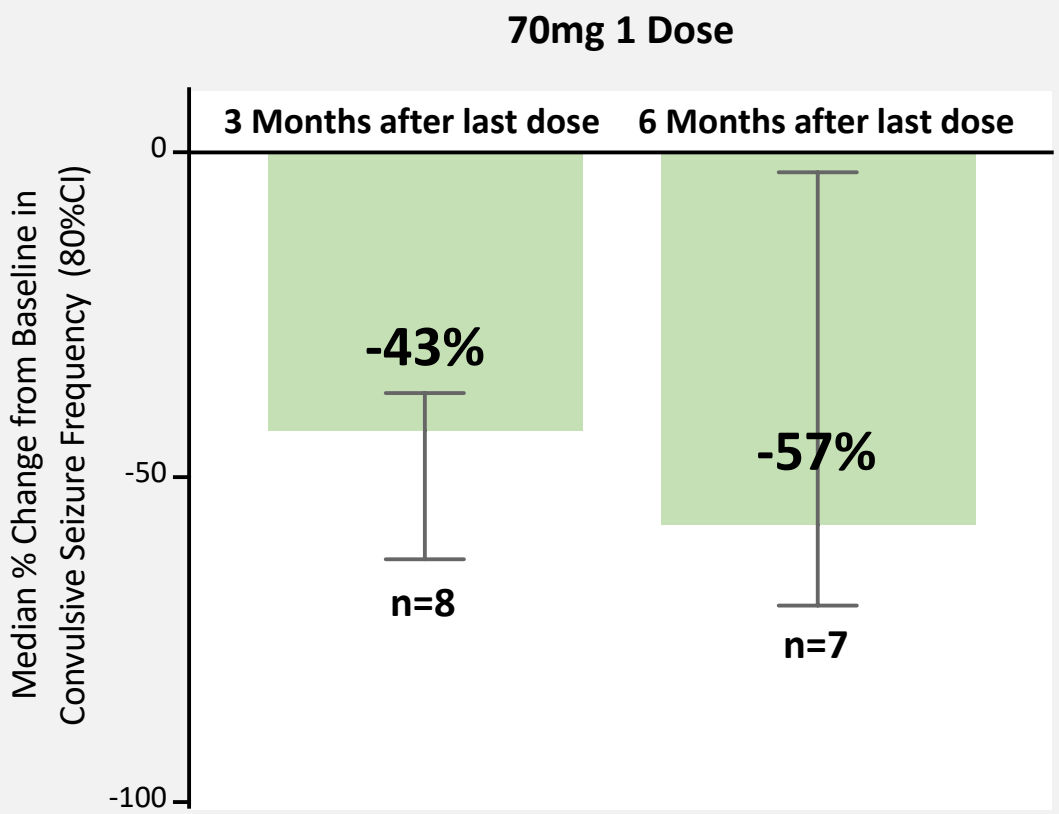
70mg Doses of Zorevunersen Demonstrated the Most Substantial Reductions in Seizure Frequency on Top of Standard of Care Medicines

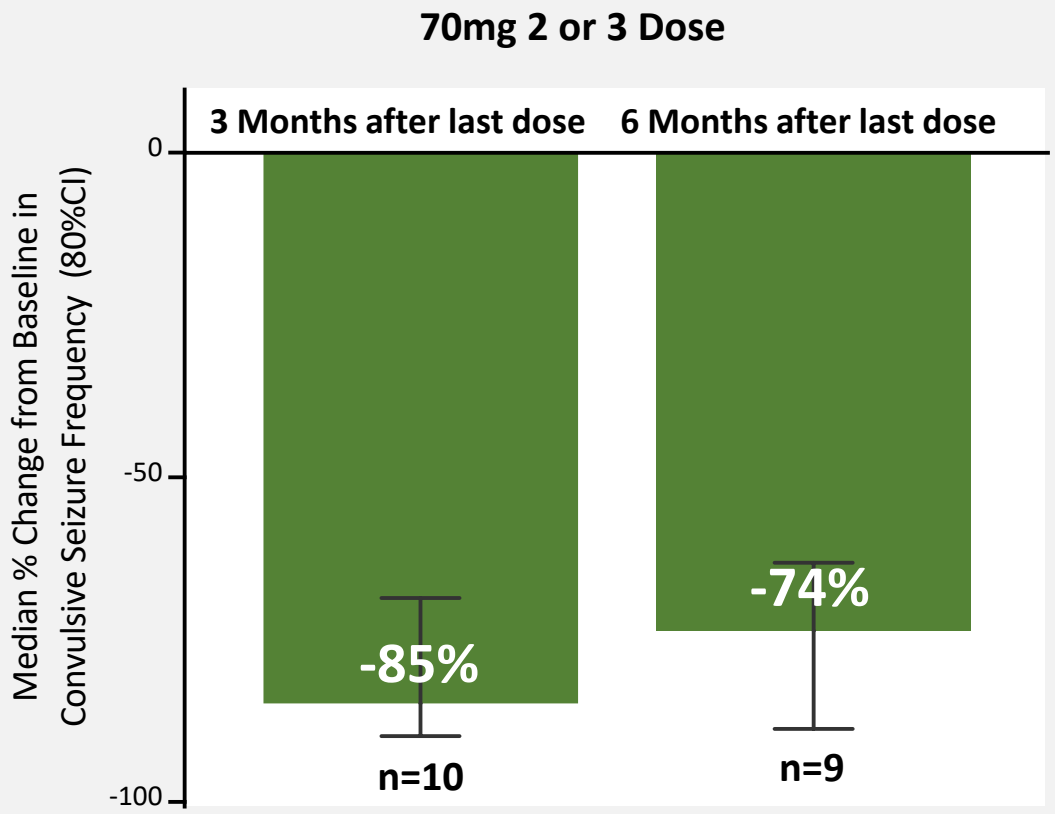


Source: Analysis of STK-001 for the treatment of Dravet syndrome, March 2024.

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

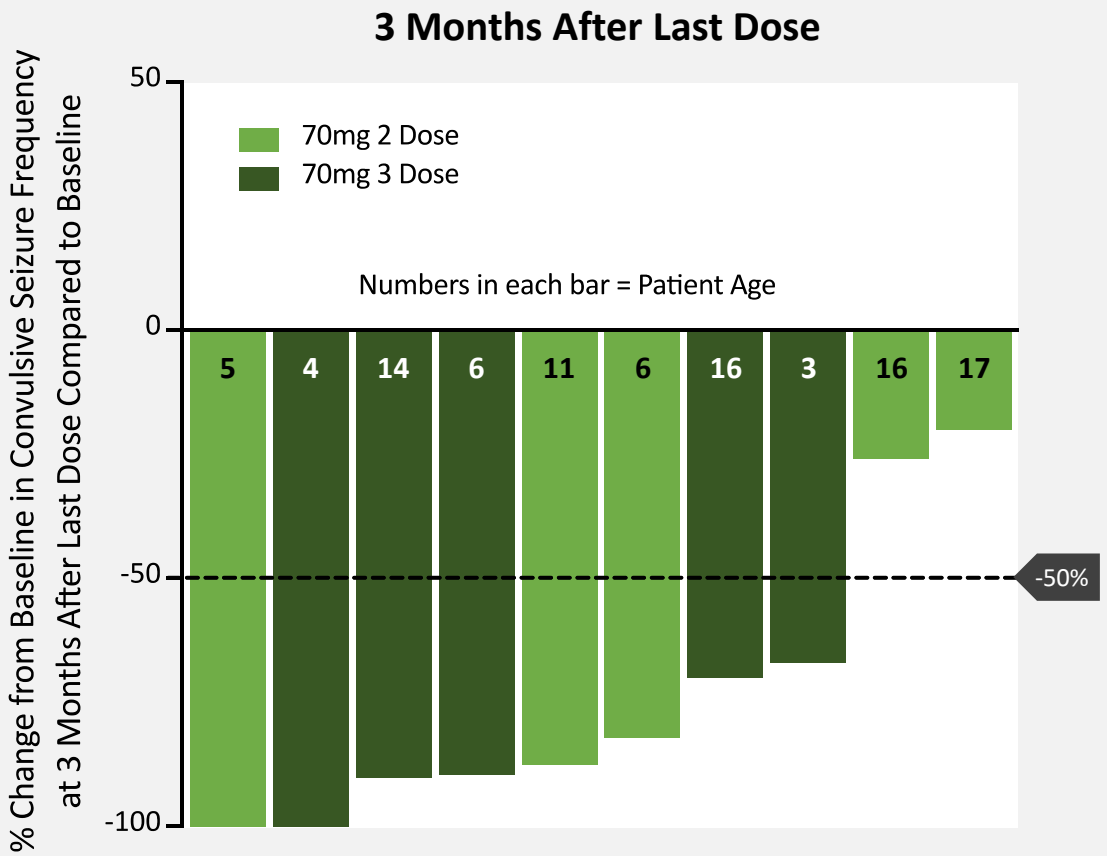


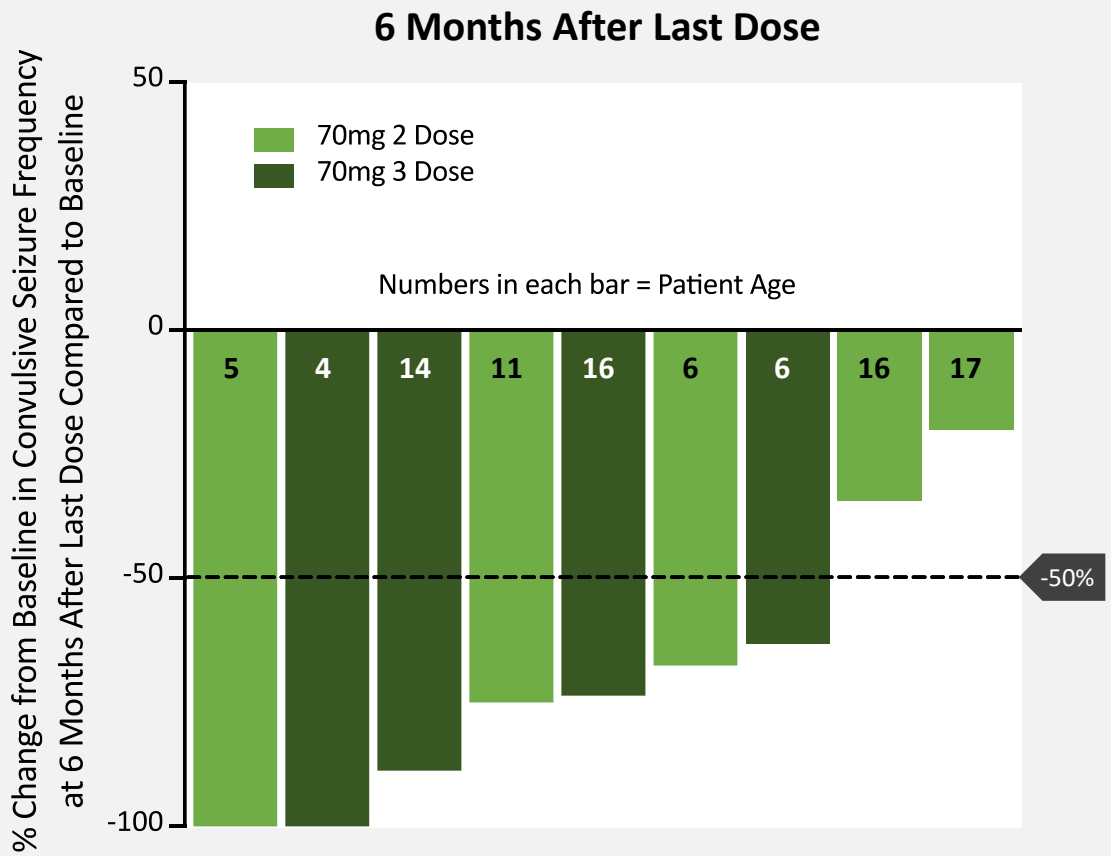


1 dose data is from the U.S. MONARCH study, 2 and 3 dose data is from UK ADMIRAL study

~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

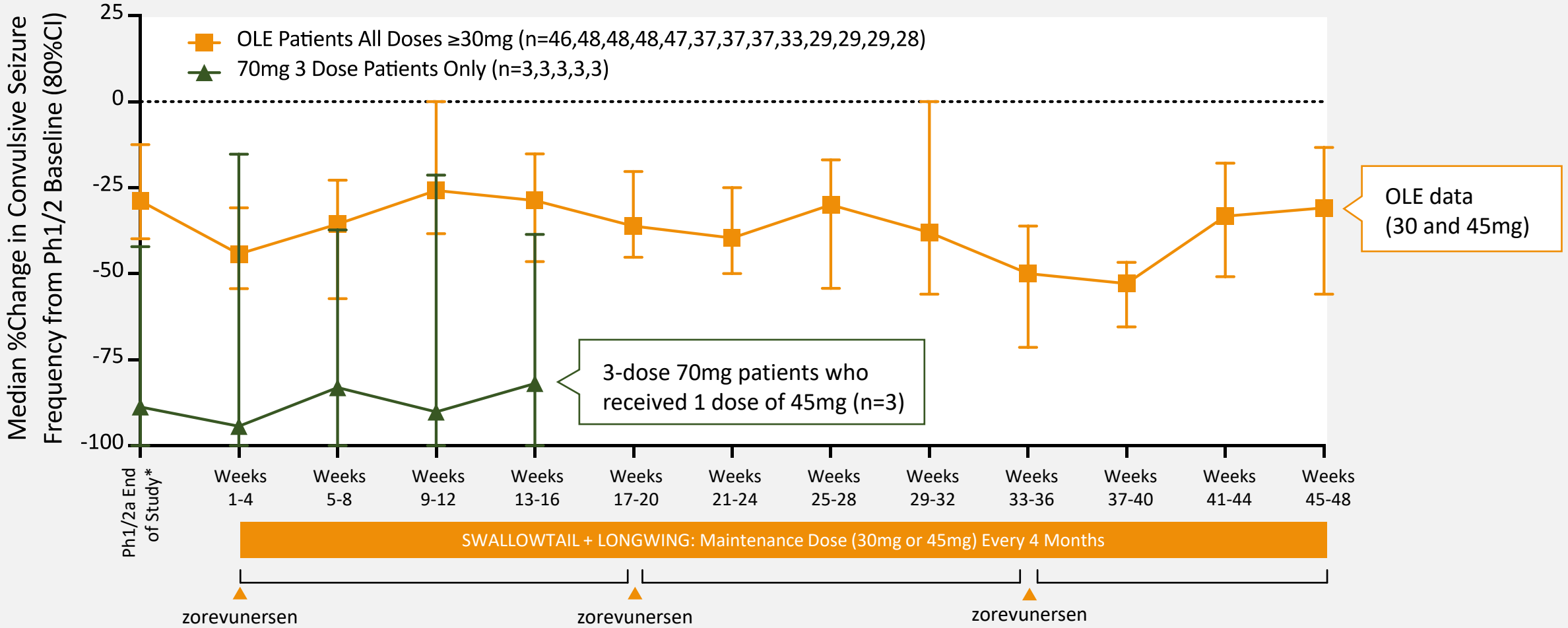
Patient Progression Through Studies

Ph 1/2a Studies (n=81)		Open Label Extension Studies (n=68)	Status**
Dosing	**6 Month Follow Up**	92% (68/74) rolled over to OLE	84% (57/68) remained on study
Single or multiple doses of zorevunersen up to 70mg	ASM regimen continues	Continued treatment with zorevunersen at 30mg or 45mg every 4 months	10 patients have received up to 10 doses of zorevunersen
1, 2 or 3 doses administered on top of existing anti-seizure regimen	No zorevunersen administered 74* patients eligible for OLE	Zorevunersen administered on top of anti-seizure regimen	

**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 ≥30mg in Phase 1/2a studies

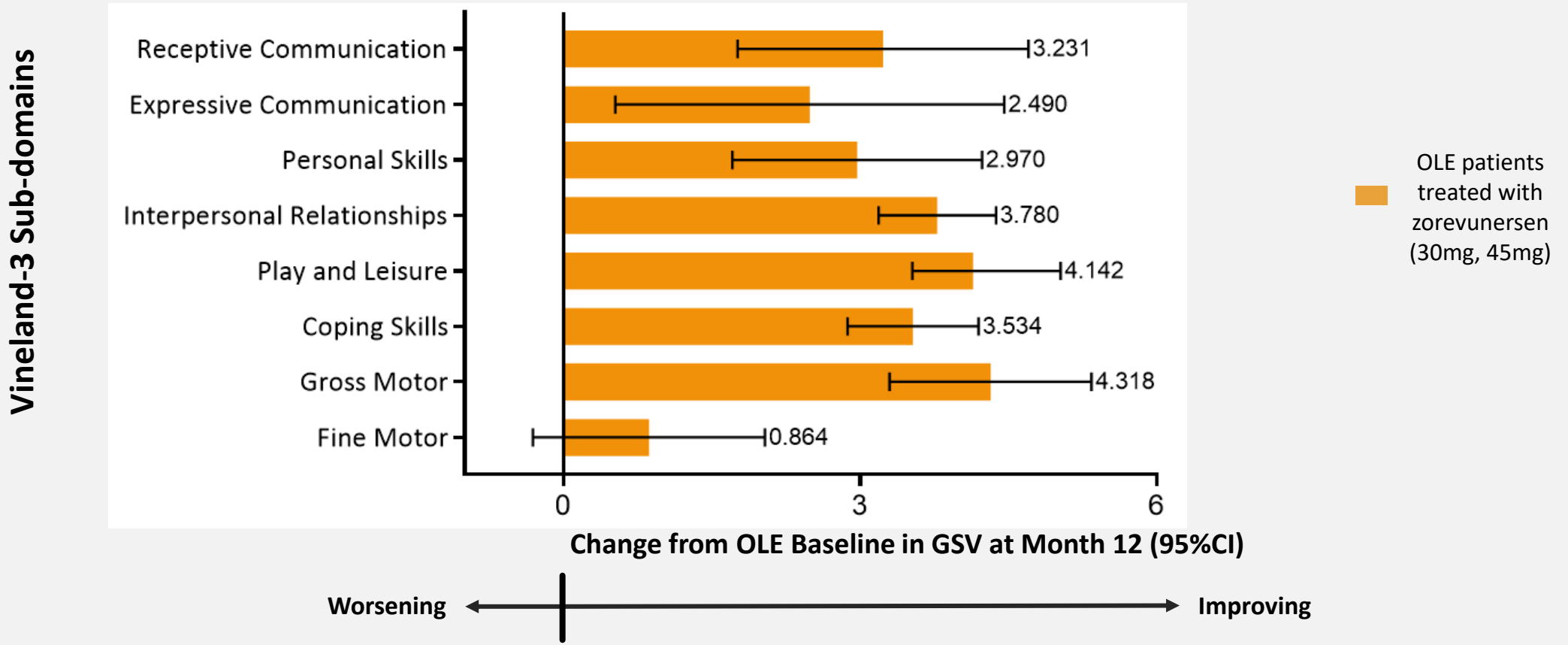


**End of Study = 24 Weeks After Last Dose in Phase 1/2 Study.*

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 <30mg 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)

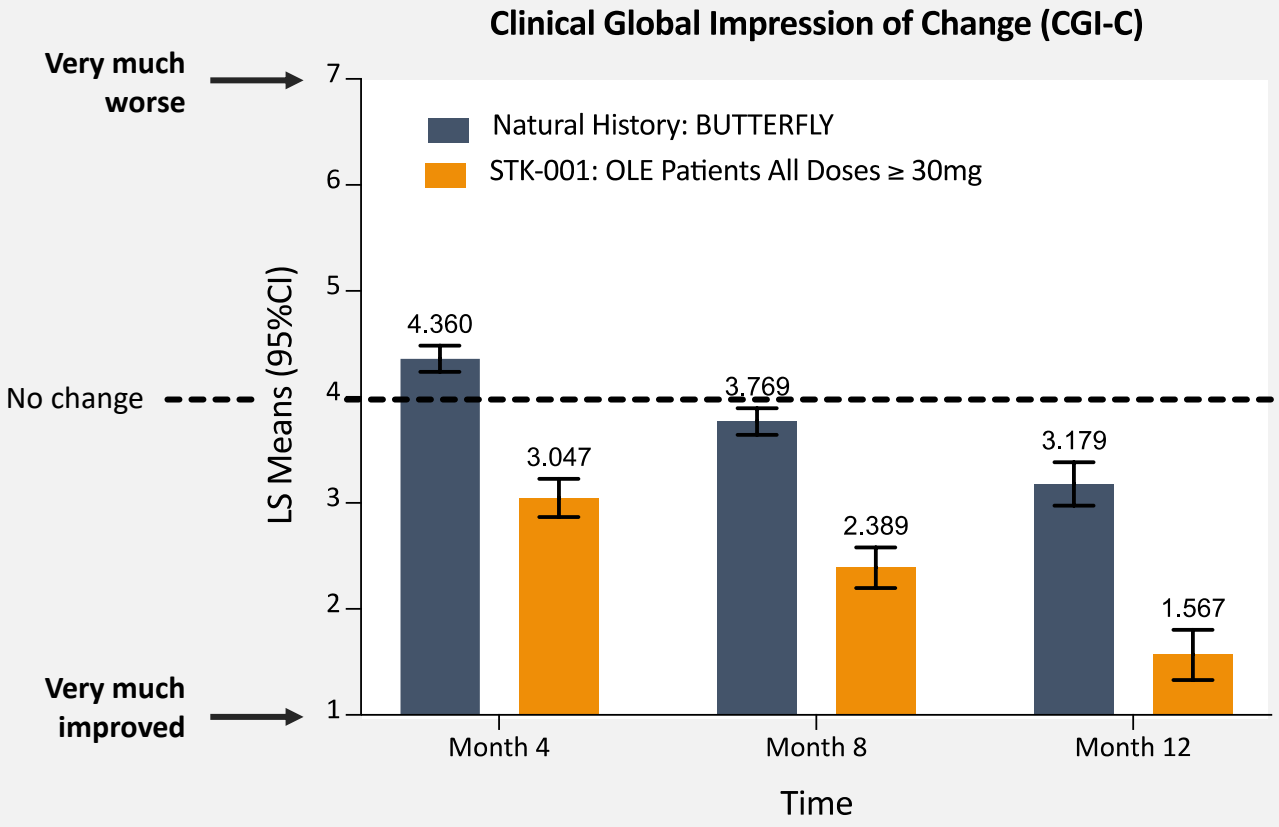
Improvements are in stark contrast to natural history study data

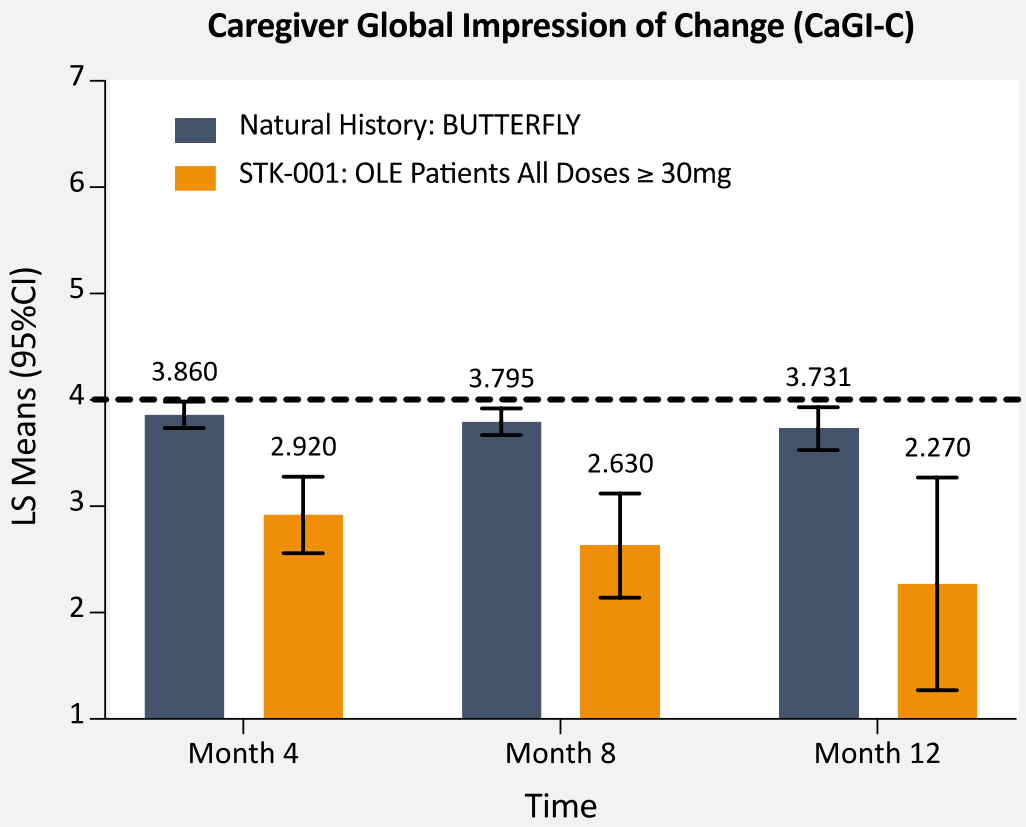


Note: Analysis based on a mixed-effects model for repeated measures (MMRM).
Vineland-3: The Vineland Adaptive Behavior Scales, Third Edition. GSV = Growth Scale Value.

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

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





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

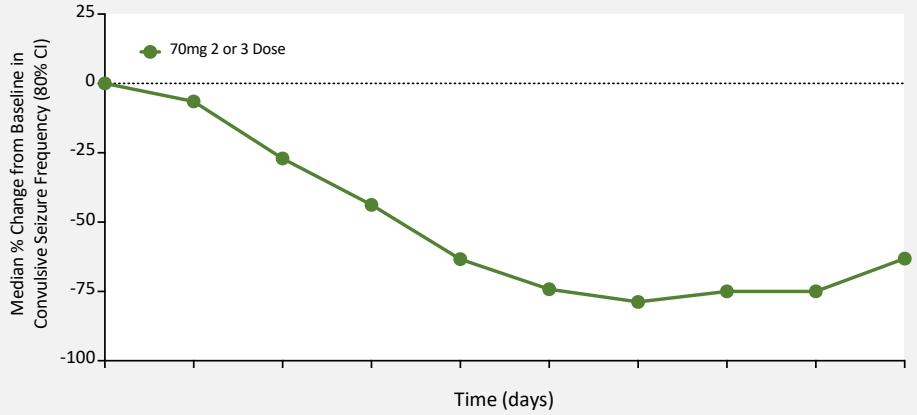
No new safety findings related to study drug

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

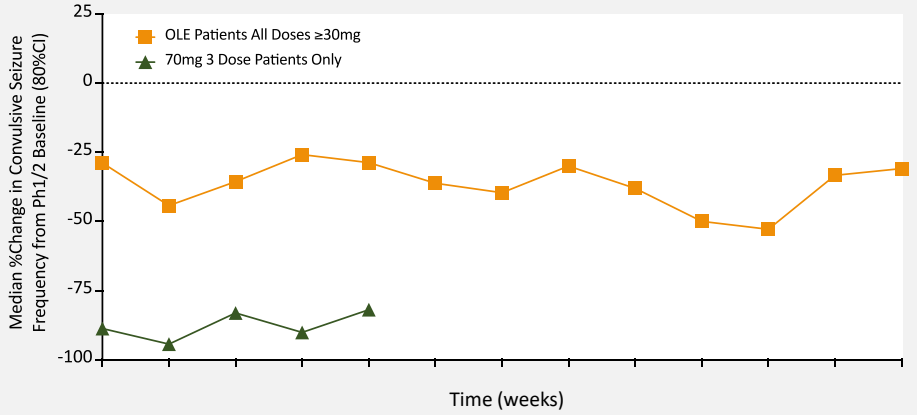
** >1 CSF protein value >50mg/dL*
TEAE: treatment-emergent adverse event.
TESAE: treatment-emergent serious adverse event
SUSARs: Suspected Unexpected Serious Adverse Reactions

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

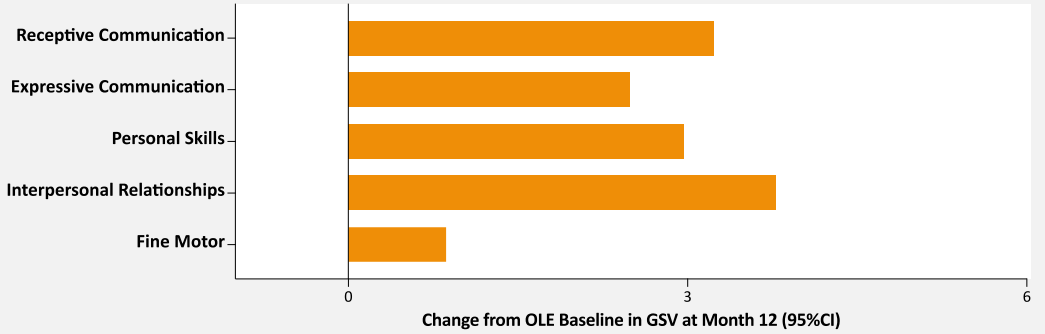


Open-Label Extensions (30mg, 45mg):
Durable reductions in seizures with dosing every 4 months



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

>400

Different *OPA1* mutations reported in ADOA patients

Up to 46%

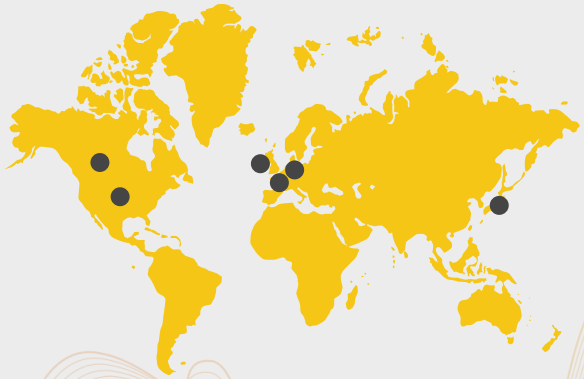
of patients are registered legally blind

80%

of patients are symptomatic by age 10

~18,000

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



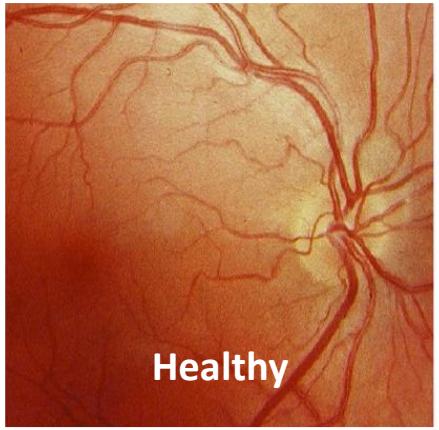
Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013; P. Amati-Bonneau P et al. *The International Journal of Biochemistry & Cell Biology*, 2009; Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol*, 2016; Le Roux B, Lenaers G, Zanlonghi X et al. *Orphanet J Rare Dis*, 2019; "What is ADOA?" Autosomal Dominant Optic Atrophy Association. Accessed May 6, 2020, from https://www.adoaa.org/what-is-adoa;

No Approved Disease-Modifying Therapies for ADOA

Healthy Vision

Simulation of Optic Neuropathy

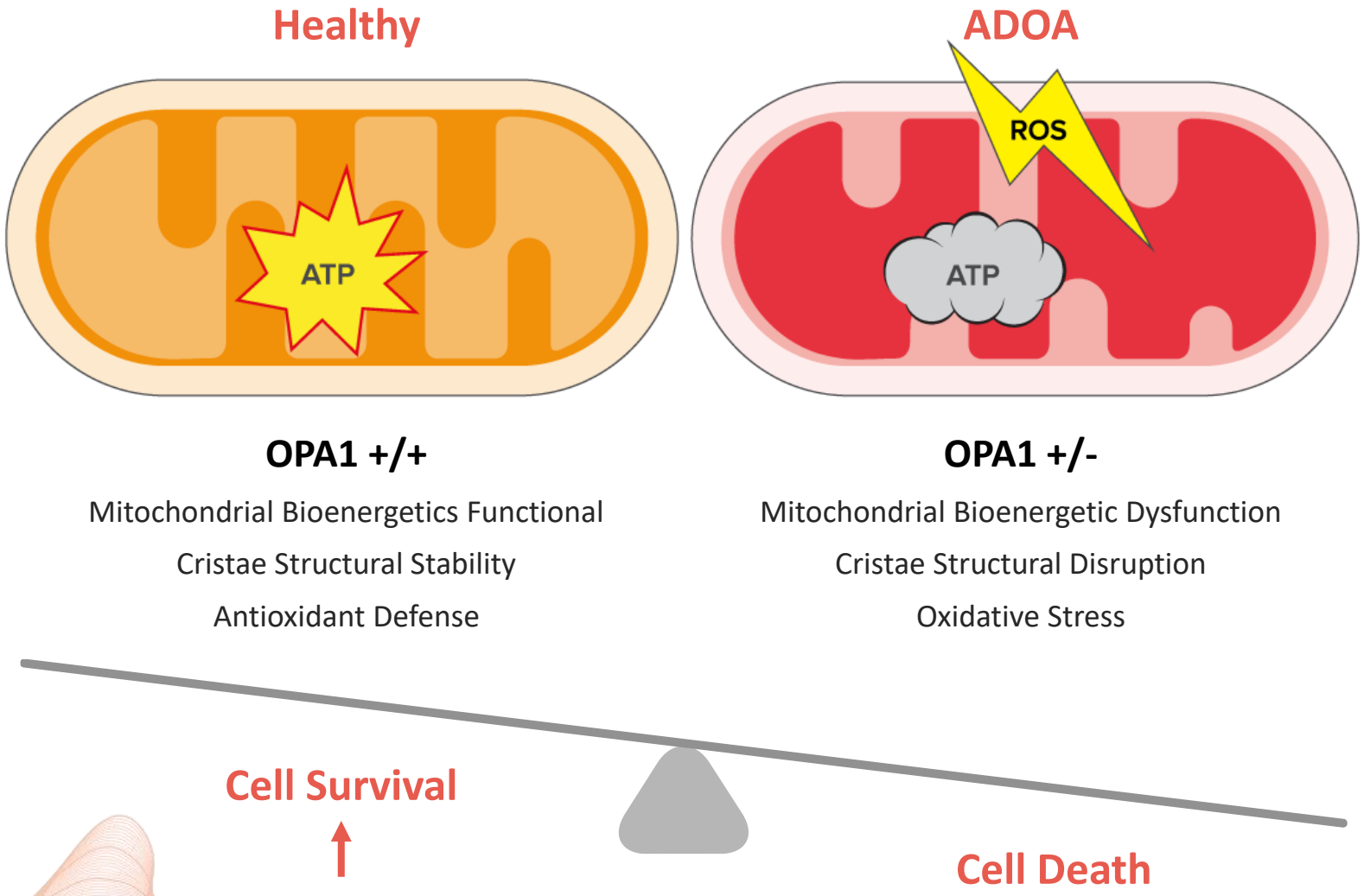
- Most common inherited optic nerve disorder
- Leads to central field defects and reduced color vision in both eyes
- Severity can vary; rate of vision loss difficult to predict
- Supportive services and low-vision aids are offered for patients



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

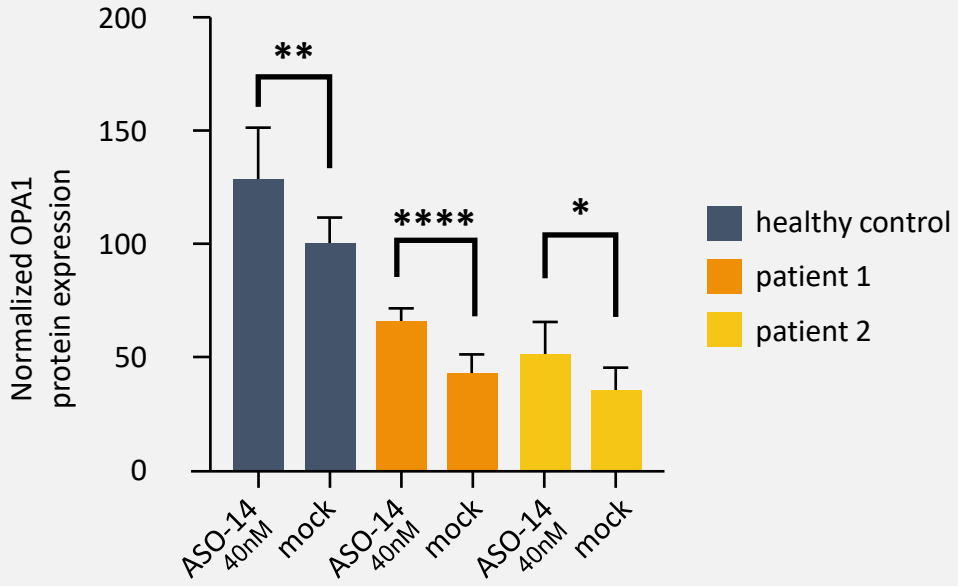
- Retinal ganglion cells have very high energy (ATP) requirements
- Impaired mitochondrial function leads to cell death
- OPA1 is critical for mitochondrial function and energy production



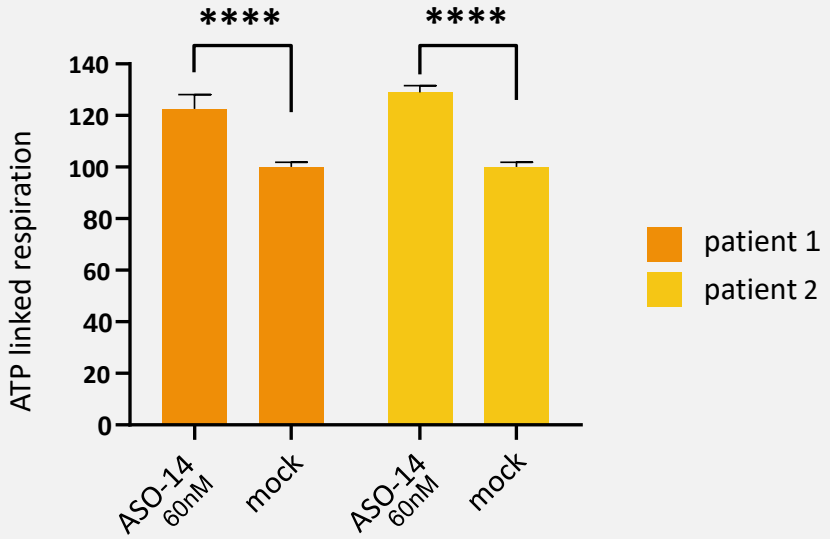
* ROS = Reactive Oxygen Species

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



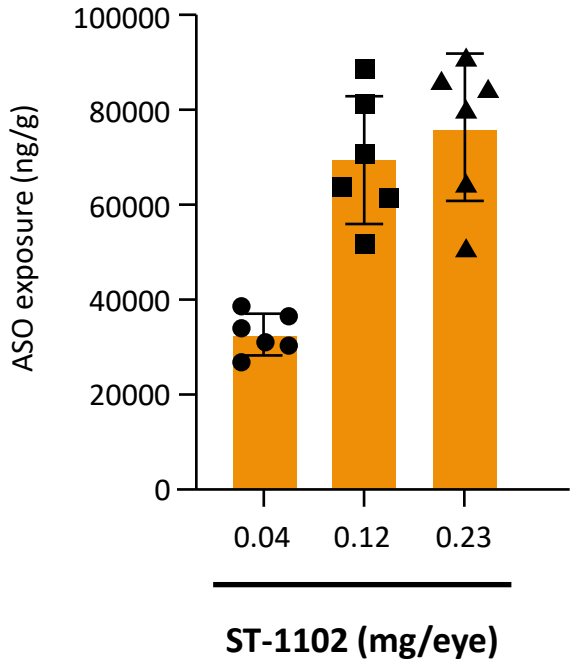
ASO treatment increased ATP linked respiration in OPA1 deficient ADOA patient cells



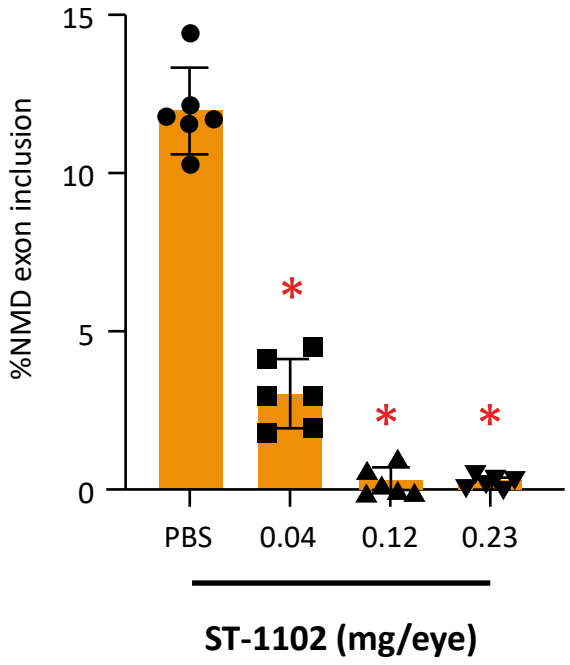
Source (left graph): Stoke data
Source (right graph): Venkatesh A, et al. Antisense oligonucleotide mediated increase in OPA1 improves mitochondrial function in fibroblasts derived from patients with autosomal dominant optic atrophy (ADOA). Presented at The Association for Research in Vision and Ophthalmology; May 1-7, 2021.

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

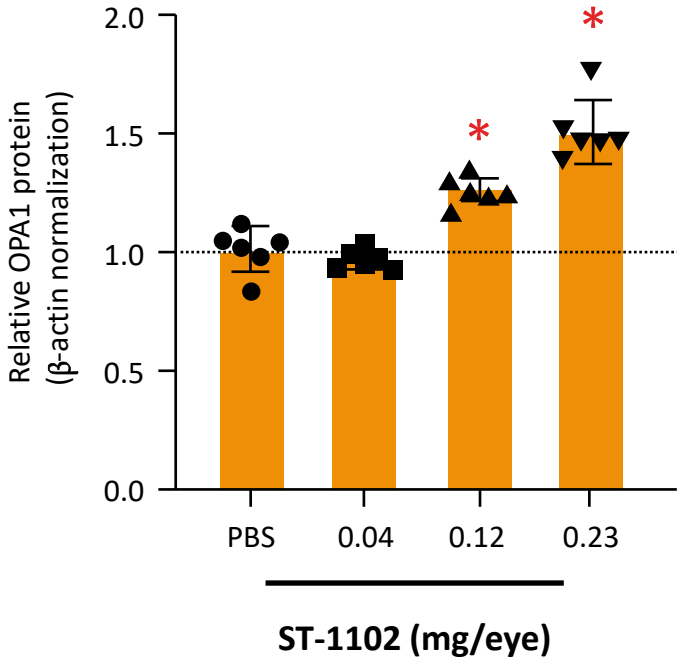
ASO exposure in retina Day 29



Target engagement Day 29



OPA1 protein Day 29

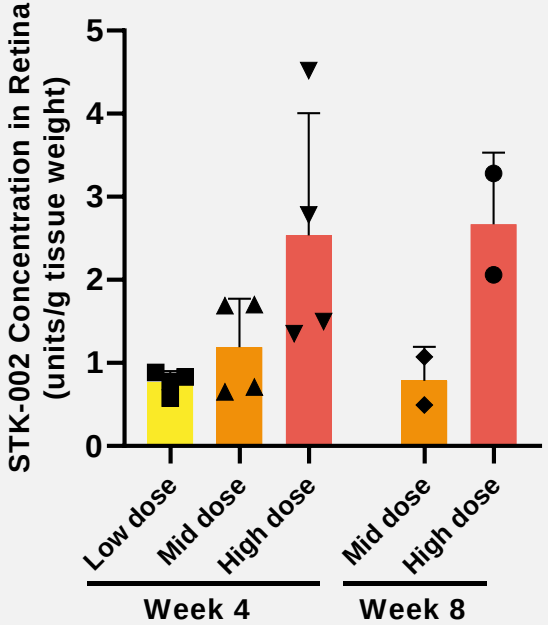


***P*<0.0005 by one-way ANOVA compared to PBS group**

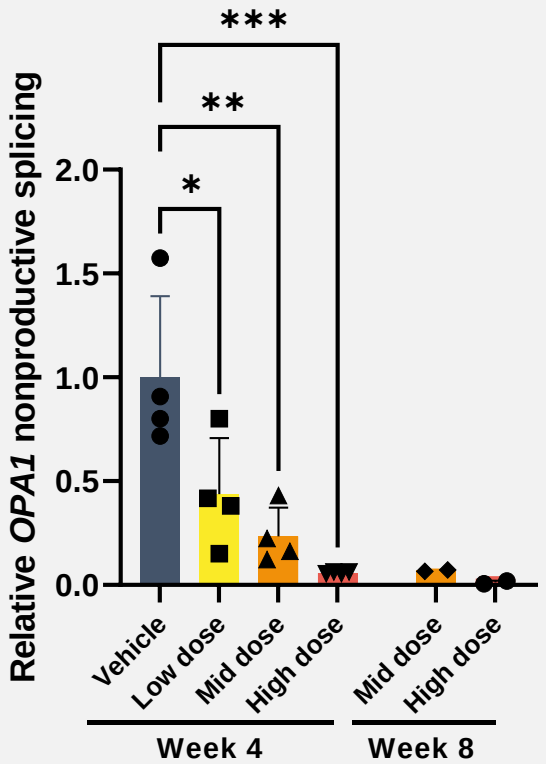
Source: Steven Gross, et al. A Prospective Natural History Study of Patients with Autosomal Dominant Optic Atrophy (ADOA) – FALCON. Presented at The North American Neuro-Ophthalmology Society; February 12-17, 2022; Austin, TX.

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

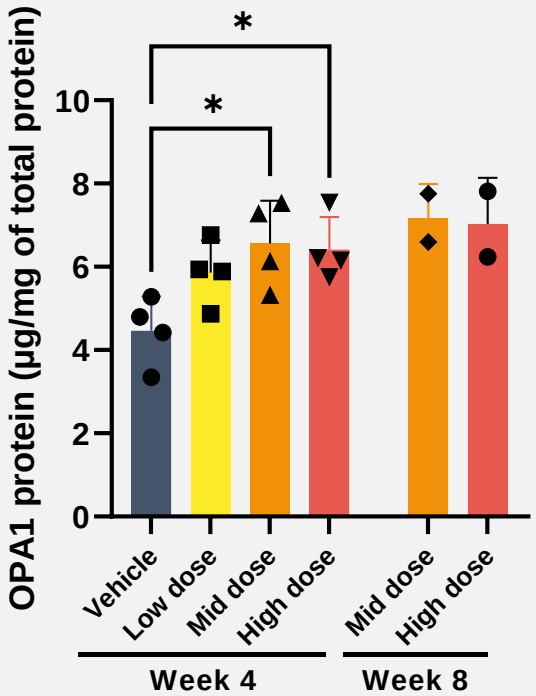
STK-002 exposure



Target engagement



OPA1 protein



NHP: Non-human primates
IVT: Intravitreal
Source: Venkatesh A, et al. STK-002, an Antisense Oligonucleotide (ASO) for the Treatment of Autosomal Dominant Optic Atrophy (ADOA), is Taken Up by Retinal Ganglion Cells (RGC) and Upregulates OPA-1 Protein Expression After Intravitreal Administration to Non-human Primates (NHPs). ASGCT; May 16-19, 2022.

Preclinical Findings Support Clinical Development of STK-002

Summary of Key Preclinical Data

- Increase in OPA1 protein and ATP linked respiration in ADOA patient fibroblasts ✓
- Dose-dependent increases in OPA1 protein expression in rabbit retina and NHP RGCs ✓
- Identified NHP model of ADOA with similar features to human ADOA (structural, electrophysiology) ✓
- Well tolerated for up to 29 days after intravitreal injection in rabbit ✓
- Single and multiple doses well-tolerated in NHPs ✓

Phase 1 study (OSPREY) of STK-002 expected to start in 2024

Sources: Venkatesh A, et al. STK-002, an Antisense Oligonucleotide (ASO) for the Treatment of Autosomal Dominant Optic Atrophy (ADOA), is Taken Up by Retinal Ganglion Cells (RGC) and Upregulates OPA-1 Protein Expression After Intravitreal Administration to Non-human Primates (NHPs). ASGCT; May 16-19, 2022.
OSPREY is a study of children and adults ages 6 to 55 who have an established diagnosis of ADOA and have evidence of a genetic mutation in the OPA1 gene

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

PROGRAM	TARGET	DISCOVERY & PRECLINICAL	PHASE 1/2	PHASE 3	PARTNER
Central Nervous System					
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
Ophthalmology					
ADOA	*OPA1*	STK-002			100% Stoke Global

ADOA: Autosomal dominant optic atrophy

Rett Syndrome: A Severe, Debilitating Neurological Disorder

~33%

of cases caused by hypomorphic mutations of the *MECP2* gene[1]

RESULTING in

Partial loss of function of the MeCP2 protein

1 out of **10,000** to **15,000** females are born with Rett syndrome[2]

Period of rapid decline typically begins between

6 to **18**

months[4]

Symptoms include[3]:

- **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**[4]

Note: All seizure types have been reported in Rett syndrome. Complex partial and generalized tonic-clonic are the most common

Sources: [1] RettBase (http://mecp2.chw.edu.au/); GnomAD (https://gnomad.broadinstitute.org); NOMAD; [2] National Institutes of Health – National Institute of Neurological Disorders and Stroke; [3] International Rett Syndrome Foundation; [4] 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[1]

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[2]

84%

of patients have **generalized epilepsy**[3]

100%

of patients have **developmental delay** or **intellectual disability**[3]

~50%

of patients have **autism and other behavioral abnormalities**[3]

Sources: [1] Parker et al., *American Journal of Medical Genetics*, 2015; Jimenez-Gomez et al., Journal of Neurodevelopmental Disorders, 2019; [2] SYNGAP1 Resource Guide, Second Edition; An Overview of SYNGAP1 Basic Biology and Clinical Description. Bridge the Gap SYNGAP (now SYNGAP1 Foundation); SynGAP Research Fund; [3] SYNGAP1-Related Intellectual Disability: https://www.ncbi.nlm.nih.gov/books/NBK537721/#_syngap1-id_Clinical_Characteristics_

2024 Summary of Priorities

Advance Zorevunersen for Dravet Syndrome toward a Phase 3 Registrational Study

- ✓ Q1 Data Readout
- Discussions with global regulatory agencies underway; Company on track to provide a regulatory update on Phase 3 registrational plans in the second half of 2024

Advance STK-002 for ADOA

- Initiate Phase 1 study (OSPREY) in 2024

Develop & Expand Pipeline

- Execute on collaboration with Acadia to advance 3 neurodevelopmental programs including Rett syndrome and SYNGAP1 programs
- Expand TANGO ASOs as a first-in-class disease-modifying approach for additional genetic diseases

$282M in Cash, Cash Equivalents, and Marketable Securities as of 6/30/24

ADOA: Autosomal dominant optic atrophy

STOKE THERAPEUTICS