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

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Disclosures

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

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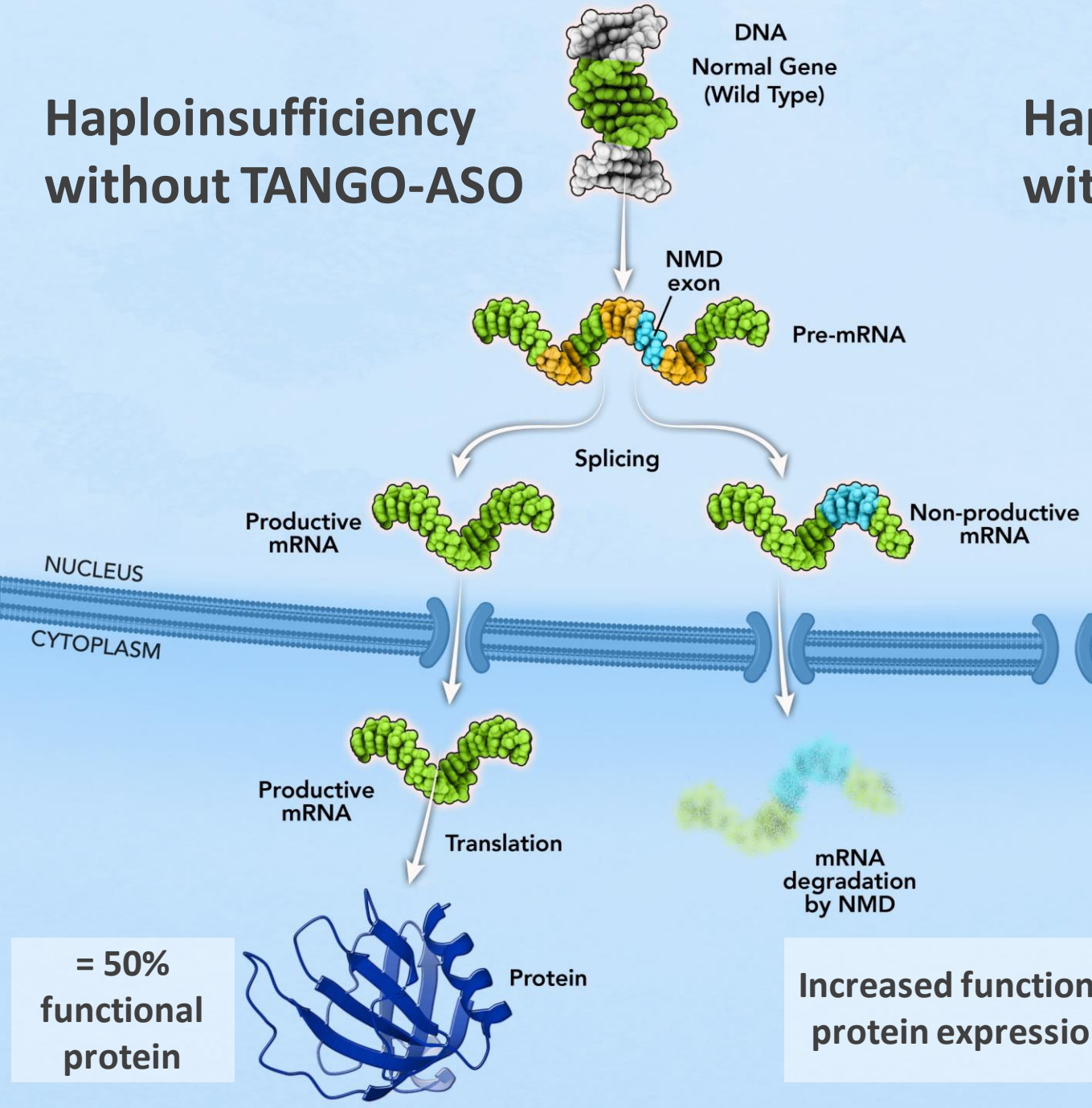
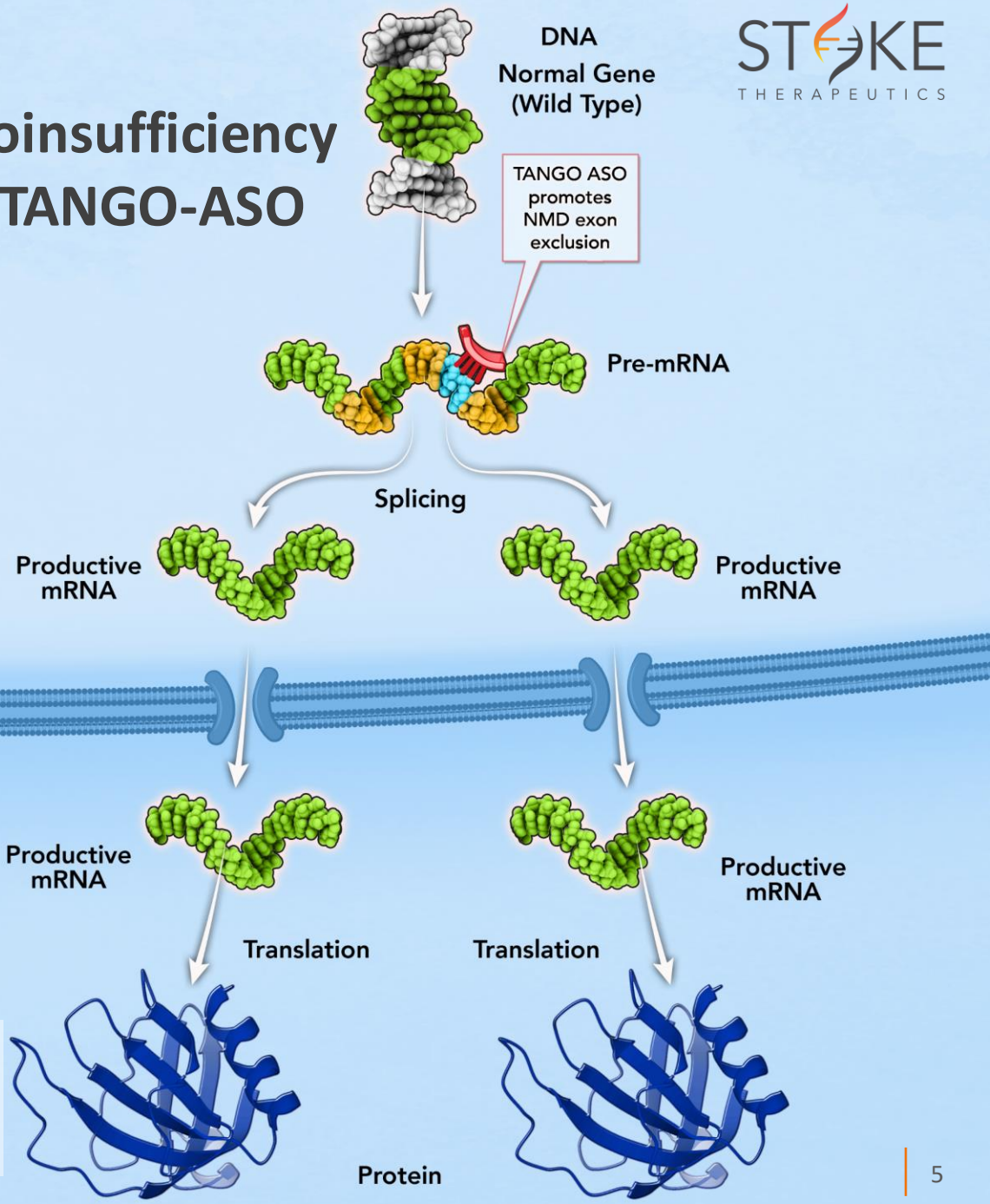
Haploinsufficiency without TANGO-ASO



= 50% functional protein

Haploinsufficiency with TANGO-ASO



Increased functional protein expression

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

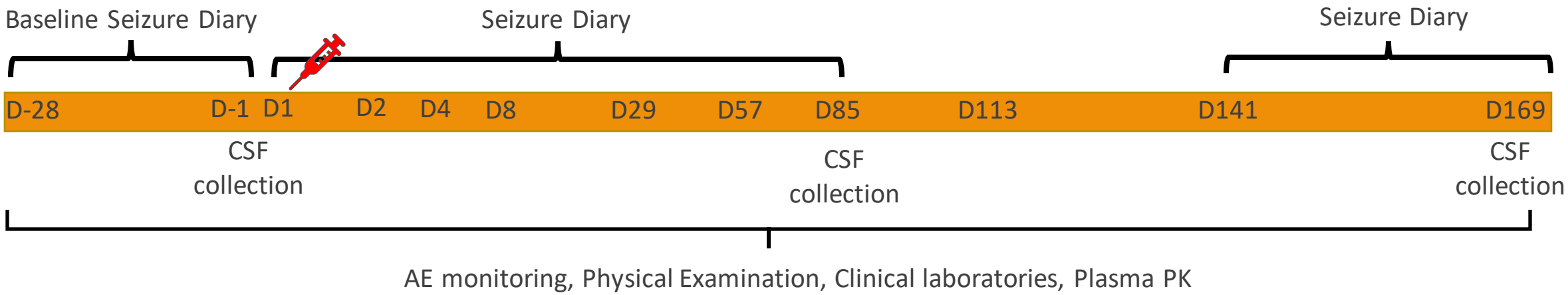
Parallel studies in the US & UK evaluating children and adolescents ages 2 to 18 years old

	monarch	admiral
Design	Evaluation of STK-001 (up to 45mg*)	Evaluation of STK-001 (up to 70mg)
Status	• MAD @30mg: Dosing complete in initial cohort. Dosing ongoing in expansion cohort • SAD & MAD @45mg: Dosing ongoing	• MAD @45mg: Dosing ongoing
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 ongoing	First patient expected to be dosed in 2Q22

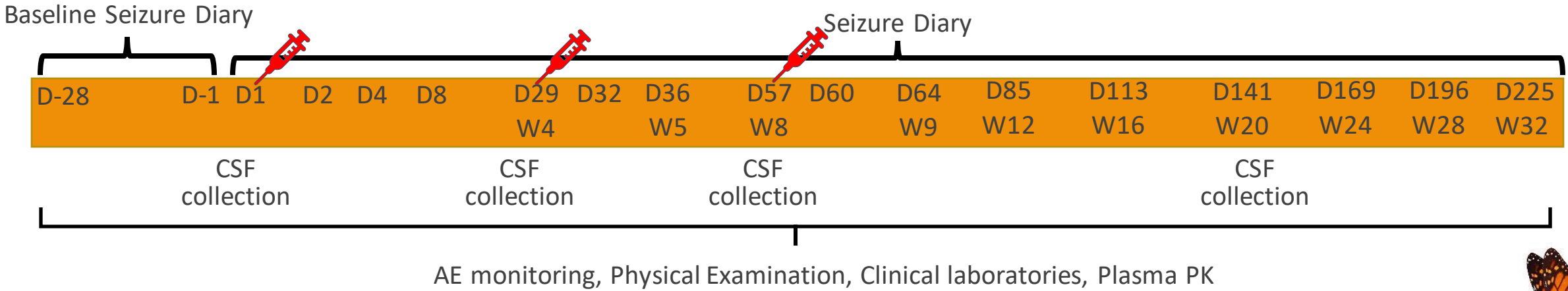
*Doses >45mg remain on FDA partial clinical hold

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) – No history of causal MRI lesion (MRI not required) – No other known etiology – Normal development at seizure onset	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 *SCN1A*	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

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).

Baseline Characteristics Summary

- 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

Adverse Event Summary

- 25 of 29 (86.2%) patients experienced at least one treatment-emergent adverse event (TEAE)
  - 5 patients experienced ≥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 ≥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

*patients only counted once per preferred term

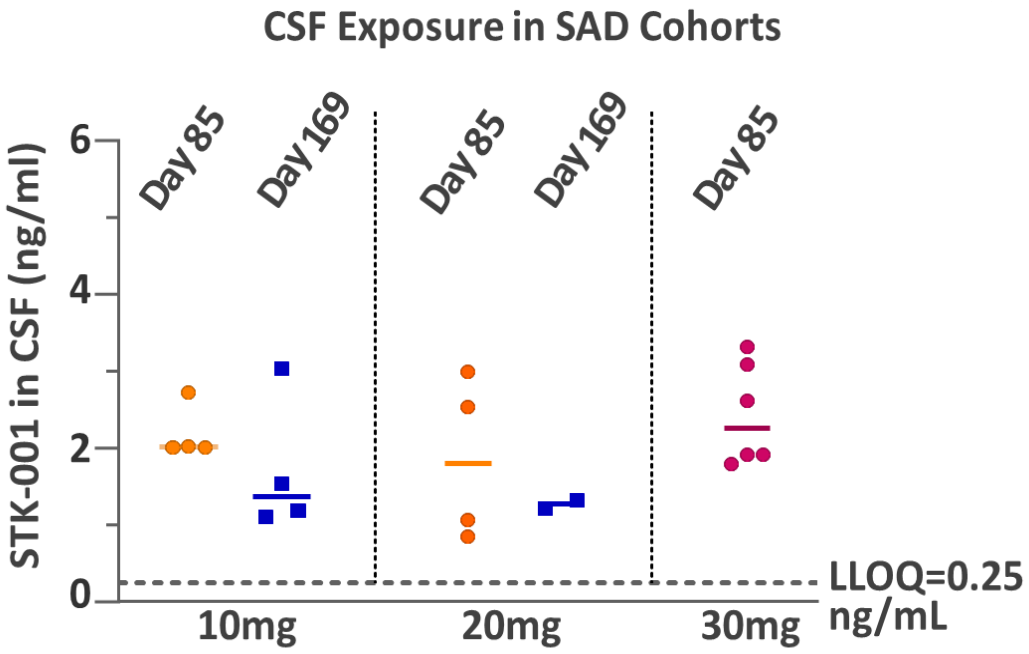
Dose-Dependent increases in plasma exposure were observed

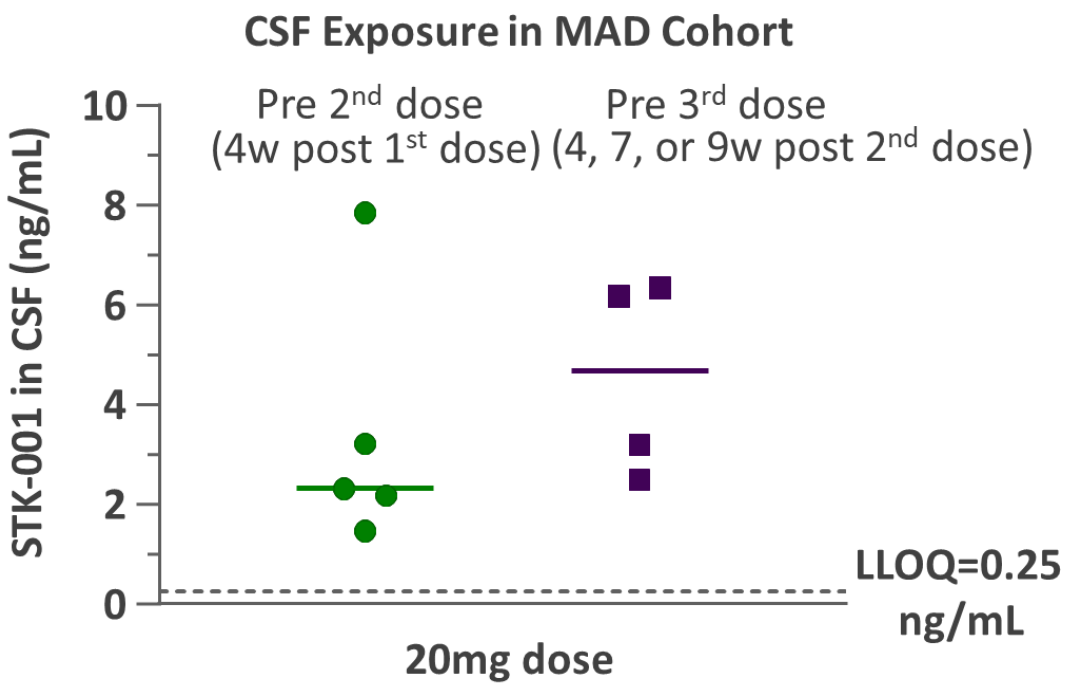
- Dose-dependent increases in plasma exposure were observed (n=21)
- Plasma AUC_{last} was similar for the 20mg SAD cohort and 1st dose in the 20mg MAD cohort

Dose (mg)	Plasma PK parameters	
	n	AUC_{last}(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 2nd dose were higher compared to levels post 1st dose indicating accumulation of STK-001 in CNS tissues with repeated monthly dosing



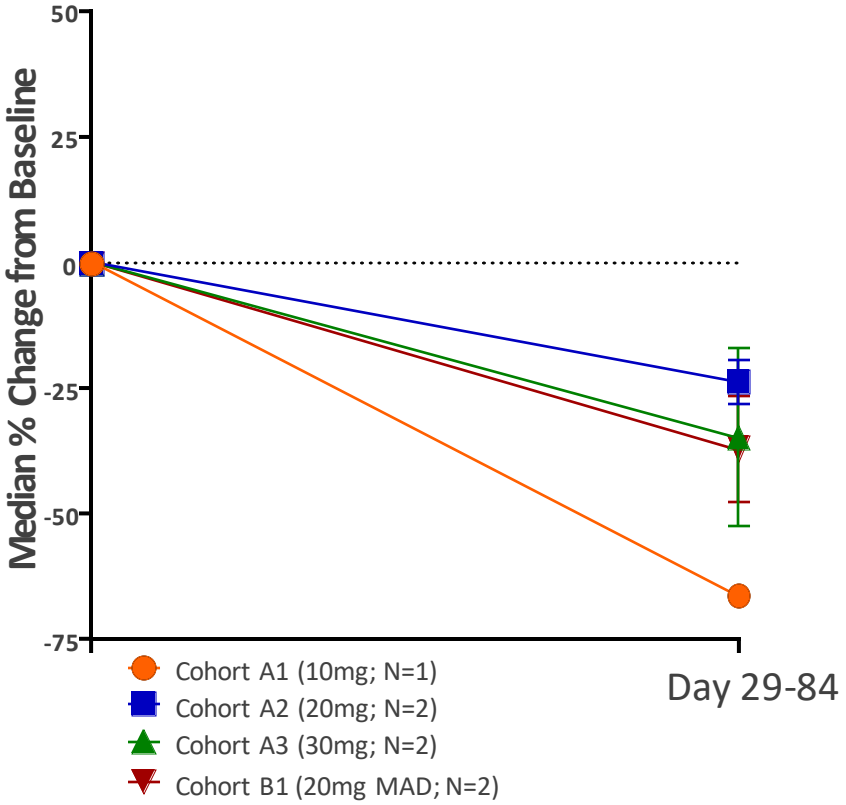


monarch
A DRAVET SYNDROME STUDY

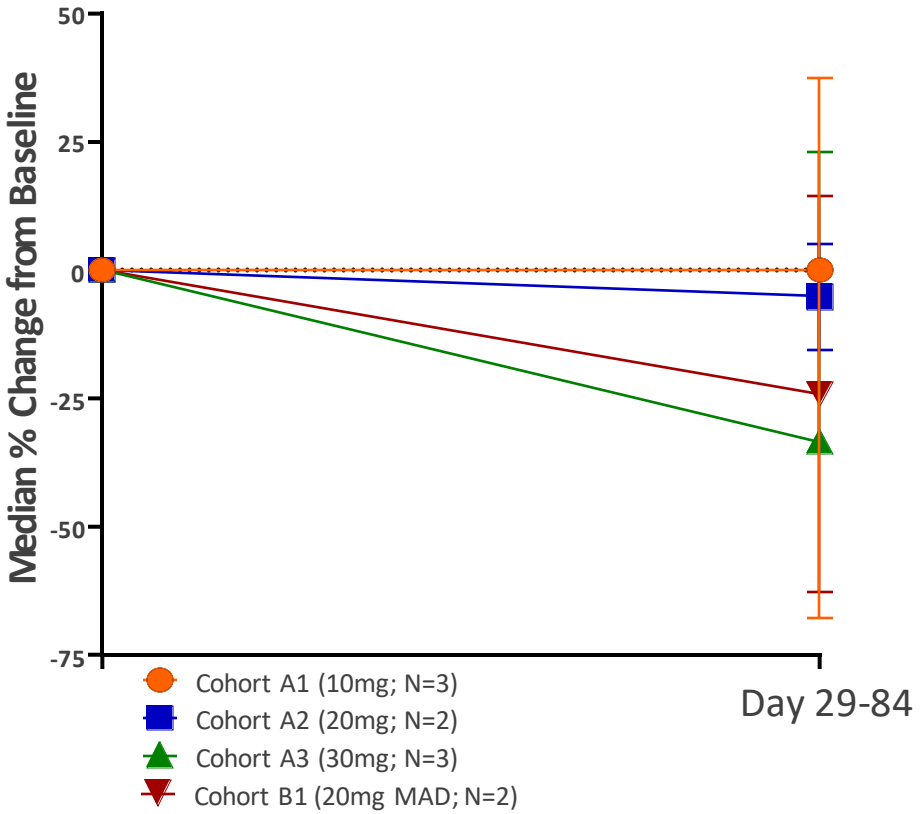
Patients Treated with STK-001 Experienced Reductions in Convulsive Seizure Frequency

- 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

Patients (2 to 12 Years) Combined by Cohort



Patients (13 to 18 Years) Combined by Cohort



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

- 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