Interim Analysis of STK-001 for the Treatment of Dravet Syndrome

Stoke Therapeutics

November 14, 2022

Agenda

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  Eric Rojas, Head of Investor Relations

- **Introductory Remarks**
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- **Phase 1/2a Interim Analysis**
  Barry Ticho, M.D., Ph.D., Chief Medical Officer

- **Closing Remarks**
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Introductory Remarks

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

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

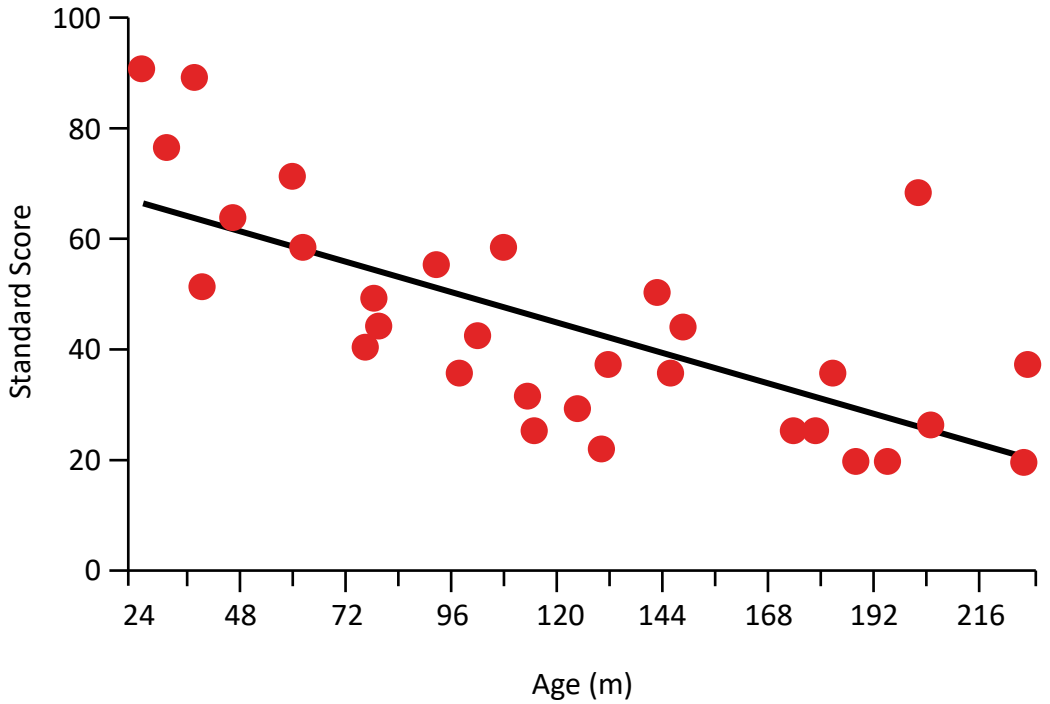
Initial findings showed:

- 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.

Results from the VABS Assessment

Adaptive Behavior Composite (ABC)*



* 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).

Boldly Restoring Genetic Health

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

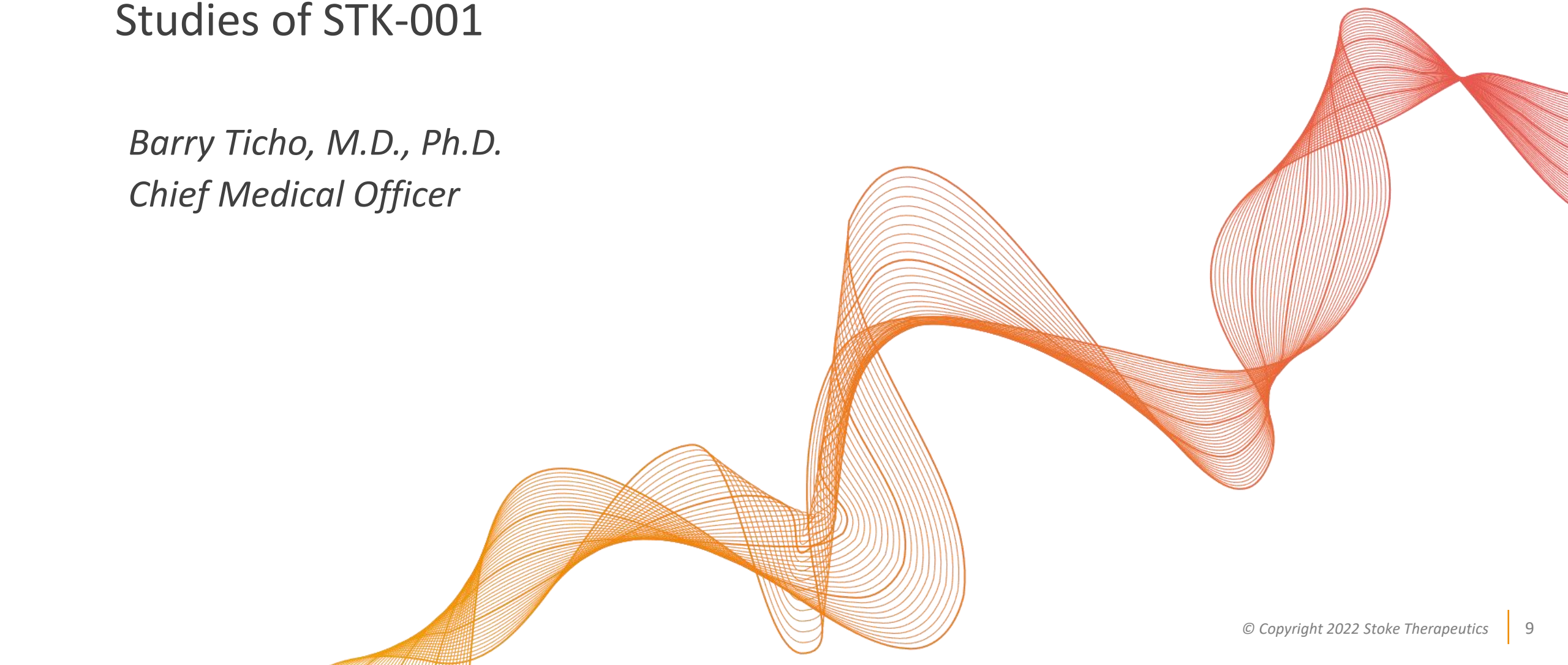
Executing in the clinic with STK-001, the first potential disease-modifying approach for the treatment of Dravet syndrome

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

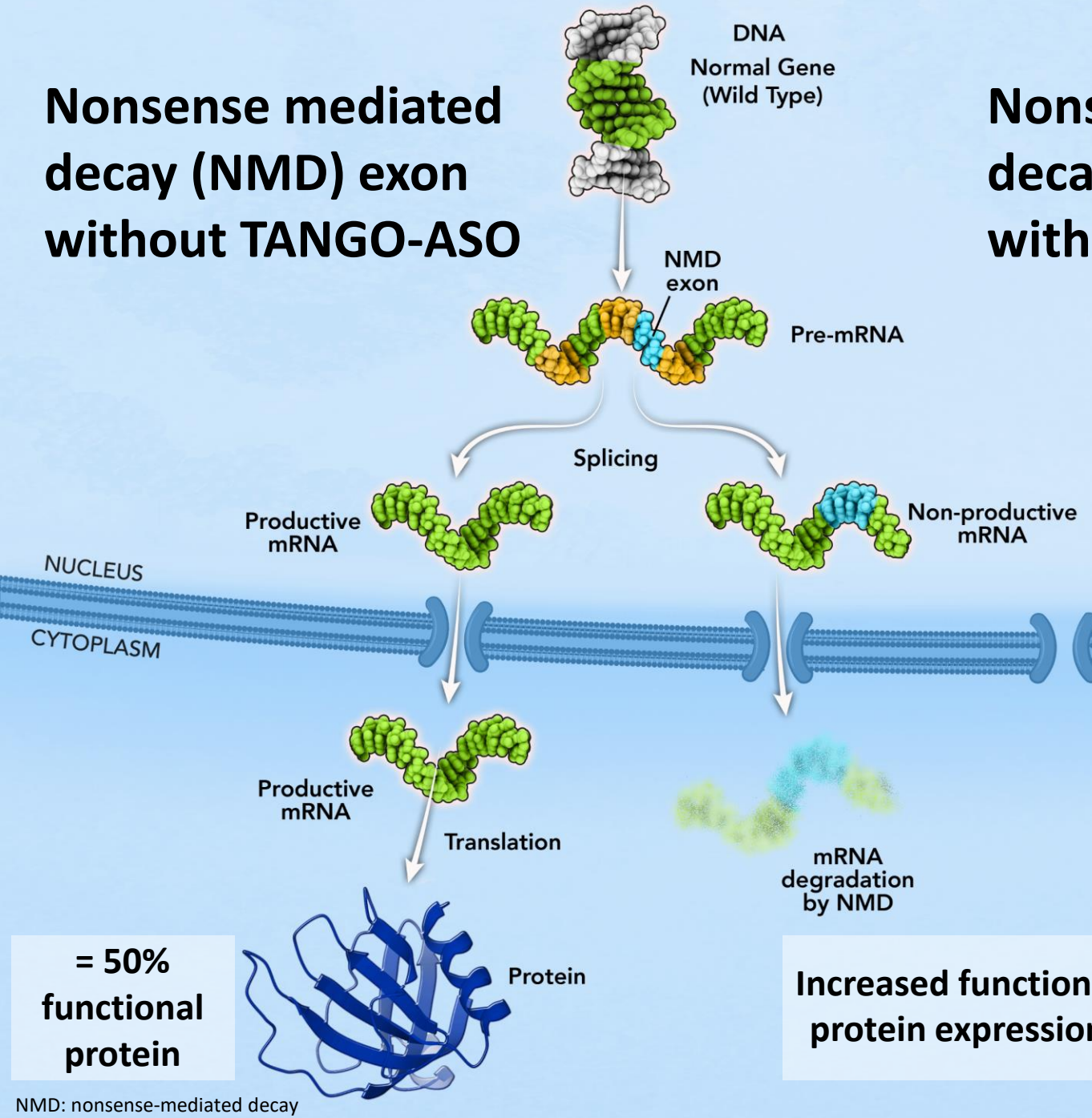
Expanding our pipeline through internal discovery and collaboration

Interim Analysis of Phase 1/2a MONARCH and ADMIRAL Studies of STK-001

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

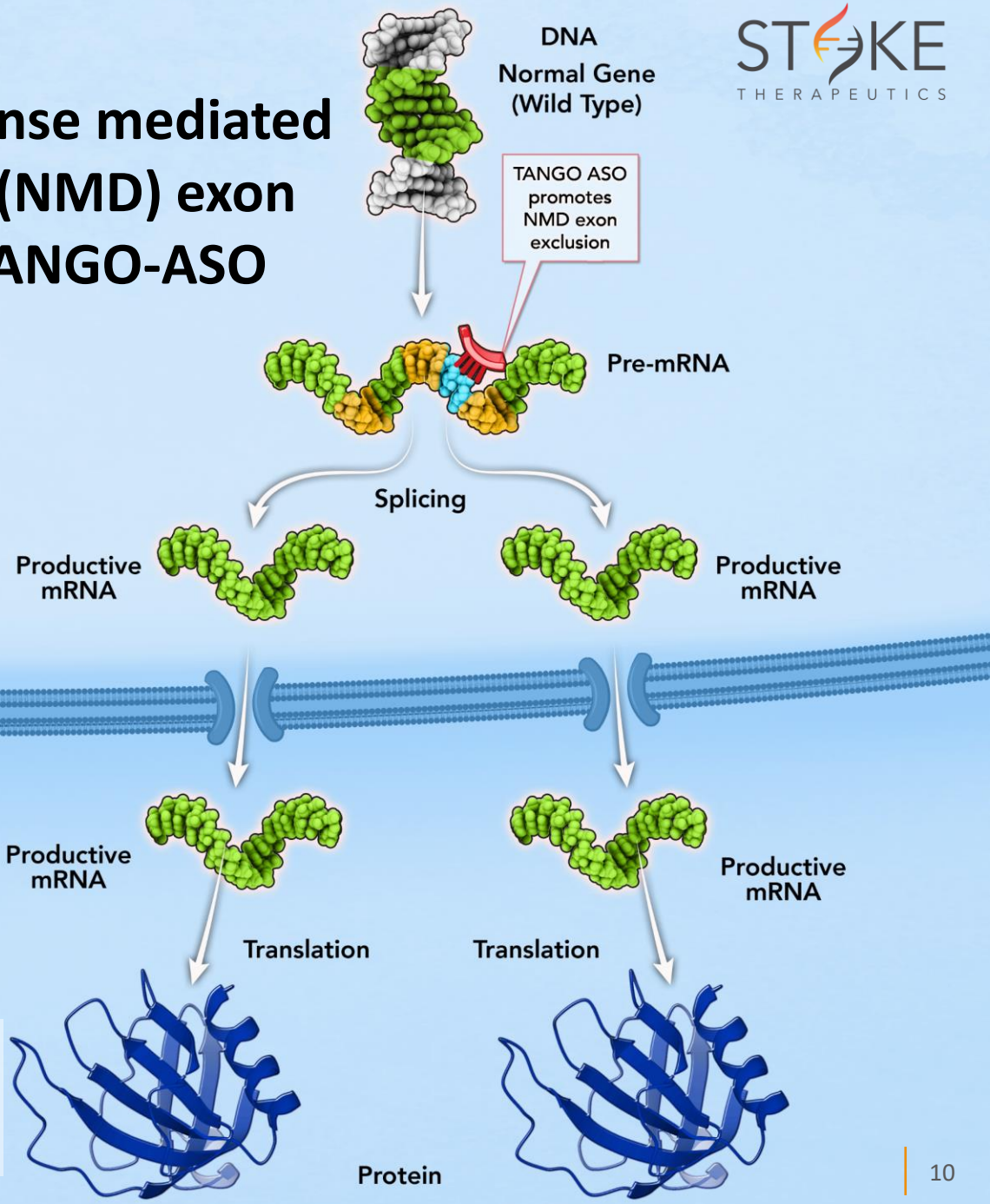


Nonsense mediated decay (NMD) exon without TANGO-ASO



= 50% functional protein

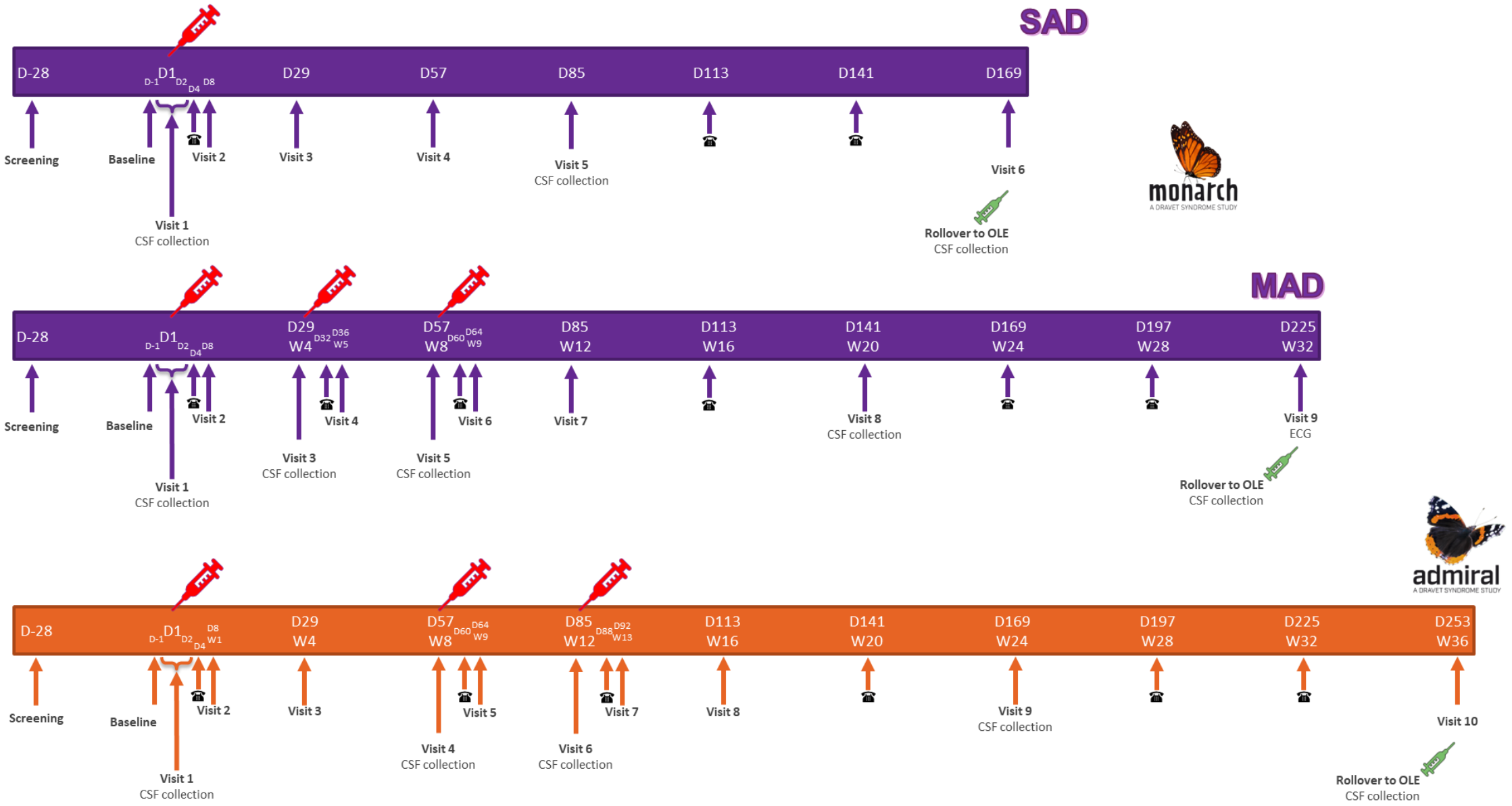
Nonsense mediated decay (NMD) exon with TANGO-ASO



Increased functional protein expression

NMD: nonsense-mediated decay

Clinical Study Designs: MONARCH SAD, MAD and ADMIRAL MAD



Demographics for 55 Patients Treated With ≥1 Dose of STK-001

Enrolled Patients Have Severe Disease and are Refractory to Standard Treatments

	Total, n (%)
N	55
Age at Screening, y	
Mean (SD)	10.5 (5.08)
Median (min, max)	13.0 (2, 18)
Sex	
Female	28 (50.9)
Race	
Asian	4 (7.2)
Black or African American	4 (7.2)
White	48 (87.2)
Ethnicity	
Hispanic/Latino	8 (14.5)
Number of Concomitant Anti-Seizure Medications	
≥3	43 (78.1)
≥4	28 (50.9)
Concomitant Fenfluramine	
%	28 (50.9)
Baseline Convulsive Seizure Frequency per 28 days Median	
Range by Cohort	8-64*

*N=45

Multiple Doses of STK-001 up to 45mg Well-Tolerated

All Adverse Events Related to Study Drug Were Mild or Moderate

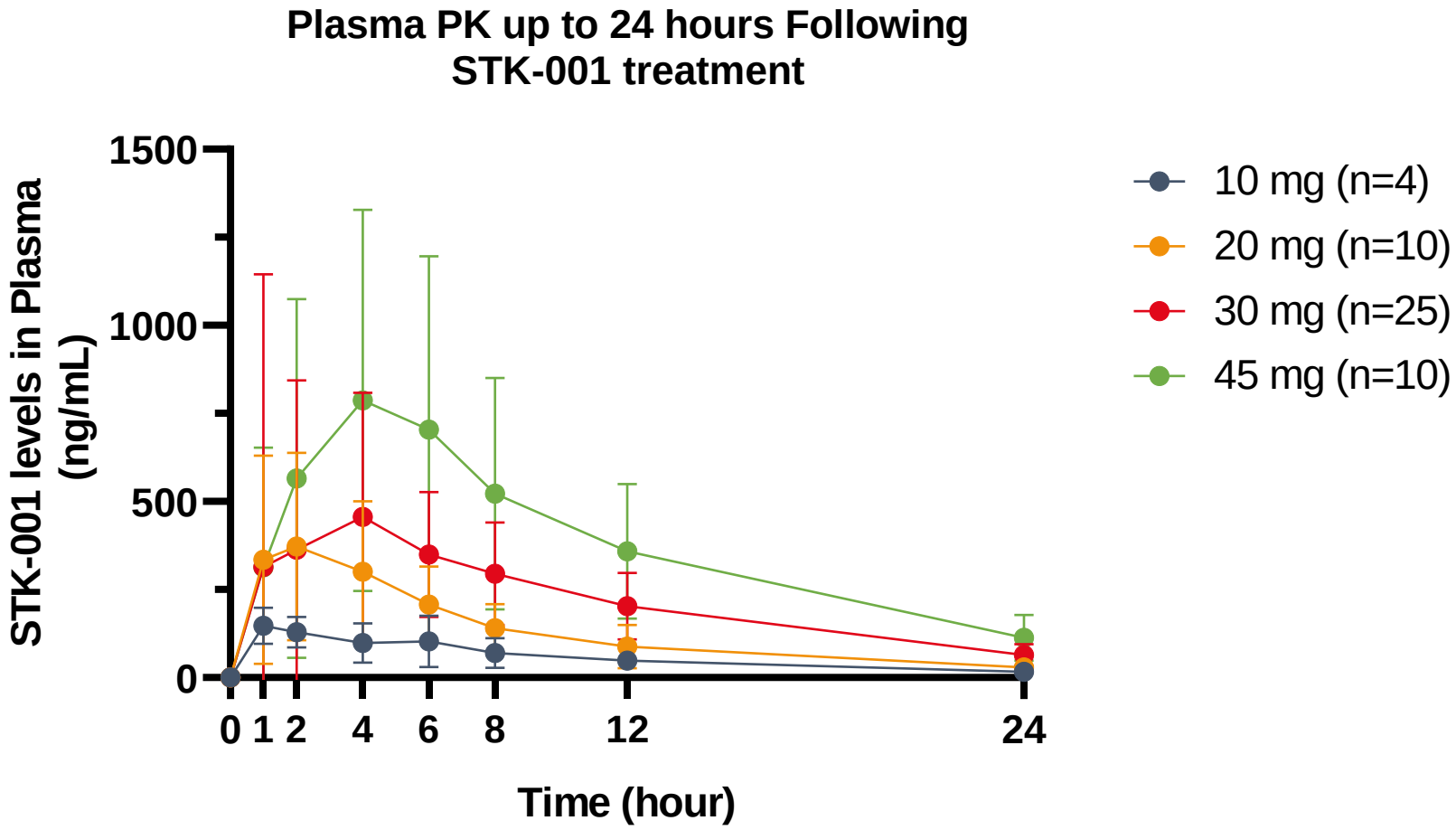
Safety Set (All patients that received ≥1 dose STK-001)					
	MONARCH			ADMIRAL	Combined
	Total SAD (10, 20, 30 or 45 mg)	Total MAD (20, 30 or 45 mg)	Overall	Total MAD (30 or 45 mg)	
N	21	26	47	8	55

- 27% (15/55) of patients experienced a TEAE related to study drug; All AEs related to study drug were mild or moderate
- 22% (12/55) of patients had a treatment-emergent SAE none related to study drug
- Most common TEAEs were vomiting, headache, and seizure
- 33% (18/55) of patients experienced CSF protein elevation (>50mg/dL) after dosing; no clinical manifestations were observed
- No new significant neurologic exam findings or lower extremity weakness emerged related to study drug

Data Cut-off date: August 11, 2022

Dose-Dependent Increases in C_{max} and AUC_{24hr} Observed in Plasma

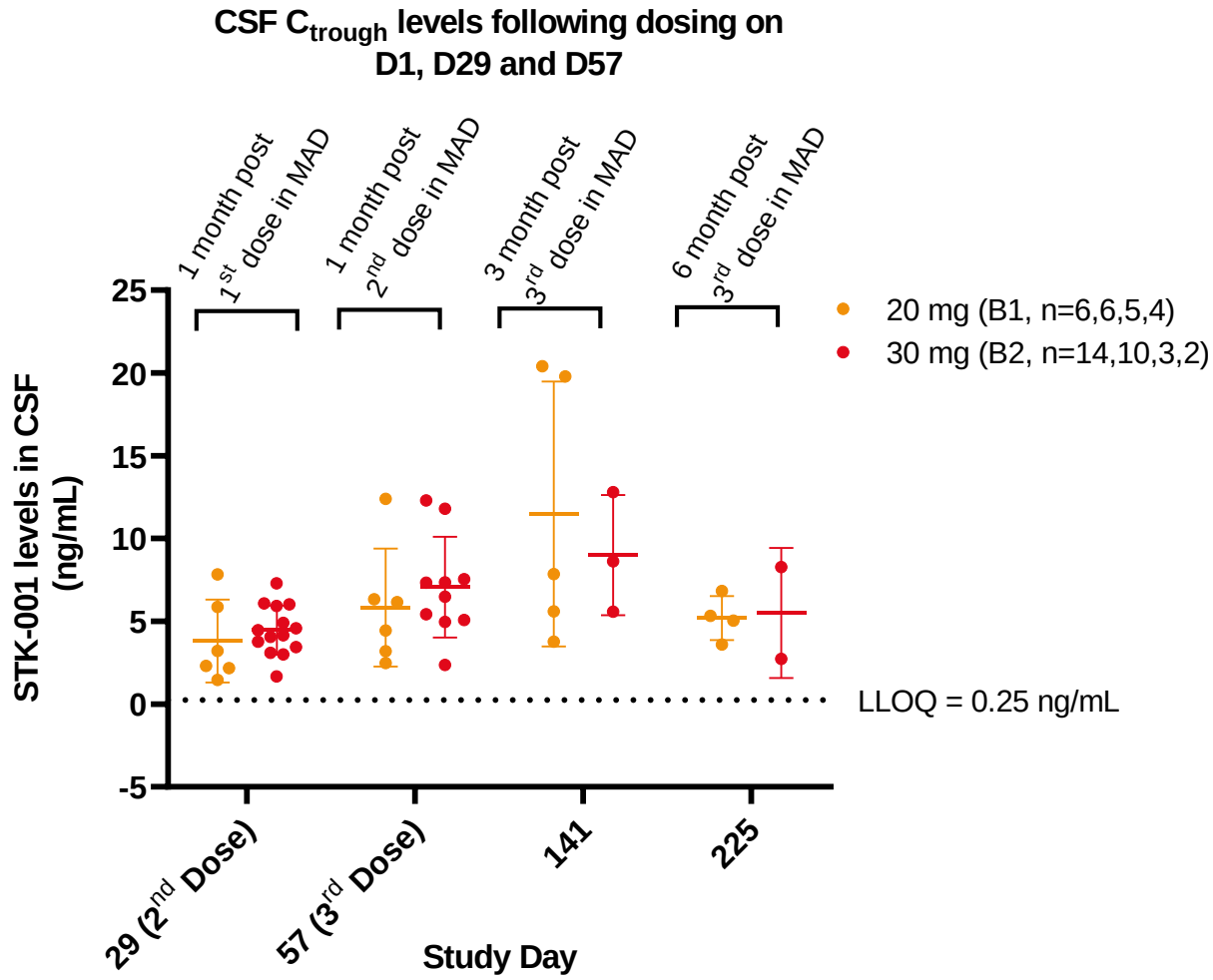
A greater increase was observed between 30mg and 45mg than between 20mg and 30mg



Data Cut-off date: April 26, 2022

CSF Exposure was Measurable up to Six Months Following Multiple Doses of STK-001 in MONARCH study

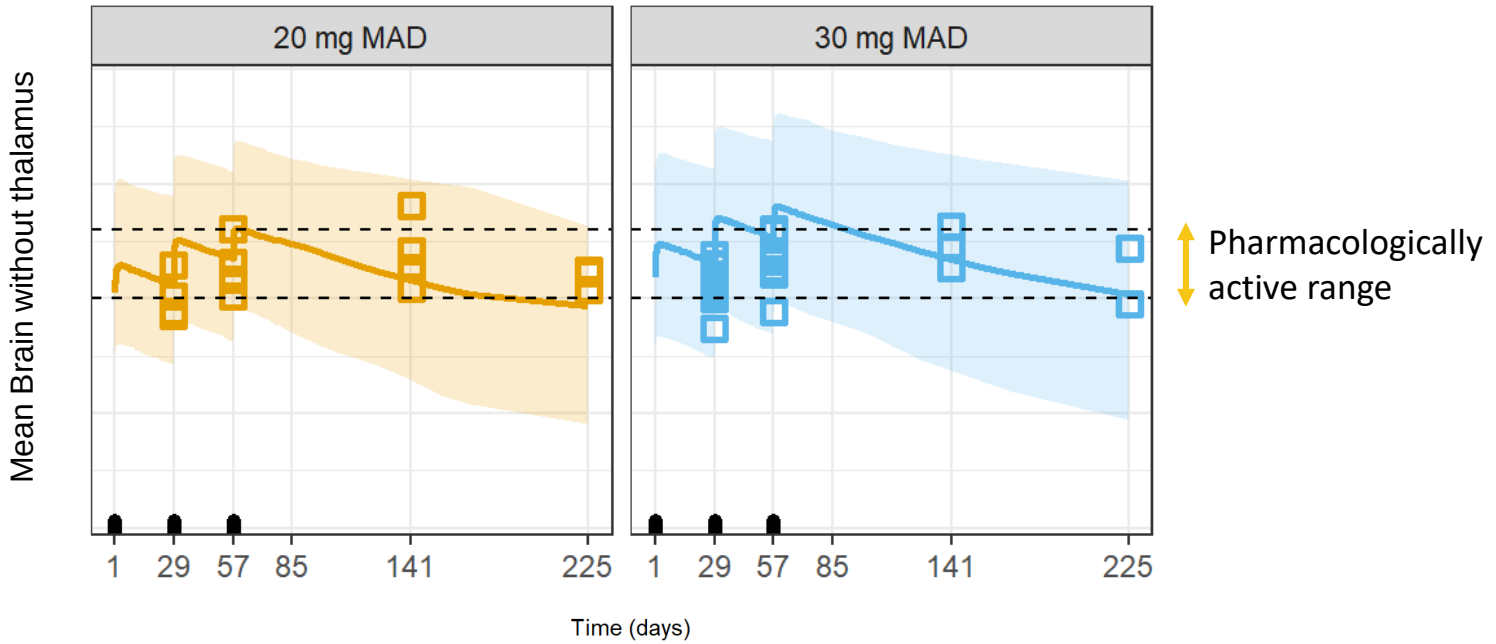
Slight increases in CSF values were observed from 20mg to 30mg



Data Cut-off date: April 27, 2022

Majority of Patients Treated with Multiple Doses (20mg or 30mg) in MONARCH Reach Pharmacologically Active Brain Levels

Clinical Data for 20mg and 30mg MAD Align with Model Simulations from Patient CSF Levels

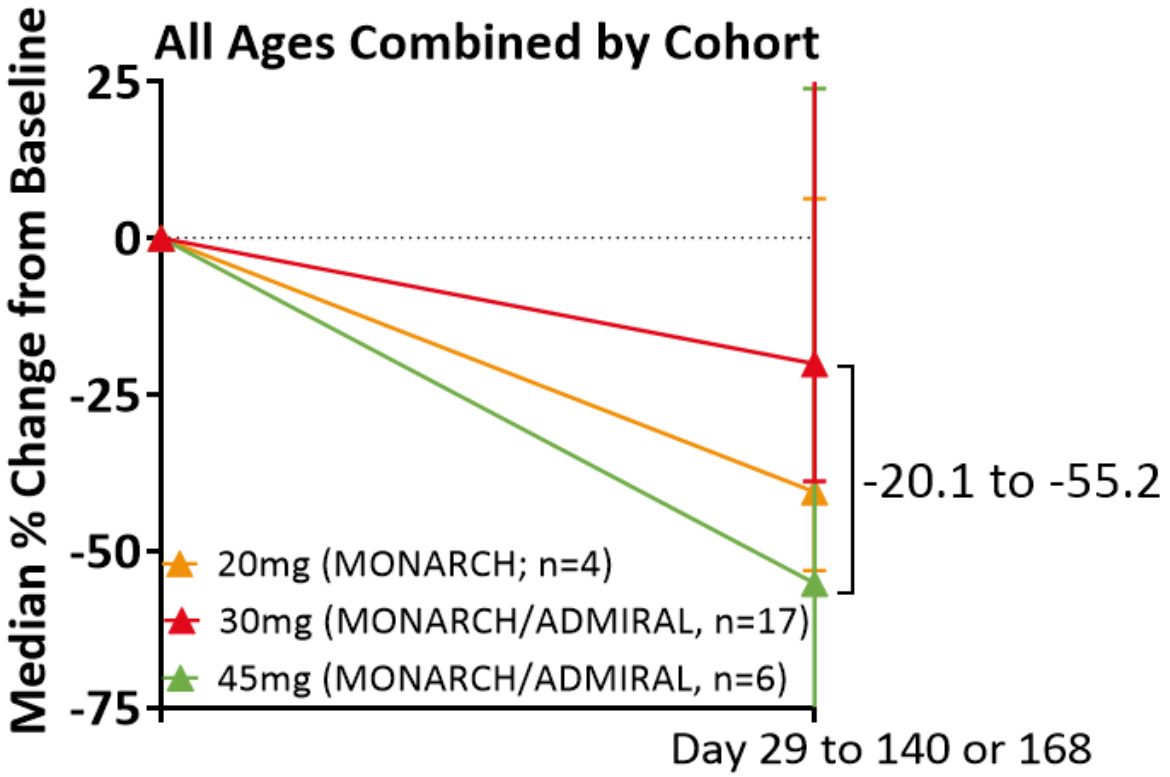


Solid line: Median of the predicted concentrations, Shaded area: 95th confidence interval (2.5th – 97.5th percentile) of the predicted concentrations, Open squares: Extrapolated concentrations. The 20mg MAD and 30mg MAD plots are for STK-001-DS-101 study. On Y axis, the dashed black lines indicate pharmacologically active concentration range

Data Cut-off date: April 27, 2022

55% Median Reduction in Convulsive Seizure Frequency Observed in Patients Treated With Three Doses of STK-001 (45mg)

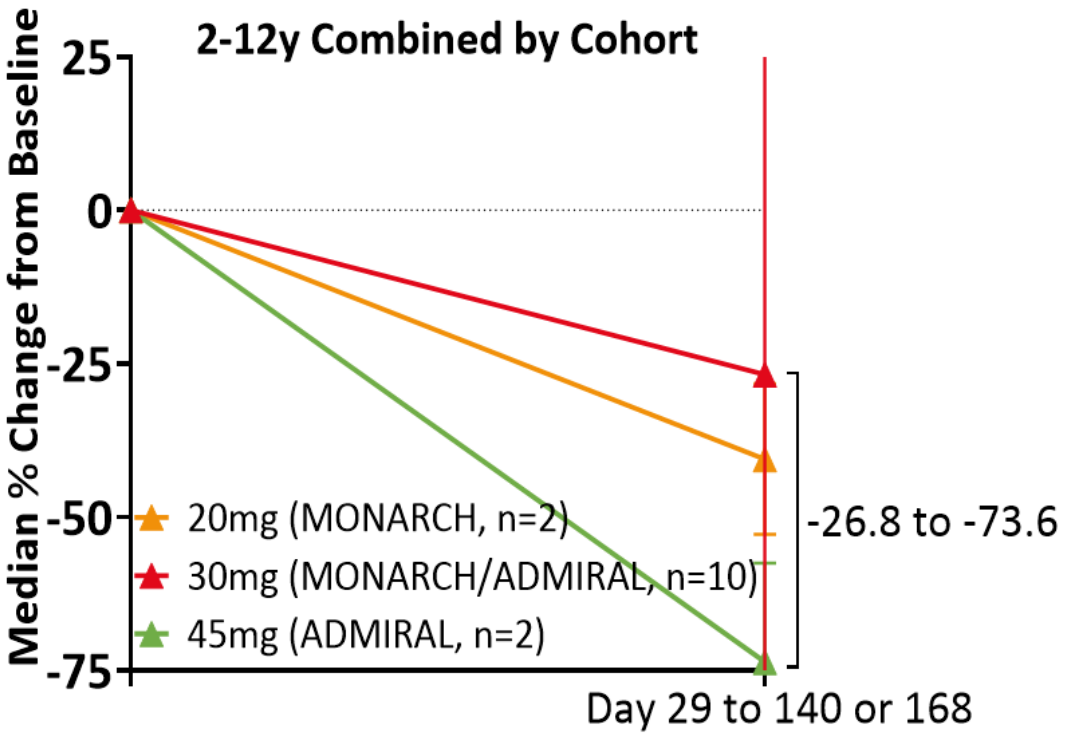
Across the multiple dose cohorts (20mg, 30mg, 45mg), 74% (20/27) of patients experienced reductions in seizures

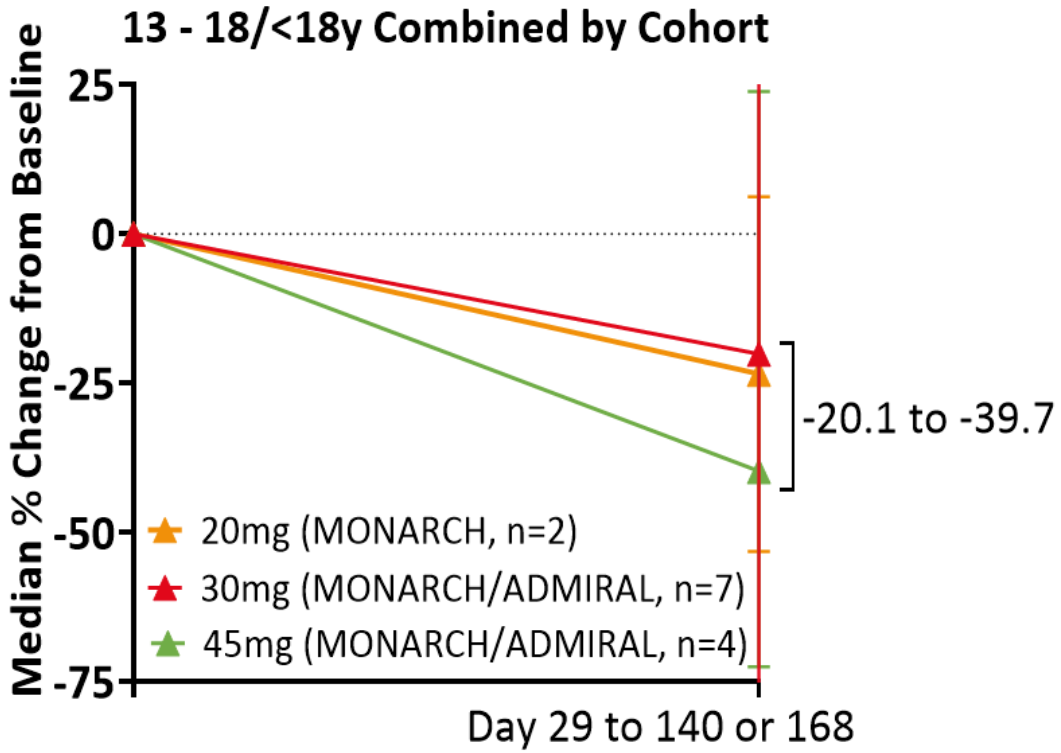


Similar seizure reduction was observed among patients taking or not taking concomitant fenfluramine (>50% of patients were taking concomitant fenfluramine)

Reductions in Convulsive Seizure Frequency Observed Across Age Groups

Seizure reductions more evident among patients ages 2-12





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

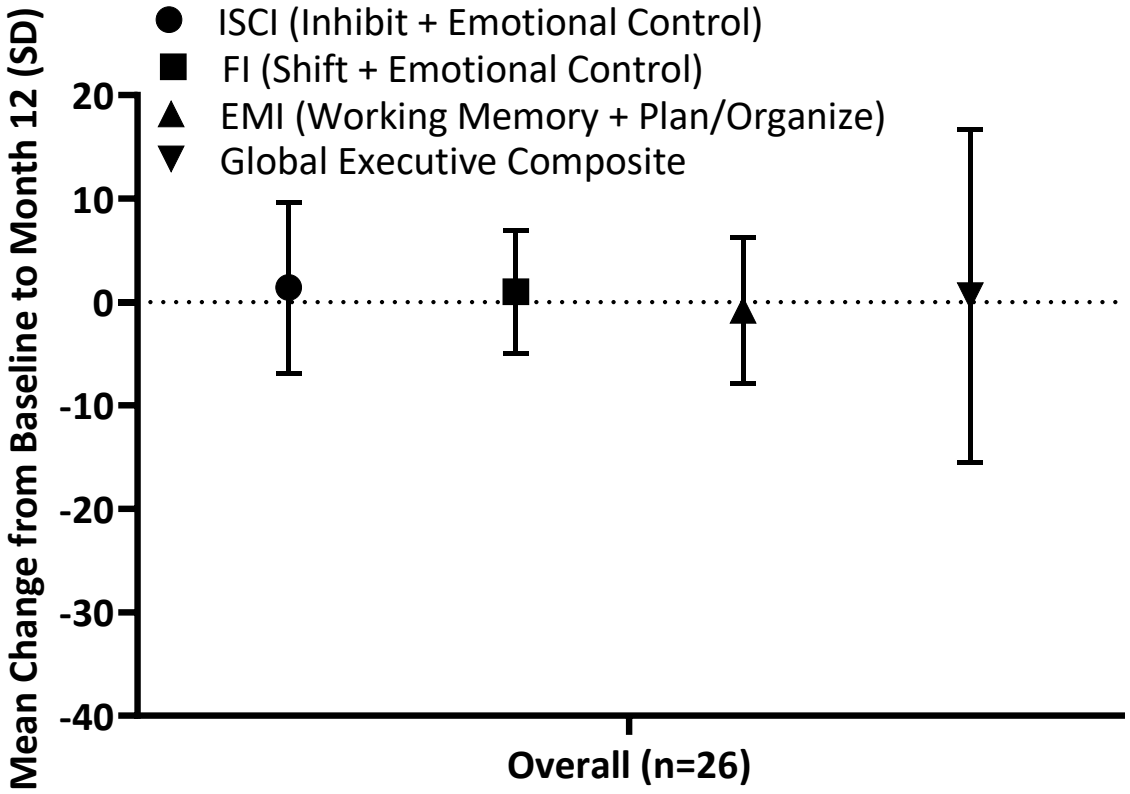
	monarch	admiral
Design	Evaluation of STK-001 (up to 45mg*)	Evaluation of STK-001 (up to 70mg)
Status	• MAD @45mg: Dosing ongoing	• MAD @70mg: Dosing ongoing
Primary Endpoint	Safety and tolerability of SAD and MAD dose levels	Safety and tolerability of MAD dose levels
	Characterize human pharmacokinetics (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 ongoing (30mg) swallowtail	Enrollment and dosing ongoing (45mg) Longwing

*Doses >45mg remain on FDA partial clinical hold

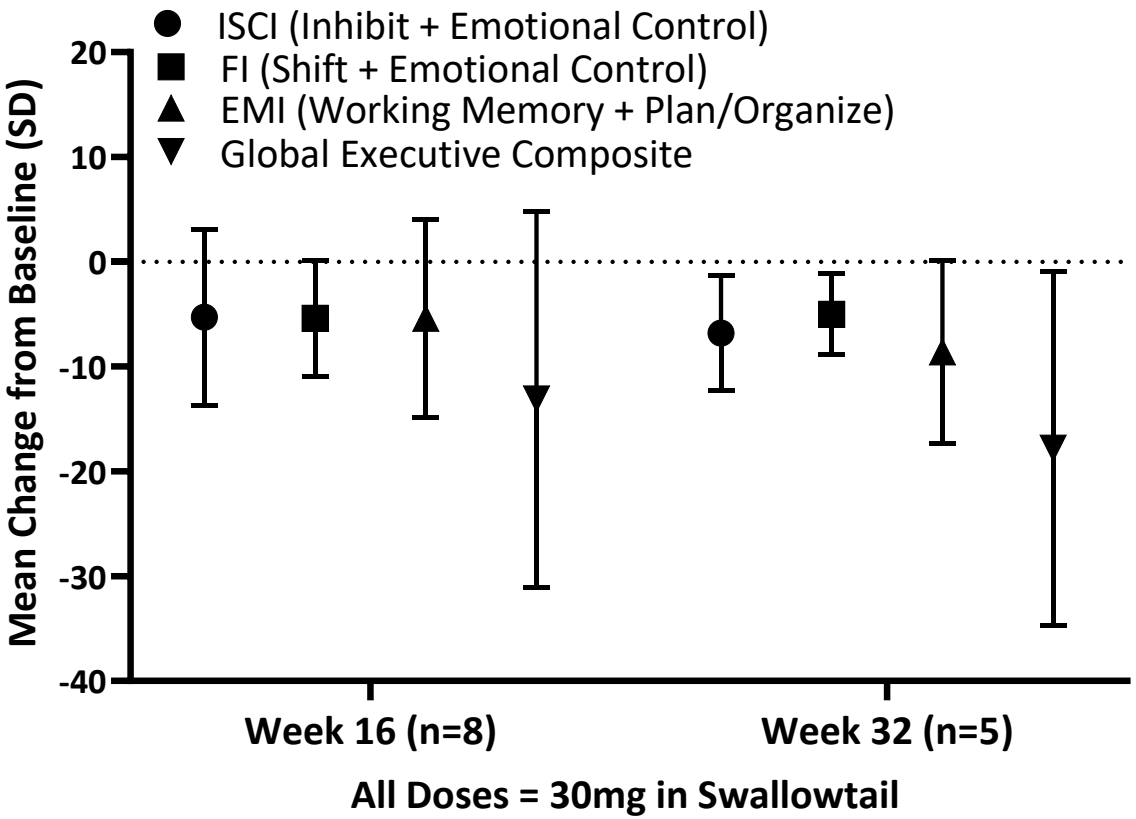
Sources: Interim Safety, PK, and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (AES 2021). ADMIRAL: A UK Study of the Safety and Pharmacokinetics of Antisense Oligonucleotide STK-001 in Children and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

Early Indication of Improvements in Non-Seizure Comorbidities as Measured by BRIEF-P*

BUTTERFLY
An observational study of Dravet Syndrome patients



swallowtail
A DRAVET SYNDROME EXTENSION STUDY



All Doses = 30mg in Swallowtail

*Behavior Rating Inventory of Executive Function–Preschool Version, an assessment of pediatric executive function

Conclusions and Next Steps

STK-001 on track as the first potential disease-modifying treatment for Dravet syndrome

- Multiple doses of STK-001 up to 45mg were well-tolerated
- Majority of patients treated with multiple doses of STK-001 experienced a reduction in seizures
    - The effects were more pronounced at higher doses and among younger patients
- Continued progress toward identifying optimal dose level and frequency with dose-dependent responses observed between 30mg and 45mg
- Phase 1/2a studies ongoing, including an expanded 45mg MAD cohort in MONARCH and dosing in the 70mg MAD cohort in ADMIRAL. Expansion of 70mg cohort planned, pending safety review.
- Preliminary analysis from a small cohort of patients in SWALLOWTAIL (30mg) showed reductions in seizure frequency were maintained and an early indication of improvements in non-seizure comorbidities as measured by BRIEF-P
- Additional data anticipated in 2023 from the 45mg and 70mg multiple dose cohorts

Closing Remarks

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

Acknowledgements

Q&A