Stoke Therapeutics

NASDAQ: STOK

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Chief Executive Officer

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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 ability of our TANGO platform to design medicines to increase protein production and the expected benefits thereof; expectations regarding our aspirations to execute in the clinic with STK-001, advance to the clinic with STK-002, and expand our pipeline through internal discovery and collaboration; the ability of STK-001 to treat the underlying causes of Dravet syndrome and reduce seizures; the ability of STK-002 to treat the underlying causes of Autosomal Dominant Optic Atrophy (ADOA); the preclinical data and study results regarding OPA1; our future operating results, financial position and liquidity; our expectations about timing and execution of anticipated milestones, responses to regulatory authorities, expected nomination of future product candidates and timing thereof; our expectations, plans, aspirations and goals, including those related to the goals of our collaboration with Acadia; and our preliminary cash, cash equivalents, marketable securities and restricted cash and shares outstanding as of December 31, 2021. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "might," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they do not fully materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such statements, including: our ability to develop, obtain regulatory approval for and commercialize STK-001, STK-002, and future product candidates, including any future product candidates nominated for SYNGAP1 or MECP2; the timing and results of preclinical studies and clinical trials; the risk that positive results in a clinical trial may not be replicated in subsequent trials or success in early stage clinical trials may not be predictive of results in later stage clinical trials; risks associated with clinical trials, including our ability to adequately manage clinical activities, unexpected concerns that may arise from additional data or analysis obtained during clinical trials, regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events; failure to protect and enforce our intellectual property and other proprietary rights; failure to successfully execute or realize the anticipated benefits of our strategic and growth initiatives, including our collaboration with Acadia; risks relating to technology failures or breaches; our dependence on collaborators, including Acadia, and other third parties for the development, regulatory approval, and commercialization of products and other aspects of our business, which are outside of our full control; the direct and indirect impact of COVID-19 on our business, financial condition and operations, including on our expenses, supply chain, strategic partners, research and development costs, clinical trials and employees; risks associated with current and potential future healthcare reforms; risks relating to attracting and retaining key personnel; failure to comply with legal and regulatory requirements; risks relating to access to capital and credit markets; environmental risks; risks relating to the use of social media for our business; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

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Boldly Restoring Genetic Health

Addressing the underlying cause of severe diseases by upregulating protein expression with RNA-based medicines

Executing in the clinic with STK-001, the first potential disease-modifying approach for the treatment of Dravet syndrome

Advancing to the clinic with STK-002, the first potential disease-modifying approach for the treatment of Autosomal Dominant Optic Atrophy (ADOA)

Expanding our pipeline through internal discovery and collaboration

A Differentiated Platform for the Discovery and Development of Novel RNA-Based Medicines

Proprietary RNA therapeutics platform (TANGO)

Targets pre-mRNA splicing to restore target protein to near-normal levels

Disease-modifying approach

We aim to address the underlying cause of severe diseases

Clinical stage with emerging pipeline

Phase 1/2a studies ongoing with STK-001 for Dravet syndrome (DS). Preclinical development initiated for STK-002 for autosomal dominant optic atrophy (ADOA)

Broad therapeutic potential

~1,200 monogenic disease genes and ~6,500 additional genes with TANGO target signatures

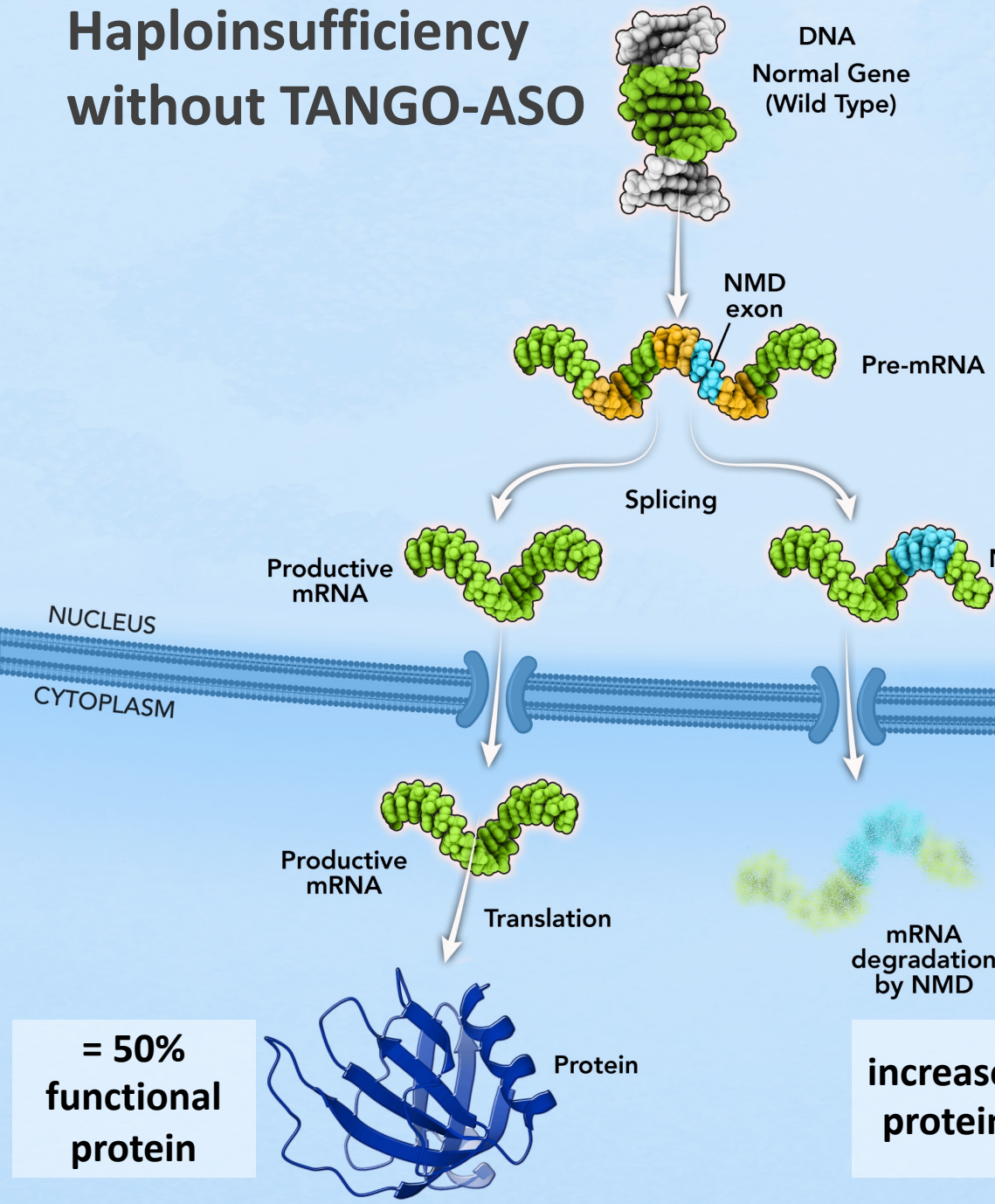
Source: Lim, K.H., Han, Z., Jeon, H.Y. et al. Antisense oligonucleotide modulation of non-productive alternative splicing upregulates gene expression. Nat Commun 11, 3501 (2020).

Targeted Augmentation of Nuclear Gene Output

Our compounds aim to restore protein levels by increasing protein production from the functional copy of a gene and:

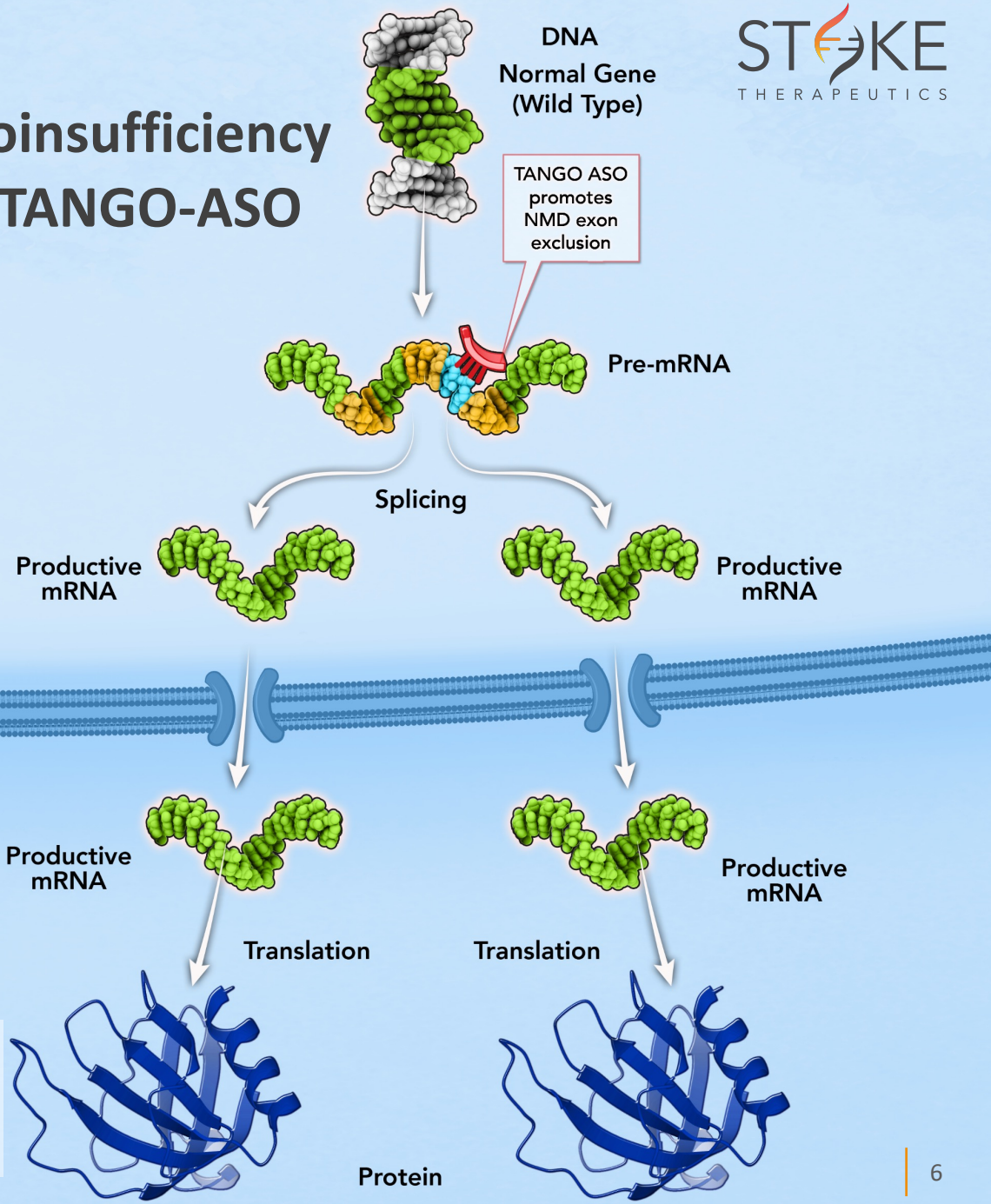
- Selectively boost expression only in tissues where the protein is normally expressed
- Offer one drug for diseases caused by many different loss-of-function mutations
- Apply to genes of diverse size: can be used to address small or large gene targets

Haploinsufficiency without TANGO-ASO



= 50% functional protein

Haploinsufficiency with TANGO-ASO



increased functional protein expression

2021 Execution

1H2021	Initiated Swallowtail Open Label Extension (OLE) study of STK-001 ✓
2H2021	Initiated multiple ascending dose (MAD) study of STK-001 (MONARCH) ✓
3Q2021	Reported preliminary safety, PK, and CSF data (SAD portion of MONARCH) ✓
2H2021	Initiated (MAD) study of STK-001 in the U.K. (ADMIRAL) ✓
2H2021	Initiated ADOA natural history data collection ✓
YE2021	Identified clinical candidate for the treatment of ADOA ✓

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: *2018 Health Advances Report*; Djémié et al., *Molecular Genetics & Genomic Medicine,* 2016; Lagae et al., *Developmental Medicine & Child Neurology,* 2017; Nabbout et al., *Orphanet Journal of Rare Diseases,* 2013

No Approved Disease-Modifying Therapies for Dravet Syndrome

Non-Seizure Comorbidities of Dravet Syndrome Are Not Addressed by Current Therapies

- Intellectual disability
- Developmental delays
- Movement and balance issues
- Language and speech disturbances
- Growth defects
- Sleep abnormalities
- Disruptions of the autonomic nervous system
- Mood disorders

Dravet syndrome is classified as a developmental and epileptic encephalopathy due to the developmental delays and cognitive impairment associated with the disease

Non-Seizure Comorbidities of DS are Progressive and Measurable

Gap in overall intellectual development and adaptive function between patients and neurotypical children appears to widen with age

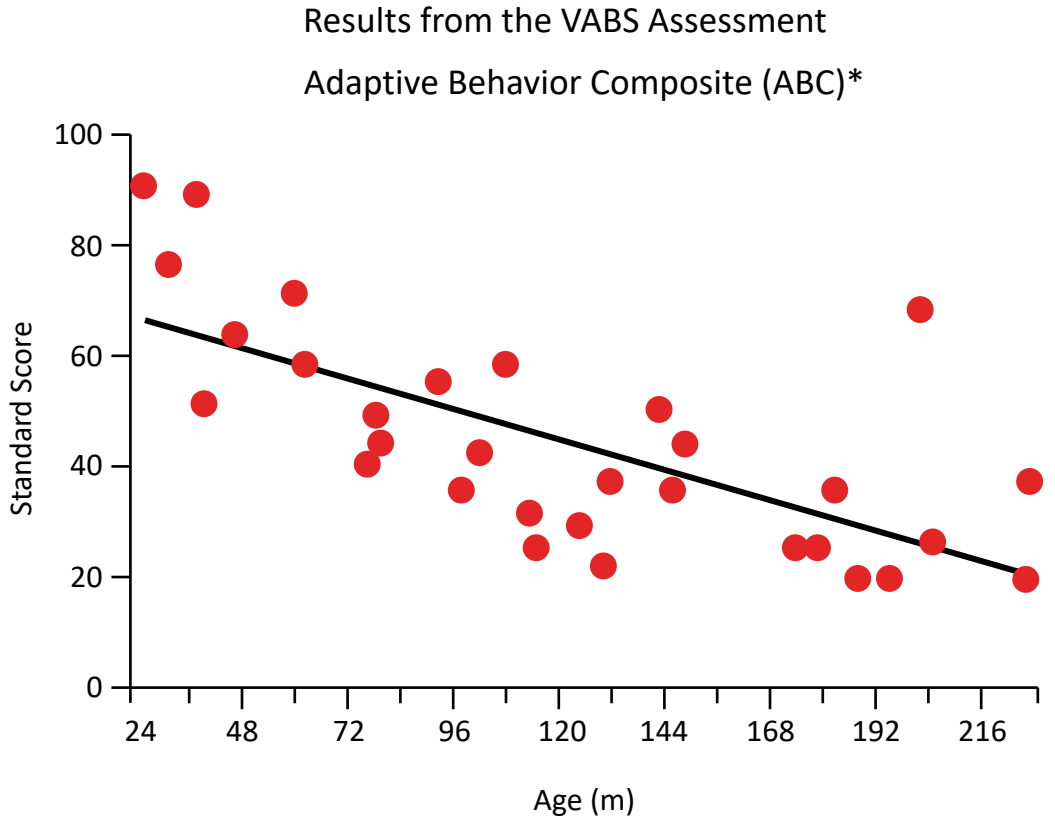
BUTTERFLY

An observational study of Dravet Syndrome patients

Initial findings showed:

- Validation of standard cognitive measures for use in DS patients
- Substantially decreased neurocognitive abilities despite the use of multiple anti-seizure medications
- A gap in adaptive functioning was observed in VABS* testing

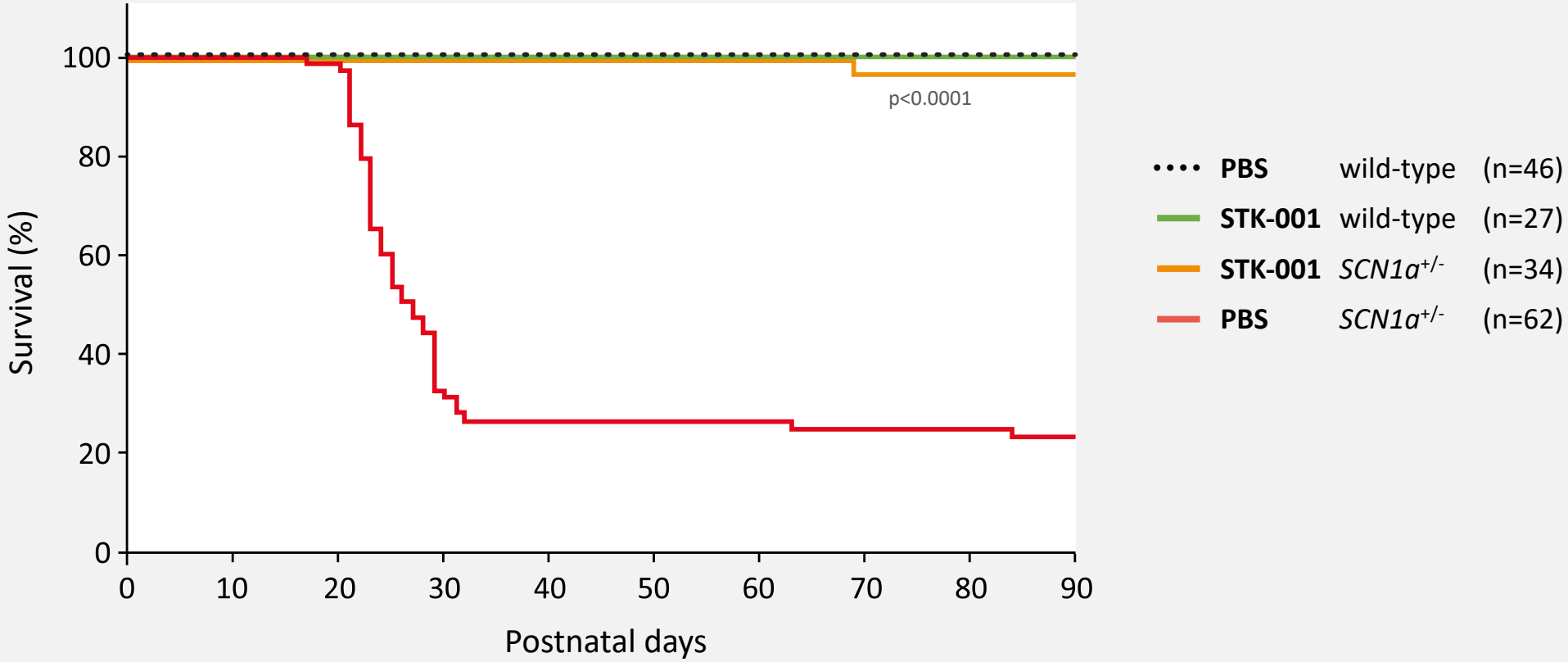
(n=36, 2-18 year-olds). Study ongoing.



* VABS = Vineland Adaptive Behavior Scales
* ABC score based on Communication, Daily Living, and Socialization domains and expressed relative to normative mean of 100
Source: BUTTERFLY: An Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS) (AES 2021).

STK-001 Significantly Reduces Premature Mortality in DS Mice After a Single Dose

Significant improvements in survival after STK-001 administration at postnatal day 2



Science Translational Medicine AAAS

Sources: Z. Han, C. Chen, A. Christiansen, S. Ji, Q. Lin, C. Anumonwo, C. Liu, S. C. Leiser, I. Aznarez, G. Liau, L. L. Isom, Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. *Sci. Transl. Med.* 12, eaaz6100 (2020).

Preclinical Findings Support Clinical Development of STK-001

- Single dose restores $Na_V1.1$ to near-normal levels for >3 months in DS mice
- Significantly reduces mortality and seizure frequency in DS mice
- Achieves broad distribution and increases $Na_V1.1$ protein expression in NHPs
- Well-tolerated as shown in single and multiple-dose toxicology studies in NHPs

Sources: Targeted Augmentation of Nuclear Gene Output (TANGO) of SCN1A reduces seizures and rescues parvalbumin positive interneuron firing frequency in a mouse model of Dravet syndrome (AES 2020). Wengert ER, Wagley PK, Strohm SM, Reza N, Wenker IC, Gaykema RP, Christiansen A, Liau G, Patel MK. Targeted Augmentation of Nuclear Gene Output (TANGO) of Scn1a rescues parvalbumin interneuron excitability and reduces seizures in a mouse model of Dravet Syndrome. Brain Res. 2022;1775:147743. Stoke data. TANGO oligonucleotides for the treatment of Dravet Syndrome: Safety, biodistribution and pharmacology in the non-human primate (AES 2019)

Phase 1/2a Trials of STK-001 for Dravet Syndrome are Ongoing

Parallel studies in the US & UK evaluating children and adolescents ages 2 to 18 years old

	monarch	admiral
Design	Evaluation of STK-001 (up to 45mg*)	Evaluation of STK-001 (up to 70mg)
Status	• SAD: Enrollment ongoing @45mg • MAD: Enrollment and dosing ongoing @30mg	• MAD: Enrollment and dosing ongoing @30mg
Target Enrollment	~90	Up to 60
Primary Endpoint	Safety and tolerability of SAD and MAD dose levels	Safety and tolerability of MAD dose levels
	Characterize human pharmacokinetics (PK) and cerebrospinal fluid (CSF) drug exposure	
Secondary Endpoint	Change in seizure frequency, overall clinical status, and quality of life	
Open-Label Extension	Enrollment and dosing is ongoing (swallowtail)	Enrollment expected to begin in 2Q22 (LongWing)

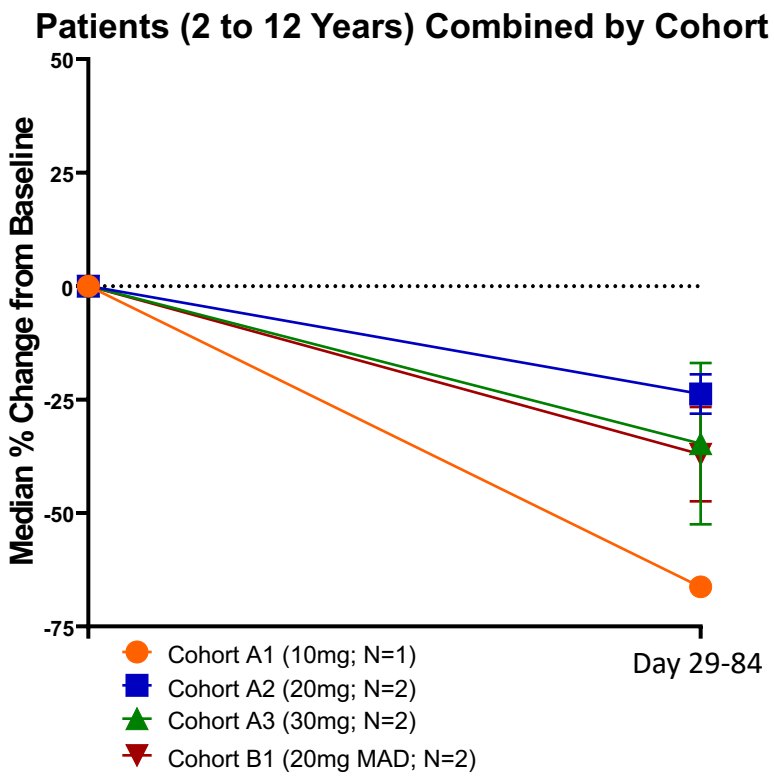
*Doses >45mg remain on FDA partial clinical hold.

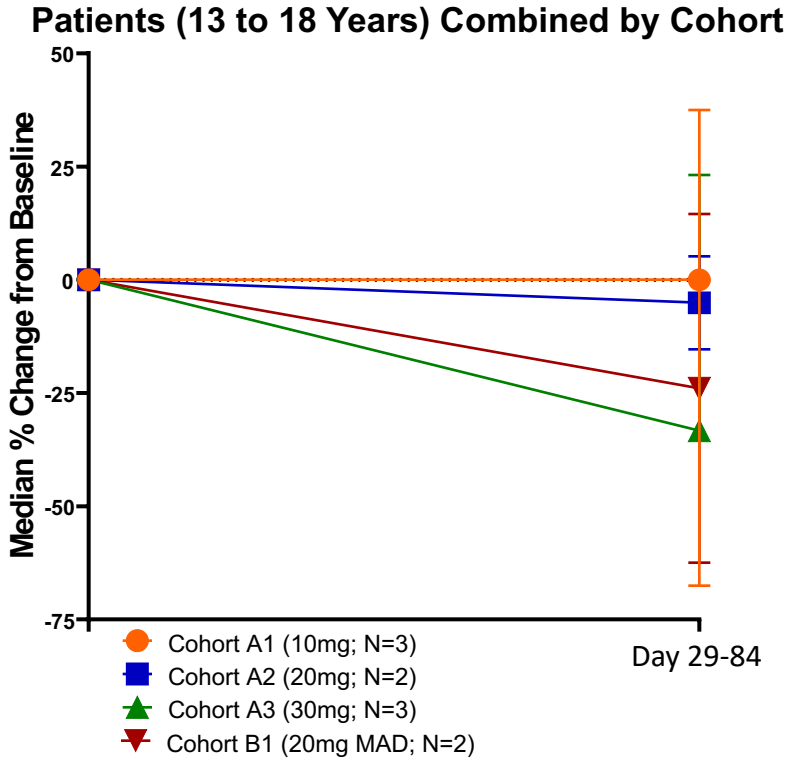
Sources: Interim Safety, PK, and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (AES 2021). ADMIRAL: A UK Study of the Safety and Pharmacokinetics of Antisense Oligonucleotide STK-001 in Children and Adolescents with Dravet Syndrome (AES 2021).

Patients Treated with STK-001 Experienced Reductions in Convulsive Seizure Frequency

70.6% (12/17) of patients including all patients ages 2-12 (n=7) experienced a reduction from baseline in convulsive seizure frequency measured from Day 29 to Day 84

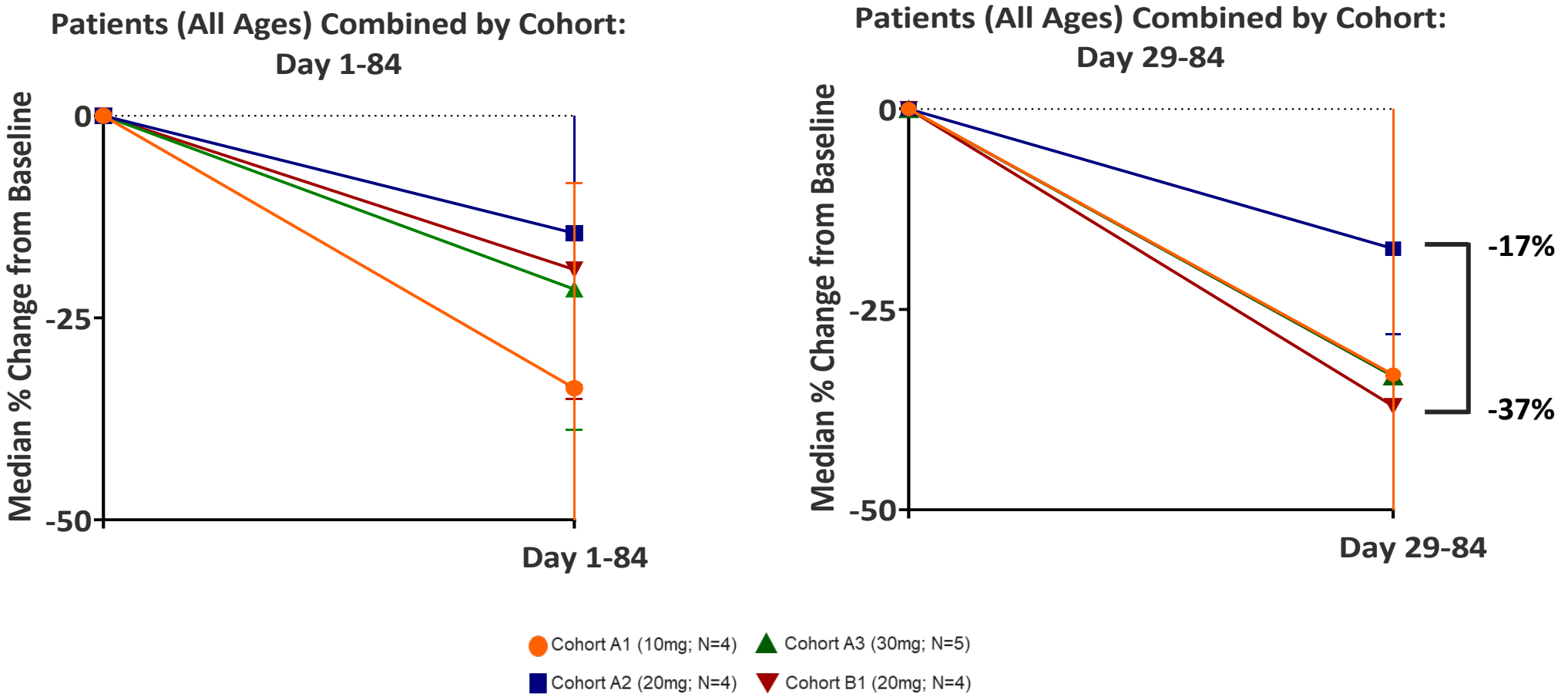
Reductions in seizure frequency were also observed among patients ages 13-18





Source: Interim Safety, PK, and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS) (AES 2021)

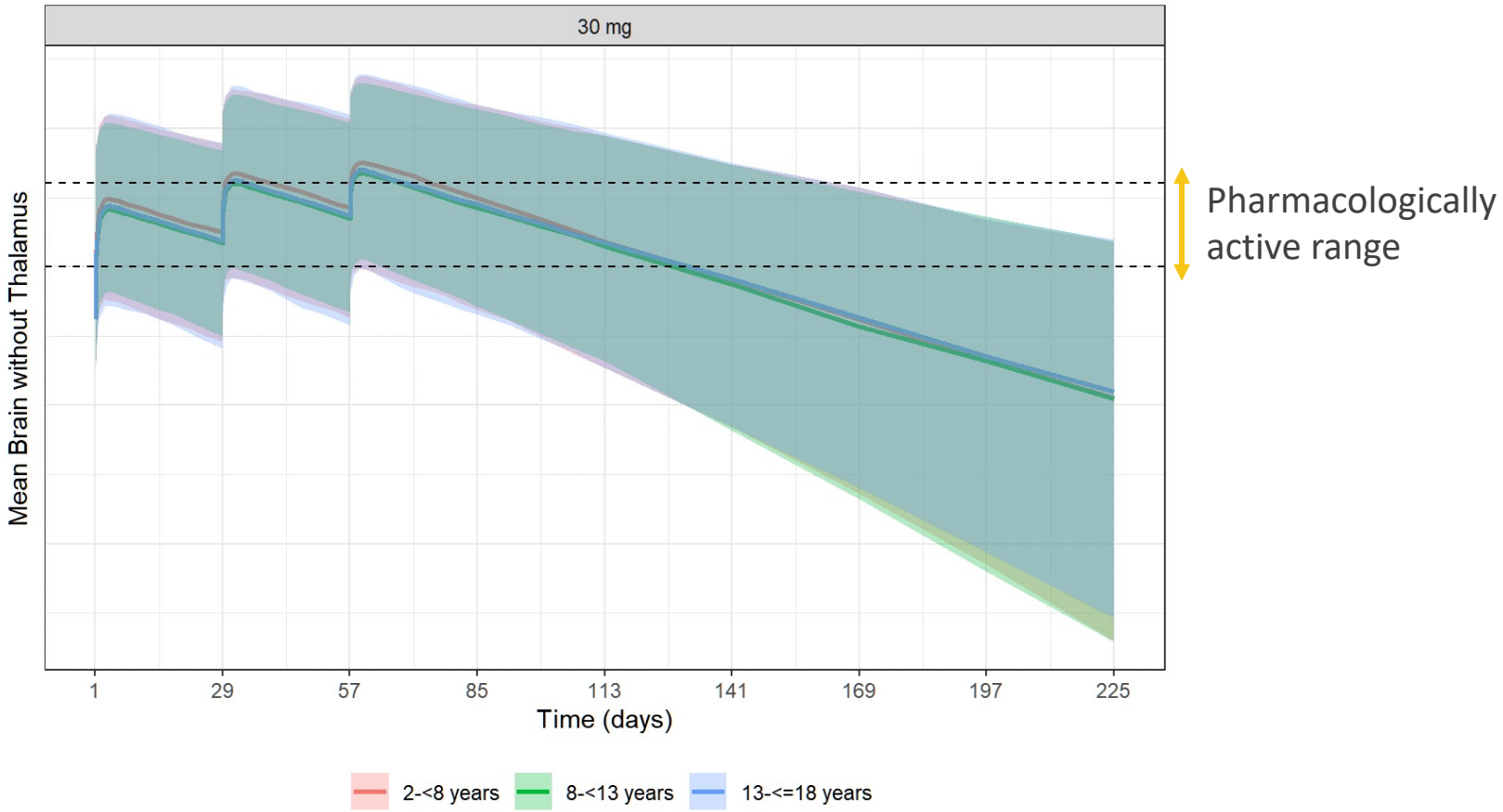
Median % Change from Baseline in Seizure Frequency More Evident >4 Weeks After Dosing



Source: Interim Safety, PK, and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS) (AES 2021)

3 Monthly 30mg Doses of STK-001 Projected to Achieve Pharmacologically Active Brain Levels in >95% of Patients

Plasma and CSF exposure data from MONARCH can be used to predict STK-001 brain levels in patients



Pharmacologic effect likely lasts beyond timepoint when STK-001 brain concentration falls below minimum level

Source: Interim Safety, PK, and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS) (AES 2021)

STK-001 Has Potential to Address the Genetic Cause of Dravet Syndrome (DS)

Summary of Ph1/2a MONARCH Interim Data

- Single doses up to 30mg and three 20mg doses were well tolerated with no safety concerns related to study drug ✓
- Plasma and CSF data from MONARCH correlated well with model and likely predict STK-001 brain levels in patients ✓
- Trend toward seizure reduction observed in DS patients following dosing of STK-001 ✓
- 3 monthly doses (30mg) predicted to achieve pharmacological active brain levels in >95% of patients ✓

Preliminary clinical data from multiple 30mg doses of STK-001 expected in the second half of 2022

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

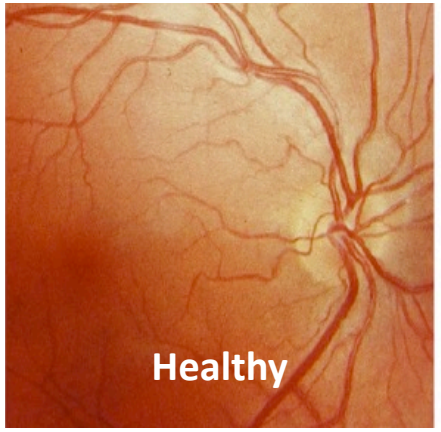
Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013; P. Amati-Bonneau P et al. *The International Journal of Biochemistry & Cell Biology*, 2009; Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol,* 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;

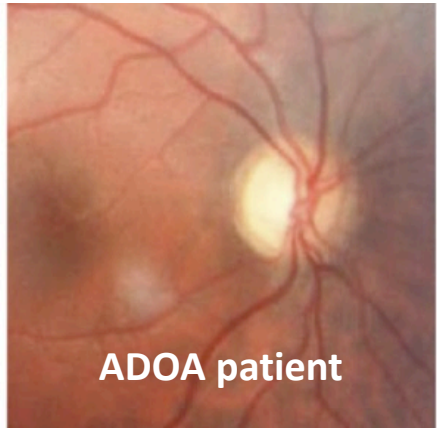
No Approved Disease-Modifying Therapies for ADOA

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

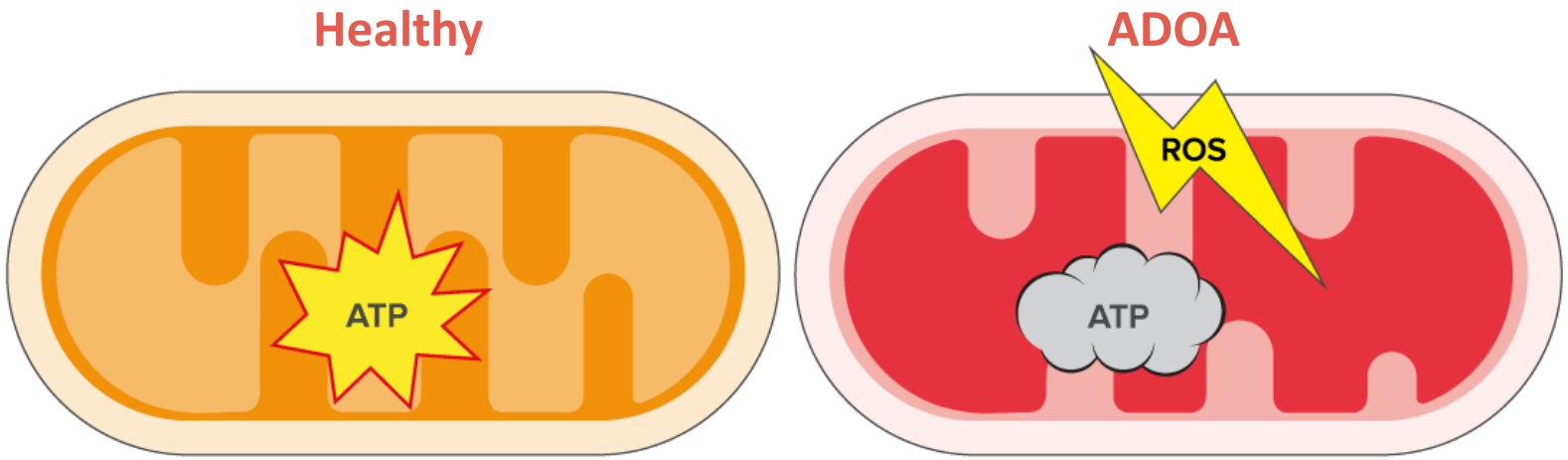




Sources: Yu-Wai-Man P et al. *Ophthalmology*, 2010; Yu-Wai-Man P, Chinnery PF. *Ophthalmology*, 2013;
Lenaers G, Hamel C, Delettre C, et al. *Orphanet J Rare Dis*, 2012; Chun BY and Rizzo JF III. *Curr Opin Ophthalmol,* 2016
Image of child sourced from ICR, Ophthalmology Center Barcelona. Accessed Jan. 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



OPA1 +/+

Mitochondrial Bioenergetics Functional

Cristae Structural Stability

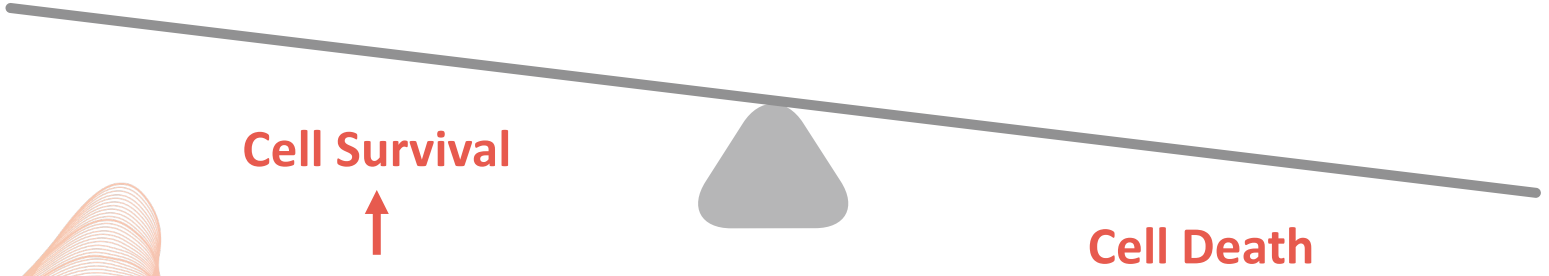
Antioxidant Defense

OPA1 +/-

Mitochondrial Bioenergetic Dysfunction

Cristae Structural Disruption

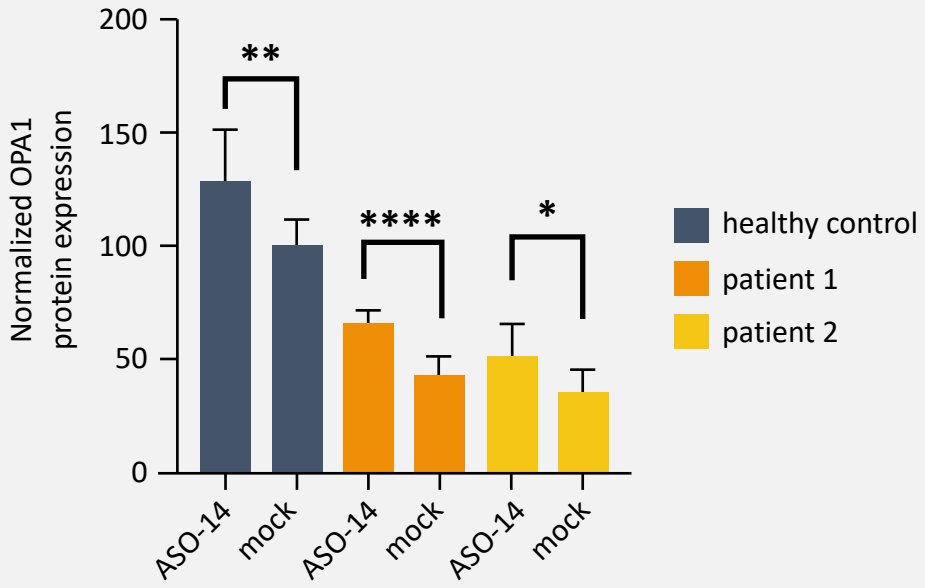
Oxidative Stress



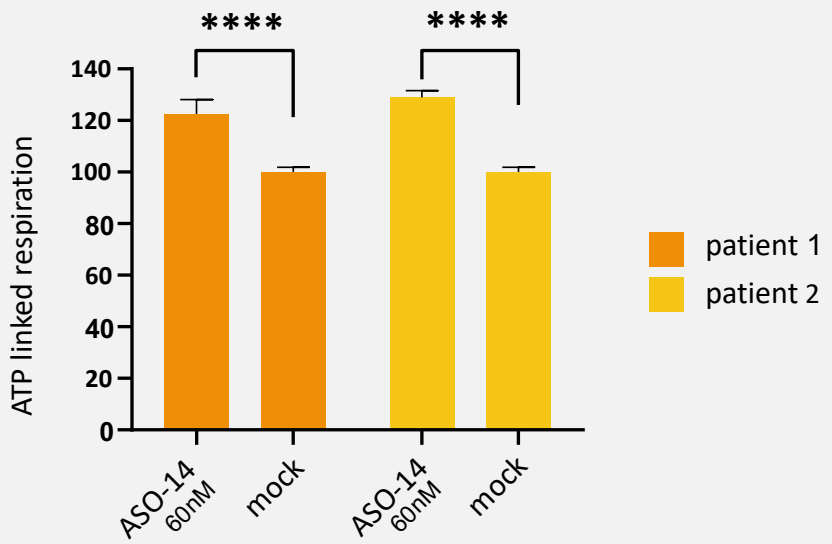
* ROS = Reactive Oxygen Species

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 ASOs Have the Potential to Address the Genetic Cause of ADOA

Summary of Key Preclinical Data

- Increase OPA1 protein and ATP linked respiration in ADOA patient cells ✓
- Result in dose-dependent increases in OPA1 protein expression in rabbit retina ✓
- Were well tolerated for up to 29 days after intravitreal injection in rabbit ✓

Preclinical toxicology studies ongoing in 2022 to support future clinical trials for STK-002

Sources: 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.Venkatesh A, et al. Antisense oligonucleotide mediated increase of OPA1 expression using TANGO technology for treatment of autosomal dominant optic atrophy. Presented at The Association for Research in Vision and Ophthalmology; May 3-7, 2020; Baltimore, MD.

Collaboration with Acadia Pharmaceuticals to Pursue RNA-Based Treatments for Severe & Rare Genetic Neurodevelopmental Diseases

Collaboration leverages Stoke's proprietary TANGO research platform and Acadia's expertise in neurology drug development and commercialization

3 targets focused on severe and rare genetic neurodevelopmental diseases of the central nervous system

- Acadia receives exclusive worldwide licenses for:
  - Rett syndrome (*MECP2*)
  - Undisclosed neurodevelopmental target
- 50:50 co-development co-commercialization of SYNGAP1

Stoke receives a $60M upfront payment and potential milestones up to $907M as well as royalties on future sales

- Acadia fully funds the research and preclinical development activities for Rett syndrome (*MECP2*) and undisclosed neurodevelopmental program
- Share 50/50 in all world-wide costs and future profits for SYNGAP1 program

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 Syndrome: 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_

Investing In Our Pipeline

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

Our Strategy For 2022

Advance our wholly owned CNS and eye programs and expand the scope of our drug discovery efforts

Advance STK-001 for Dravet Syndrome

- Additional clinical data on STK-001 (30mg MAD) anticipated in 2H22
- Initiate dosing >30mg in MONARCH and ADMIRAL

Advance STK-002 for ADOA

- Conduct preclinical toxicology studies to support future clinical trials for STK-002
- Begin enrollment in prospective ADOA natural history study
- Present additional preclinical data for STK-002 at scientific forum

Develop & Expand Pipeline

- Continue discovery efforts to identify new targets
- Execute on collaboration with Acadia

Current Liquidity Including Upfront from Acadia Anticipated to Fund Operations into the Second Half of 2024

$220.4M*

Cash, Cash Equivalents, Marketable Securities, and Restricted Cash

(unaudited) as of 12/31/2021

36.9M

Common Shares Outstanding

(unaudited) as of 12/31/2021

*Does not include the $60 Million Upfront from Acadia

Q&A