MONARCH study in Dravet Syndrome
Interim Analysis

September 21, 2021

Agenda

- **Introduction**
  Eric Rojas, Head of Investor Relations
- **Disease Overview, Patient Need, and STK-001 Mechanism of Action**
  Edward M. Kaye, M.D., Chief Executive Officer
- **Phase 1/2a MONARCH Interim Analysis**
  Barry Ticho, M.D., Ph.D., Chief Medical Officer
- **Closing Remarks**
  Edward M. Kaye, M.D., Chief Executive Officer
- **Q&A**

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Dravet Syndrome Disease Overview
STK-001 Mechanism of Action

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

RESULTS 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

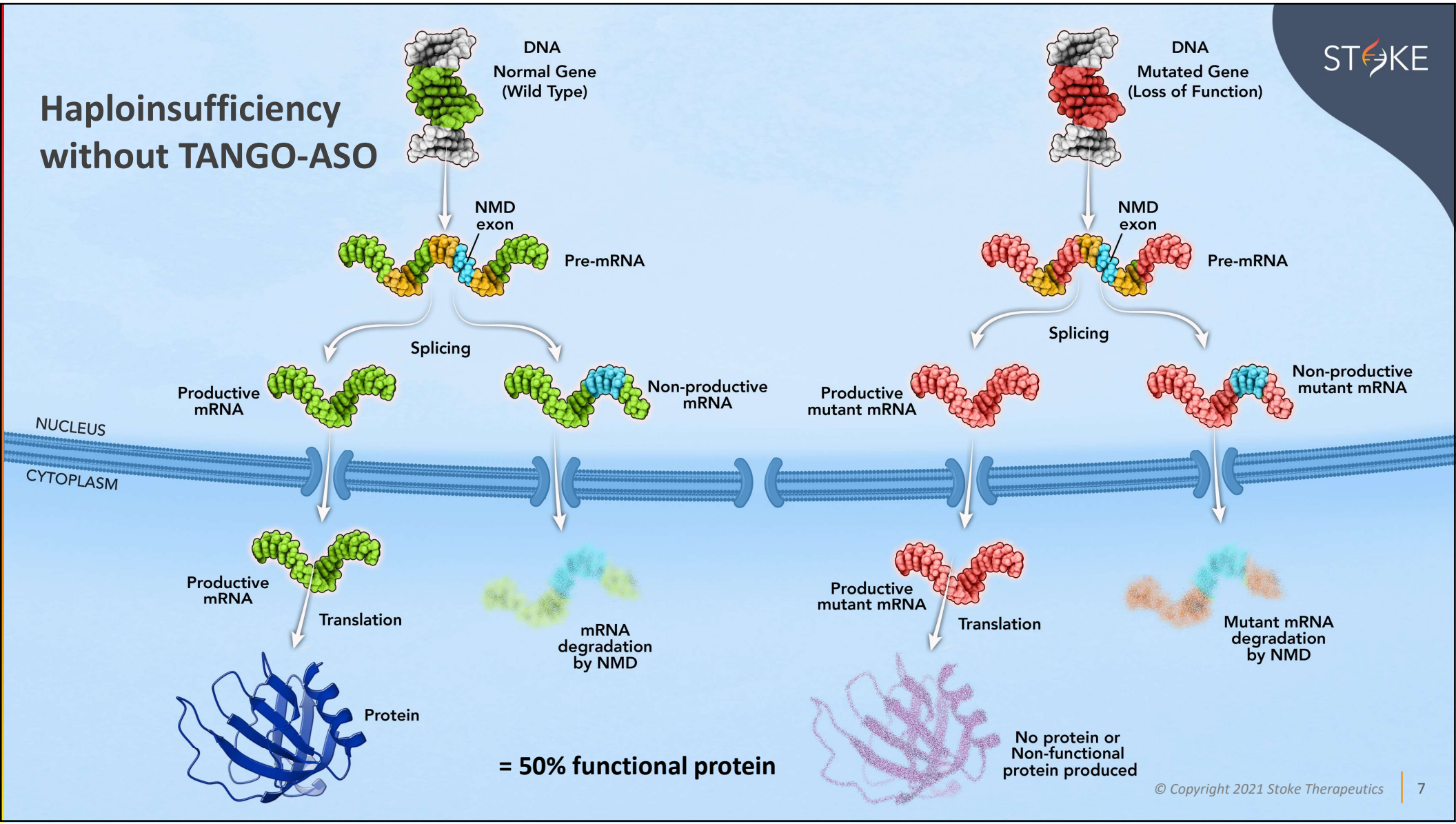
Sources: *2018 Health Advances Report*; Djémié et al., *Molecular Genetics & Genomic Medicine,* 2016; Lagae et al., *Developmental Medicine & Child Neurology,* 2017; Nabbout et al., *Orphanet Journal of Rare Diseases,* 2013

No Approved Disease-Modifying Therapies for Dravet Syndrome

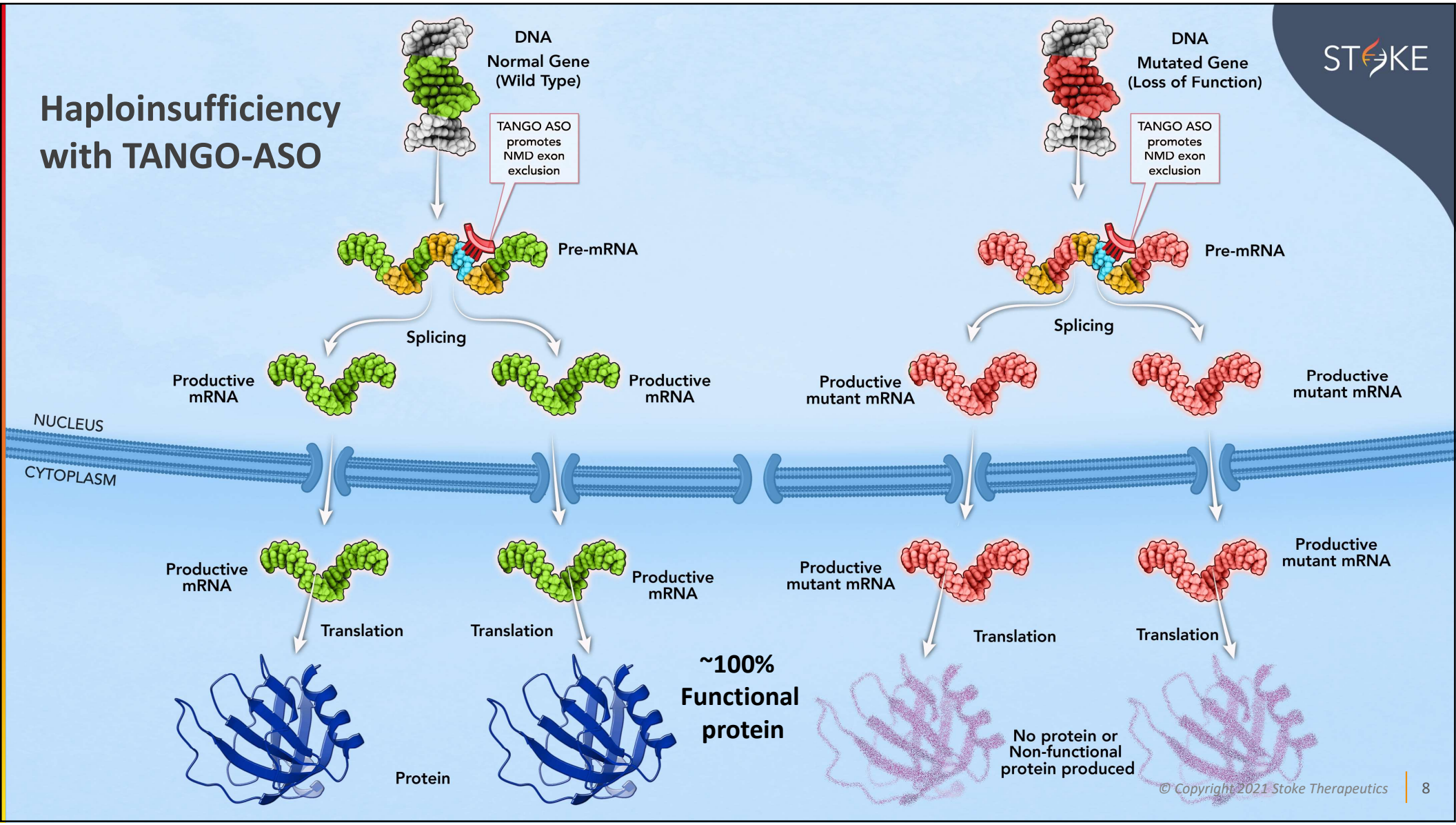
Non-Seizure Comorbidities of Dravet Syndrome Are Not Addressed by Current Therapies

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

Haploinsufficiency without TANGO-ASO



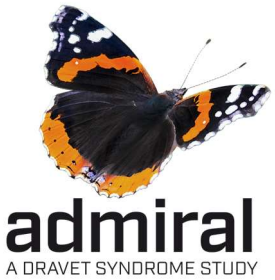
Haploinsufficiency with TANGO-ASO



Studies of STK-001 Ongoing in the U.S. and UK

Open-label evaluation of single and multiple ascending doses of STK-001 in the U.S.

- Interim results show single doses of STK-001 up to 30mg and multiple doses of 20mg were well-tolerated with no safety concerns related to the study drug
- First patient dosed in MAD portion at 30mg
- FDA will allow the evaluation of an additional higher dose level (45mg)



Open-label evaluation of multiple ascending doses of STK-001 (up to 70mg) in the UK

- First patient dosed at 30mg

Phase 1/2a MONARCH Interim Analysis

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

MONARCH Study Design and Objectives

Design:

- Multi-center, open-label, SAD and MAD study of STK-001 in patients with Dravet syndrome conducted in U.S.
- SAD: 3 cohorts (10 mg, 20mg, 30mg) with study drug administration at Day 1
- MAD: 2 cohorts (20mg, 30mg) with study drug administrations at Day 1, Week 4 (Day 29), and Week 8 (D57)
- All patients in SAD and MAD portion of study are followed for 6 months after last dose
- Study duration for each patient approximately 7 months (SAD) and 9 months (MAD)

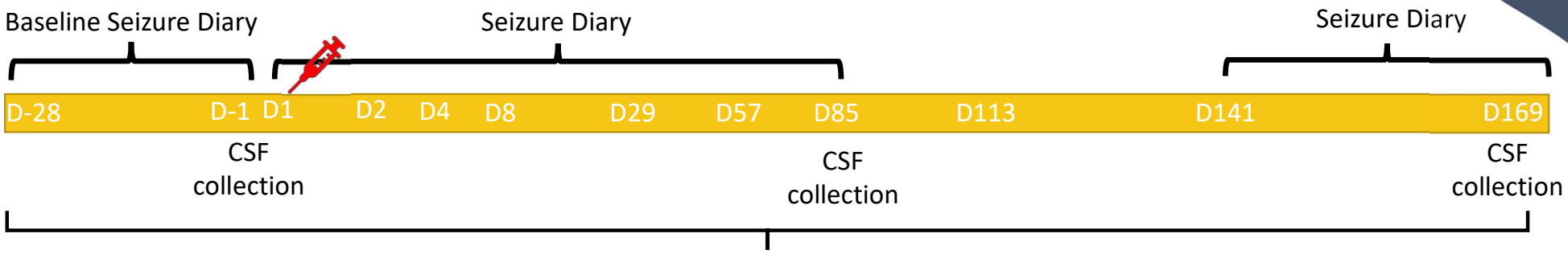
Primary Objectives:

- Evaluate safety and tolerability of SAD and MAD of STK-001
- Determine pharmacokinetics (PK) of SAD and MAD of STK-001 in plasma and exposure in CSF

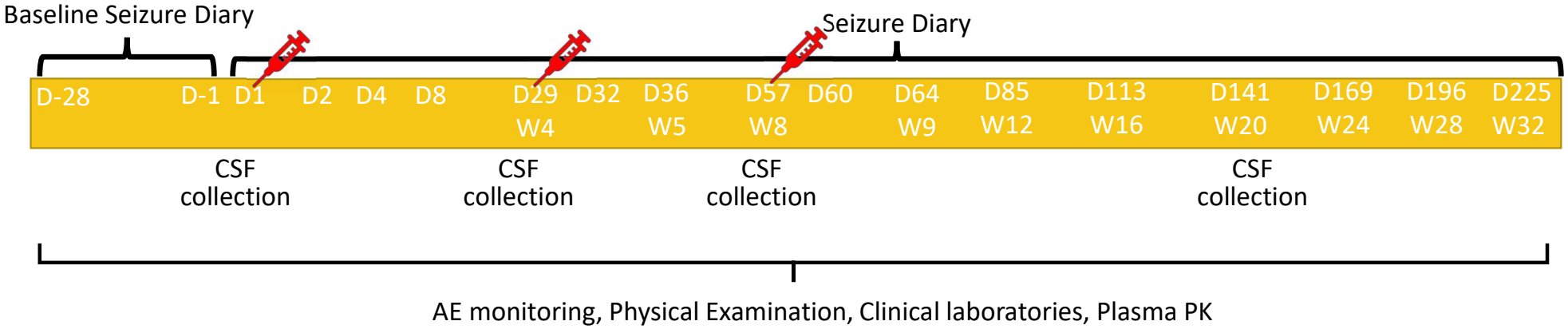
Secondary Objectives:

- Assess effect of SAD and MAD of STK-001:
  - As an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency
  - On overall clinical status and quality of life (not included in this interim analysis)

MONARCH SAD Study Assessments



MONARCH MAD Study Assessments



= Study Drug Administration

MONARCH Study Interim Analysis Included 21 Patients, All of Whom Had Severe Disease Despite Use of Anti-Seizure Medications

No patients withdrew from the study

Cohort A1
10mg SAD
(n=5)

Cohort A2
20mg SAD
(n=4)

Cohort A3
30mg SAD
(n=6)

Cohort B1
20mg MAD
(n=6)

Analysis conducted 3-months after the last patient was treated with 30mg (SAD)

All patients received ≥1 dose of STK-001

Age at Screening, years	
Median (min, max)	13.0 (2, 18)
Age of onset of first seizure type (months)	
Mean (SD)	4.85 (2.242)
Median (min, max)	4.00 (2.0, 11.0)
Observed baseline convulsive seizure frequency (per 28 days)	
Mean (SD)	54 (128.564)
Median (min, max)	17 (3.0, 591.0)
Number of concomitant anti-seizure medications as maintenance therapy	
85% (18/21) of patients used ≥3 concomitant anti-seizure medications; 66.7% (14/21) used ≥4	Most common medications were clobazam (61.9%) and fenfluramine (47.6%)

Single Doses of STK-001 up to 30mg and Multiple Doses of 20mg Were Well-Tolerated and No Safety Concerns Related to STK-001

- 3 of 21 (14.3%) patients experienced a TEAE related to study drug
  - None observed in 30mg SAD or 20mg MAD cohorts
- 4 of 21 (19.0%) patients had a treatment-emergent SAE
  - None related to study drug
- No new significant neurologic exam findings emerged and no sign of lower extremity weakness
- No increase in seizures were identified in 1 hour EEG recorded ~24 hours post-dose
- No clinically significant changes in blood coagulation, liver function, or renal function parameters were observed

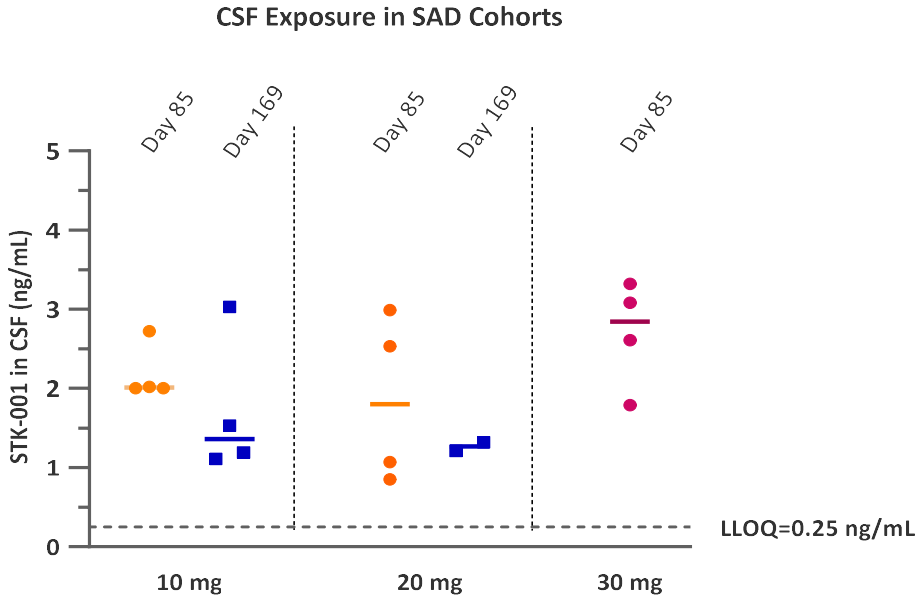
Increases in Plasma Exposure **and** Mean CSF Concentration Observed in Patients Who Received Doses From 10mg to 30mg

A dose-proportional increase in study drug exposure was observed in plasma PK

Dose (mg)	Plasma PK parameters	
	N	AUC_{last} (h*ng/mL) (Mean ± SD)
10	4	2450 ± 1690
20	4	6460 ± 2820
30	5	11600 ± 7110

- Mean group AUC_{last} increased 2.6- and 4.7-fold for dose increase of 2- and 3-fold, respectively

A dose-proportional increase in CSF concentration was observed from 20mg to 30mg

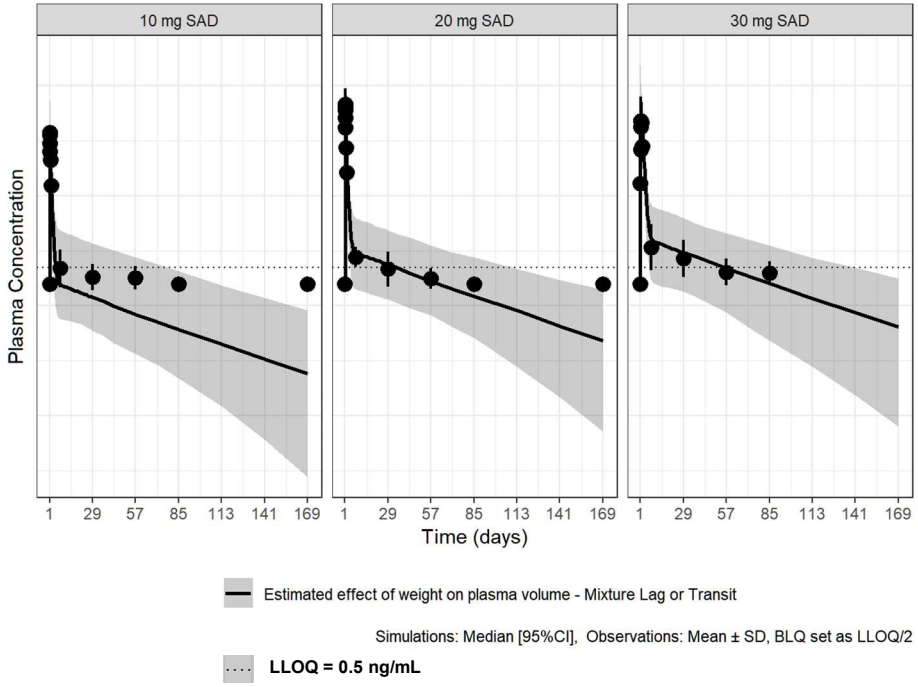


- STK-001 levels were detected in CSF to last collection i.e., Day 169 for 10 and 20 mg Cohorts, and Day 85 for 30 mg Cohort
- Measurable CSF Exposure up to 6 Months Post Single IT Dose Indicated Sustained Exposure in Brain

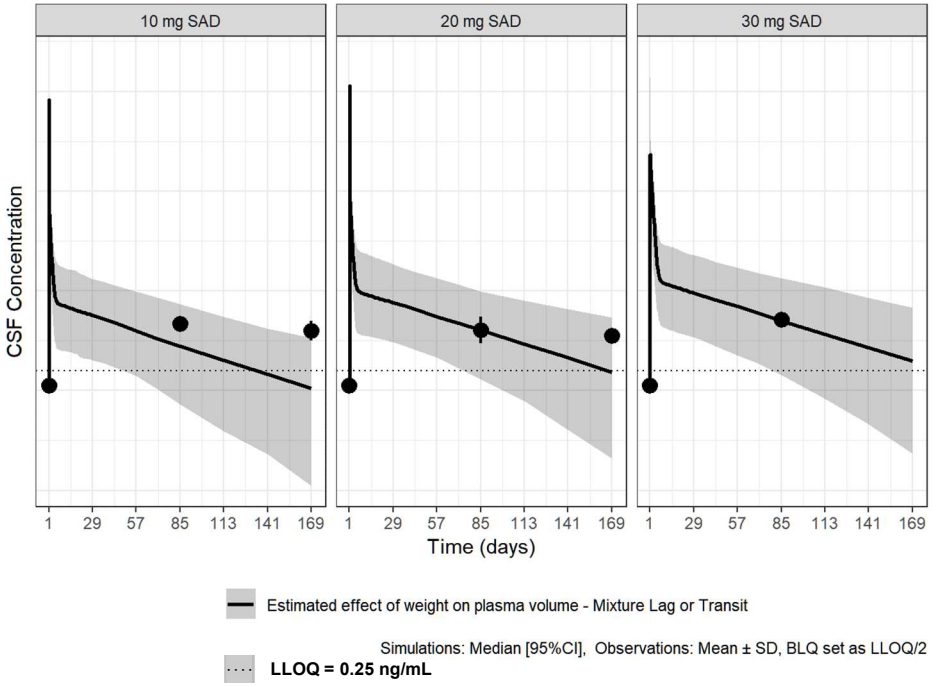
Note: AUC=Area Under the Curve; CSF=Cerebrospinal Fluid; IT=Intrathecal; LLOQ=Lower Limit of Quantification; PK=Pharmacokinetic; SAD=Single Ascending Dose

Observed Plasma and CSF Levels in Patients Correlated Well with Model Predictions

Comparison of PK Model Predictions
With Mean Observed **Plasma** Data



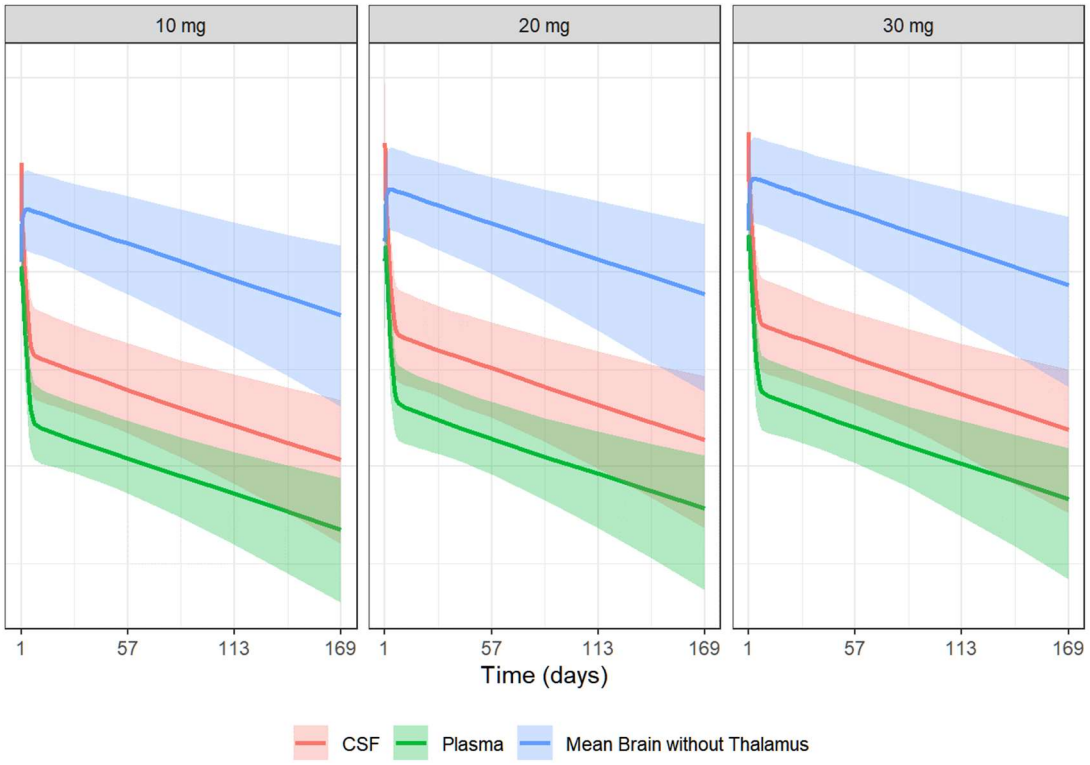
Comparison of PK Model Predictions
With Mean Observed **CSF** Data



Solid lines represent median and shaded areas represent 95% CI.
Black dots represent observed data from clinical trial

- CSF was drawn on Days 85 and 169 post single dose for STK-001 analyses

Steady State Plasma and CSF STK-001 Levels are Good Predictors of STK-001 Brain Levels in Patients

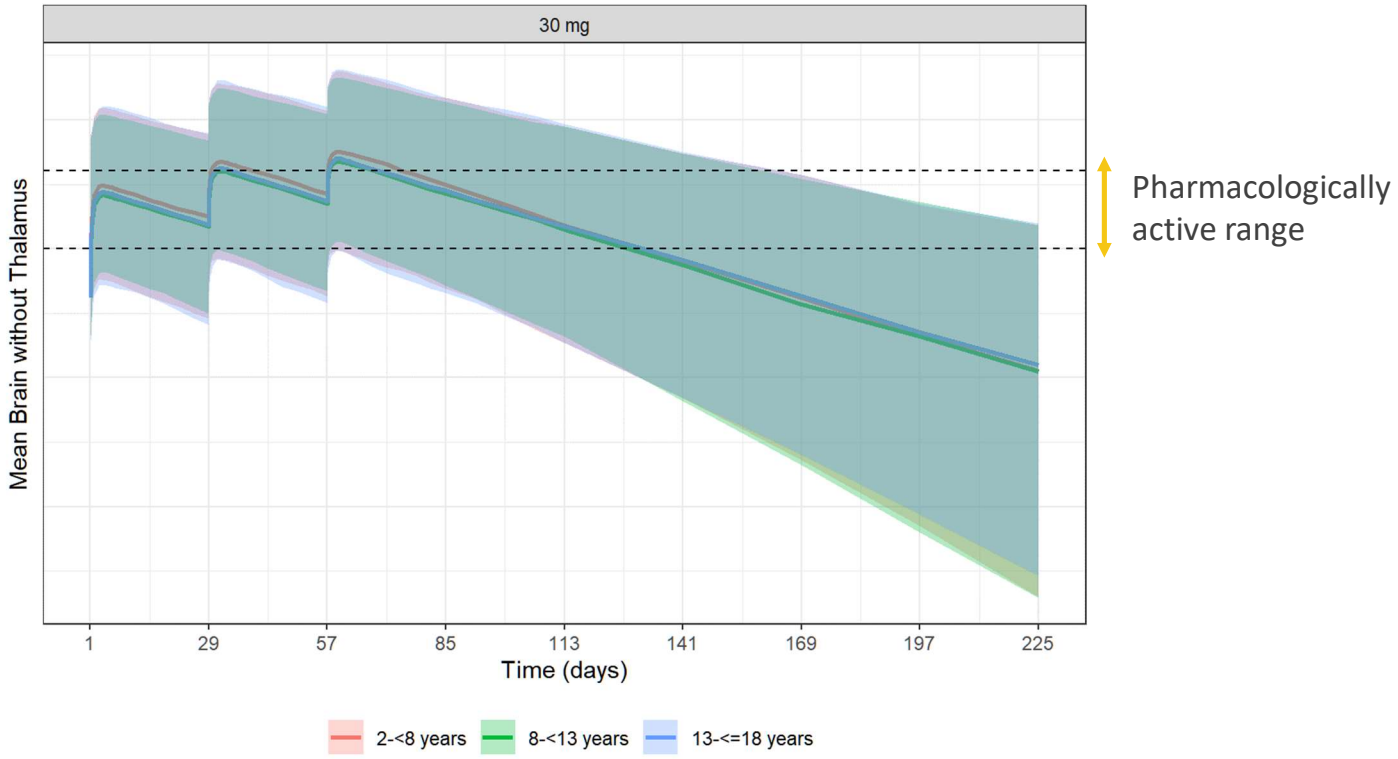


- Projected plasma, CSF, and brain levels were strongly correlated across time and dose groups following single IT STK-001 doses
- Therefore, CSF and/or plasma levels in MONARCH can be used to estimate STK-001 levels in brain

Note: Solid lines represent median and all shaded areas represent 95% CI

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

~50% of patients anticipated to remain at active levels approximately 3 months after their last dose



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

Secondary Endpoint: Trend Toward Seizure Reduction Observed

Based on data available from 11 patients in the SAD cohorts (10mg, 20mg, 30mg)

- 8/11 patients experienced a reduction in convulsive seizure frequency
- Trend more evident in patients 2 to 12 years old
- Patients in the study were taking multiple anti-seizure medicines: 85% on ≥3 and 67% ≥4
- Data being prepared for presentation at the American Epilepsy Society annual meeting in early December

Dravet Syndrome Program Continues to Progress

swallowtail
A DRAVET SYNDROME EXTENSION STUDY

All patients who have completed dosing in the SAD portion of MONARCH have continued treatment in SWALLOWTAIL

monarch
A DRAVET SYNDROME STUDY

First patient dosed in MONARCH MAD at 30mg

FDA will allow the evaluation of STK-001 up to 45mg in MONARCH

admiral
A DRAVET SYNDROME STUDY

First patient dosed at 30mg in ADMIRAL UK Study evaluating multiple doses up to 70mg

We expect to share clinical data from multiple doses of 30mg in the second half of 2022

Acknowledgements

Closing Remarks

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

Overall Summary of MONARCH Interim Analysis Results

- Single doses of STK-001 up to 30mg and multiple doses of 20mg were well-tolerated and no safety concerns related to the study drug
- Interim analysis confirms our pre-clinical work and gives us greater understanding of dose levels that are likely to be pharmacologically active in patients
- Interim findings support the advancement of STK-001 as the first potentially disease-modifying treatment for patients with Dravet syndrome

2021 Milestones as of September 2021

1H2021	Initiate Swallowtail Open Label Extension (OLE) study of STK-001	✓
2H2021	Initiate MAD study of STK-001 (MONARCH) – COMPLETED IN 1H2021	✓
3Q2021	Preliminary safety, PK, CSF, and modeling data from SAD portion of MONARCH	✓
2H2021	Initiate MAD study of STK-001 in the U.K. (ADMIRAL)	✓
2H2021	Initiate ADOA natural history data collection	
YE2021	Identify a clinical candidate for the treatment of ADOA	
YE2021	Demonstrate *in vivo* proof of mechanism & safety for a third TANGO ASO program	

Q&A