



Interim Analyses: An Open-Label  
Study to Investigate the Safety  
and Pharmacokinetics of Single  
and Multiple Ascending Doses of  
Antisense Oligonucleotide STK-  
001 in Children and Adolescents  
with Dravet Syndrome

Linda Laux, MD  
Ann & Robert H. Lurie Children's Hospital of Chicago  
Associate Professor  
Northwestern University Feinberg School of Medicine

The presenter is a consultant of Stoke Therapeutics, Inc. (“Stoke”).

This presentation is for educational purposes only. The opinions expressed in this presentation are those of the presenter and not necessarily those of Stoke. The content of this deck is accurate to the best of the presenter’s knowledge at the time of production and Stoke does not guarantee the accuracy or reliability of the information provided herein.

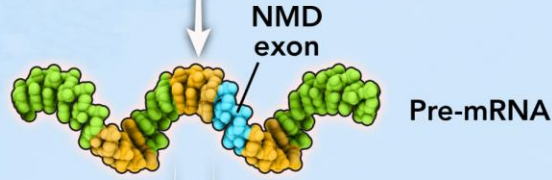
Some of the material described herein is reproduced with authorization from third-parties and may be copyrighted, proprietary or otherwise protected. Unauthorized reproduction of the presentation material is prohibited. Some compounds, methods, and therapeutic targets described in this presentation may be covered by intellectual property rights of Stoke or unrelated third parties. This presentation does not provide or waive any rights under the intellectual property.

STK-001 is an investigational drug and has not yet been approved by the U.S. Food and Drug Administration or any regulatory authority.

Linda Laux is a Pediatrician and Attending Physician in the Neurology and Epilepsy Center of the Ann & Robert H. Lurie Children’s Hospital, as well as an Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA. She receives funding for research and consultation for Biocodex, Jazz/GW Pharma, Encoded Therapeutics, Stoke Therapeutics, Epygenix Therapeutics, Takeda, and Zogenix.

# Haploinsufficiency without TANGO-ASO

DNA  
Normal Gene  
(Wild Type)

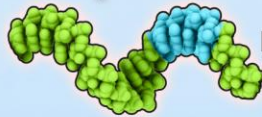


Splicing

Productive mRNA



Non-productive mRNA



Productive mRNA



Translation



= 50%  
functional  
protein

mRNA  
degradation  
by NMD

Increased functional  
protein expression

# Haploinsufficiency with TANGO-ASO

DNA  
Normal Gene  
(Wild Type)

TANGO ASO  
promotes  
NMD exon  
exclusion



Splicing

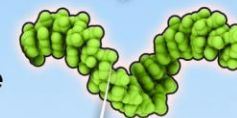
Productive mRNA



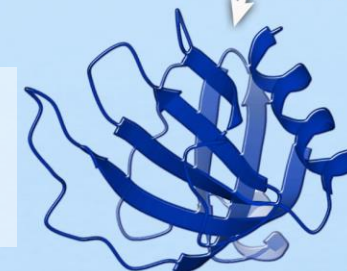
Productive mRNA



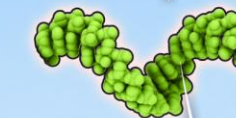
Productive mRNA



Translation



Translation





Productive mRNA

Protein

# 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

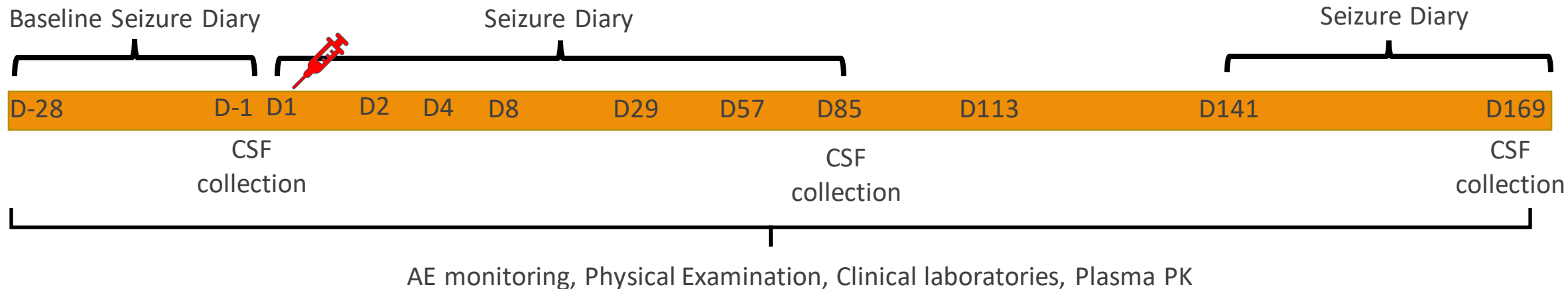


<b>Design</b>	Evaluation of STK-001 (up to 45mg*)	Evaluation of STK-001 (up to 70mg)
<b>Status</b>	<ul style="list-style-type: none"> <li>MAD @30mg: Dosing complete in initial cohort. Dosing ongoing in expansion cohort</li> <li>SAD &amp; MAD @45mg: Dosing ongoing</li> </ul>	<ul style="list-style-type: none"> <li>MAD @45mg: Dosing ongoing</li> </ul>
<b>Target Enrollment</b>	~90	Up to 60
<b>Primary Endpoint</b>	Safety and tolerability of SAD and MAD dose levels Characterize human pharmacokinetics (PK) and cerebrospinal fluid (CSF) drug exposure	Safety and tolerability of MAD dose levels
<b>Secondary Endpoint</b>	Change in seizure frequency, overall clinical status, and quality of life	
<b>Open-Label Extension</b>	Enrollment and dosing ongoing 	First patient expected to be dosed in 2Q22 

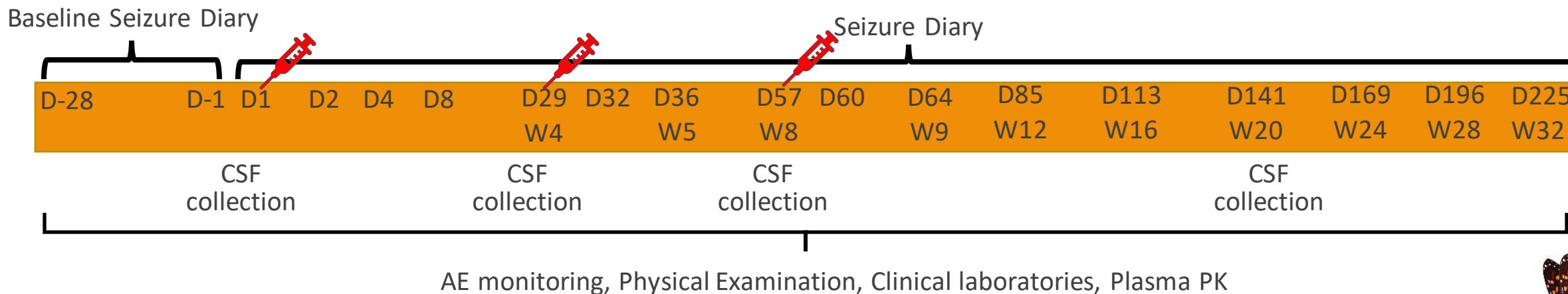
\*Doses >45mg remain on FDA partial clinical hold

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)

# MONARCH SAD Study Assessments



# MONARCH MAD Study Assessments



= Study Drug Administration

# Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
Aged 2-18 years (inclusive)	Known pathogenic mutation in another gene that causes epilepsy
DS onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic) <ul style="list-style-type: none"> <li>– No history of causal MRI lesion (MRI not required)</li> <li>– No other known etiology</li> <li>– Normal development at seizure onset</li> </ul>	Currently being treated with an anti-epileptic drug acting primarily as a sodium channel blocker, as maintenance treatment
Documented pathogenic, likely pathogenic variant, or variant of uncertain significance in <i>SCN1A</i>	Clinically significant unstable medical condition(s) other than epilepsy
≥2 prior treatments for epilepsy that lacked adequate seizure control or had to be discontinued due to AEs	Clinically relevant symptoms or clinically significant illness in 4 weeks prior to screening or prior to dosing on day 1, other than epilepsy
≥1 anti-epileptic drug (and any other treatments) at a stable dose for ≥4 weeks	Any other significant disease or disorder, in investigator's opinion, that may put the patient at risk, influence study results, or affect patient's ability to participate



- Data cutoff was Feb 21, 2022
- 29 patients received at least one dose of STK-001 at the 10, 20, or 30 mg dose levels
  - Cohort A1 (10 mg SAD; n=5), A2 (20 mg SAD; n=4), Cohort A3 (30 mg SAD; n=7)
  - Cohort B1 (20 mg MAD; n=6), B2 (30 mg MAD; n=7)
  - 1 patient with early termination in 20 mg MAD cohort; all other patients completed or ongoing in study
- Study population enrolled ranged in age from 2 to 18 years of age and was well-balanced by gender

- 25 of 29 (86.2%) patients experienced at least one treatment-emergent adverse event (TEAE)
  - 5 patients experienced  $\geq 1$  Grade 3 (severe, life-threatening, or fatal) event, none were related to study drug
  - No clear dose-dependent effects were observed across reported TEAEs
- 6 of 29 (20.7%) patients experienced a TEAE related to study drug
  - 4 events were mild and 2 (headache, irritability) events were moderate in severity
- 7 of 29 (24.1%) patients experienced  $\geq 1$  treatment-emergent serious adverse event (SAE)
  - None were related to study drug



# Summary of Most Frequent TEAEs by Preferred Term\*

Preferred Term (in descending order)	Number of Patients (n=29)
Headache	7
Vomiting	7
Seizure	6
Irritability	4
Pyrexia	5

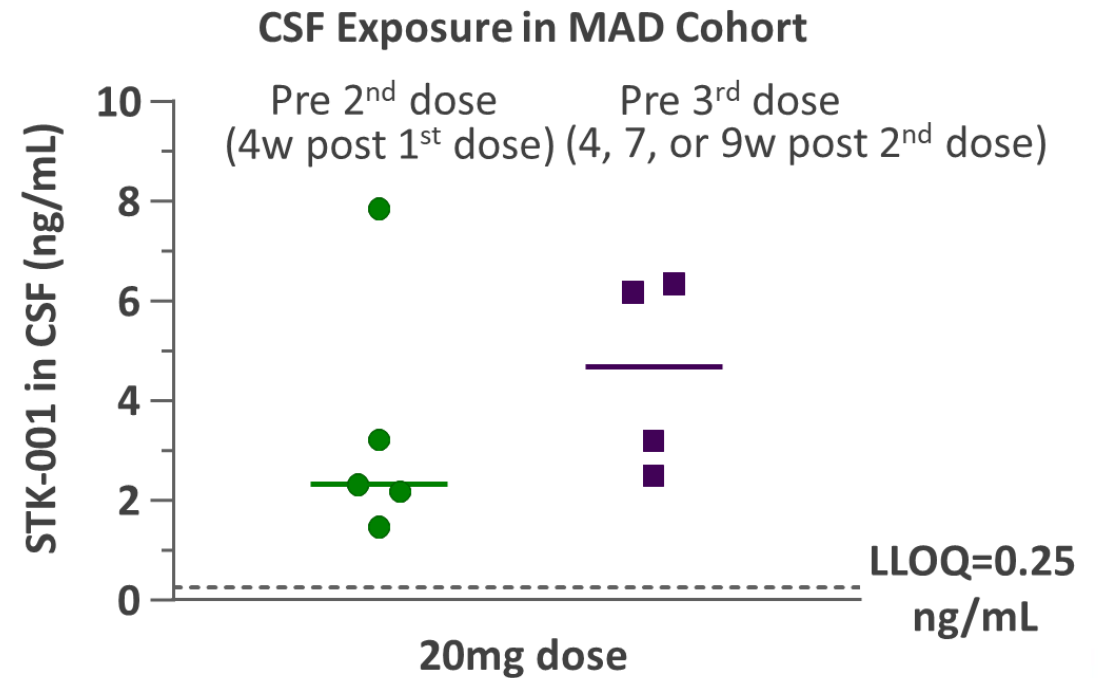
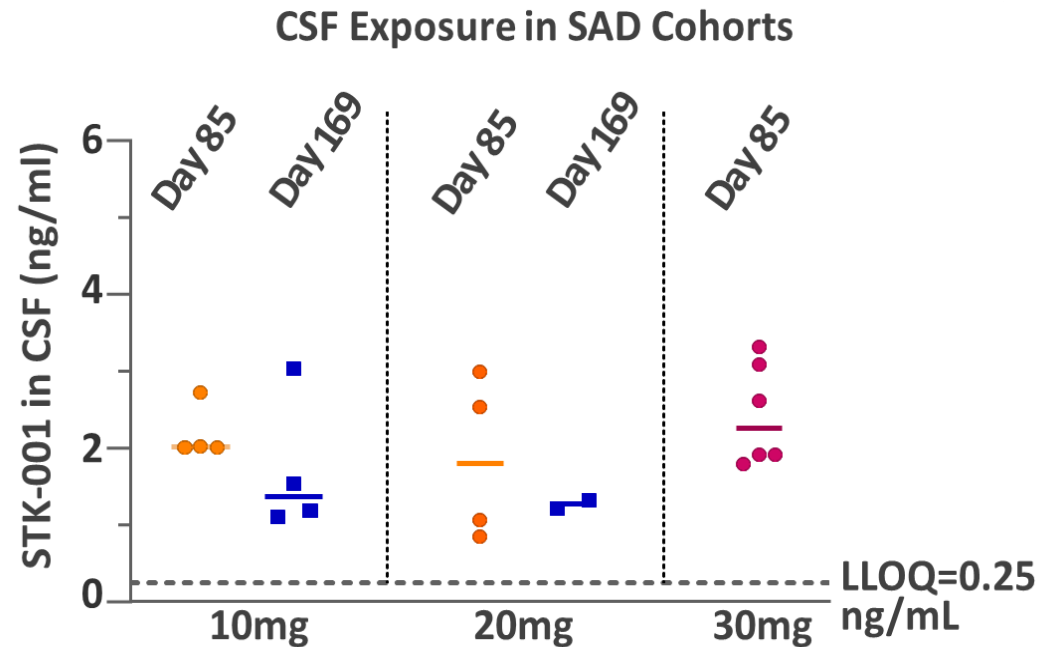
# Dose-Dependent increases in plasma exposure were observed

- Dose-dependent increases in plasma exposure were observed (n=21)
- Plasma AUC<sub>last</sub> was similar for the 20mg SAD cohort and 1st dose in the 20mg MAD cohort

Dose (mg)	Plasma PK parameters	
	n	AUC <sub>last</sub> (h*ng/mL) (Mean ± SD)
SAD 10	4	2450 ± 1690
SAD 20	4	6460 ± 2820
SAD 30	7	15300 ± 12100
MAD 20 (dose 1)	6	4450 ± 3110

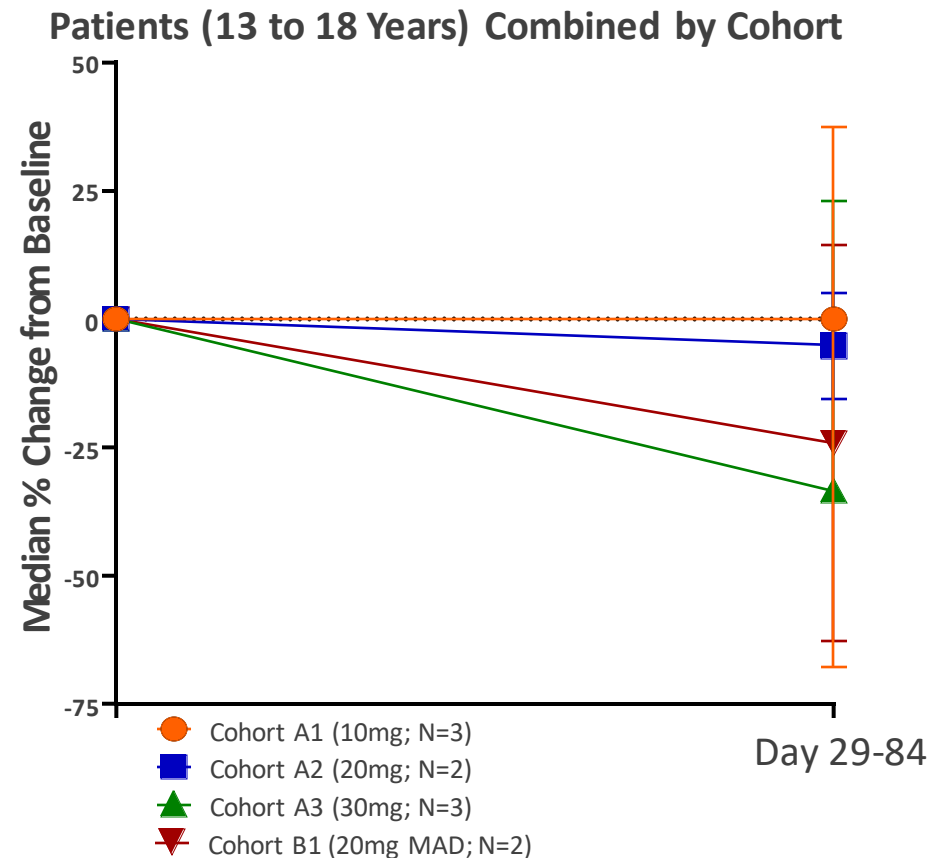
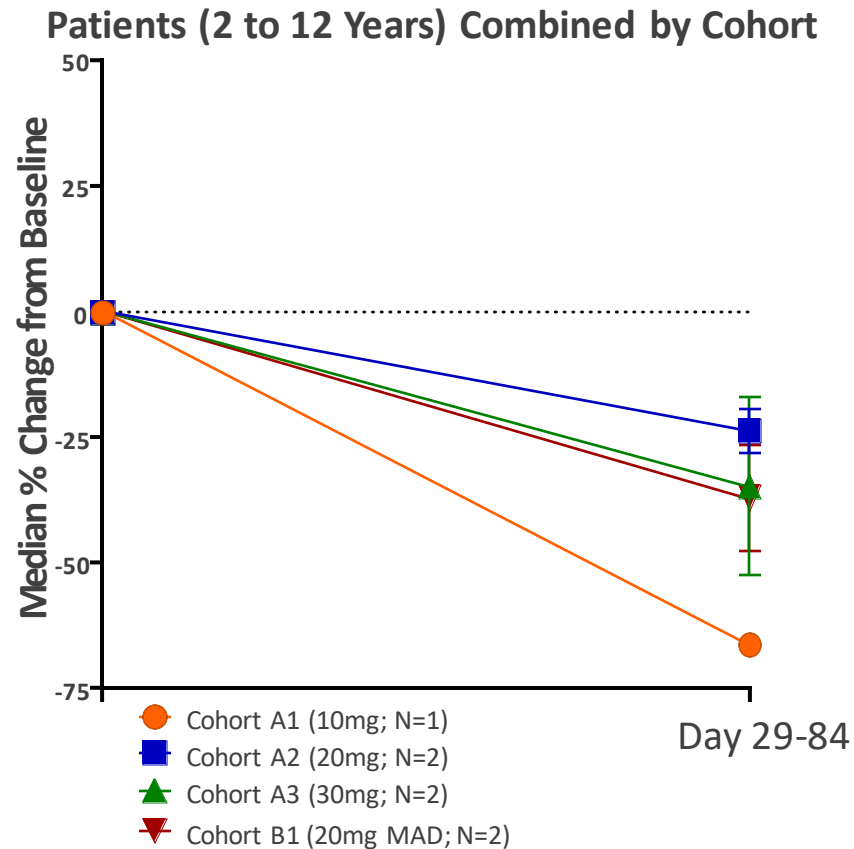
# Measurable CSF Exposure up to 6 Months Post Single Intrathecal Dose Indicated Sustained Exposure in Brain

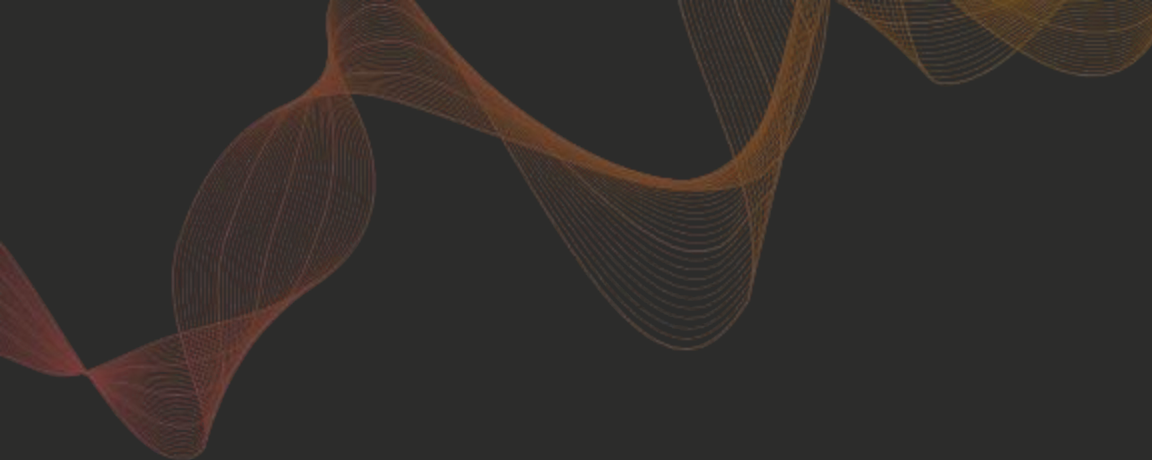
- STK-001 levels were detected in CSF to last collection i.e., Day 169 for 10 and 20 mg groups and Day 85 for 30 mg group
- Overall, mean CSF concentration at Day 85 increased from 10 to 30 mg
- Mean CSF levels post 2<sup>nd</sup> dose were higher compared to levels post 1<sup>st</sup> dose indicating accumulation of STK-001 in CNS tissues with repeated monthly dosing



# 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





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

### Summary of Ph1/2a MONARCH Interim Data

---

Data to date indicate that single and multiple doses up to 30mg are well tolerated with no safety concerns related to study drug



---

STK-001 levels were detected in CSF up to 6 months post single dose



---

Trend toward seizure reduction observed in DS patients following dosing of STK-001



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