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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)

Linda Laux[1], Colin Roberts[2], Kelly G Knupp[3], John M Schreiber[4], Matt Lallas[5], Elaine Wirrell[6], Orrin Devinsky[7], James Stutely[8], Charlene Brathwaite[8], Javier Avendaño[8], Kimberly A Parkerson[8], Meena[8], Nancy Wyant[8], Barry Ticho[8], Joseph Sullivan[9]

[1]Ann & Robert H Lurie Children's Hospital of Chicago; [2]OHSU; [3]University of Colorado; [4]Children's National Hospital; [5]NeuroNetwork Partners, [6]Mayo Clinic, [7]NYU Langone Health, [8]Stoke Therapeutics; [9]UCSF

INTRODUCTION

- DS is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year (y) of life
- Available therapies do not adequately control seizures in 90% in patients with DS, and they do not address other comorbidities, including intellectual disability, ataxia/motor abnormalities, behavioral problems, speech impairment, sleep disturbances, and a high risk for SUDEP
- Disease complications often contribute to a poor quality of life for patients and their caregivers
- In approximately 85% of cases, DS is caused by spontaneous, heterozygous loss of function mutations in the *SCN1A* gene, which encodes the voltage-gated sodium channel type 1 α subunit ($Na_v1.1$) protein
- Upregulating $Na_v1.1$ protein may restore functioning neurons and prevent seizures and reduce non-seizure related comorbidities in DS

STK-001

- STK-001 is an investigational proprietary ASO designed to upregulate $Na_v1.1$ protein expression by leveraging the non-mutant (wild type) copy of *SCN1A* to restore physiological $Na_v1.1$ protein levels
- The proprietary TANGO platform aims to increase protein production from the healthy gene
- In DS, patients have one functional gene (wild type) copy and one mutated copy, resulting in half as much protein as needed to maintain health
  - These genes are transcribed into pre-messenger RNA (pre-mRNA); most pre-mRNA is productive, becoming a template for protein production, but some is non-productive pre-mRNA due to the naturally occurring nonsense-mediated mRNA decay (NMD)
  - Synthesized TANGO ASOs bind to specific stretches of pre-mRNA, reducing synthesis of non-productive mRNA via NMD exon exclusion, and increasing productive mRNA synthesis
  - Increased levels of productive mRNA from functional gene copies increase protein production, thereby restoring target protein to near normal levels
- STK-001 may be the first disease-modifying therapy to address the genetic cause of DS by upregulating $Na_v1.1$ protein levels

STUDY DESIGN

Protocol Amendment v3.0	
Open-label, Single and Multiple Ascending Doses (SAD and MAD) of STK-001 in 2–18y (NCT04442295)	
Duration	7-9 months / patient
# patients	<70
Sites	Approximately 20 in US
Population	Scan QR Code
Cohorts	Each dose cohort enrolls 4 patients, with option for 6 more for safety evaluation • SAD at 10, 20, and 30mg • MAD at 20 and 30mg every 28 days for 3 doses
Dosing	• Dose escalation based on safety and tolerability assessed by Safety Committee (with external reviewers) • Dosing begins in 13 to 18y cohorts, with internal safety team approving dosing in 2 to 12y
Study Flow	Scan QR code

Data cutoff was 19Oct21, after all patients in Cohort A3 (30mg SAD) completed visit 5 (day 85) and Cohort B1 (20mg MAD) completed visit 7 (week 12). All received ≥1 dose of STK-001.

STUDY OBJECTIVES

Primary Assessments	
Safety and Tolerability	Adverse events (AEs), vital signs, physical examination, electrocardiogram, laboratories
Pharmacokinetics (PK)	STK-001 plasma concentrations
Cerebrospinal Fluid (CSF) Exposure	STK-001 CSF concentrations
Secondary Assessments	
Convulsive seizure frequency	Daily paper seizure diary
Overall Clinical Status and Quality of Life	Caregiver and Clinical Global Impression of Change; EQ-5D-Y [Not included in this analysis]

MORE INFORMATION

To find out more: MONARCHstudy.com. By contacting us, your patient is under no obligation to take part in the study. For PK modeling, please see poster 3.264.

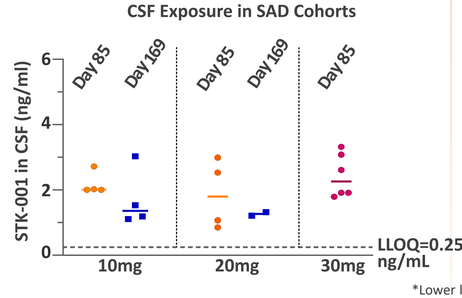
DEMOGRAPHICS AND SAFETY

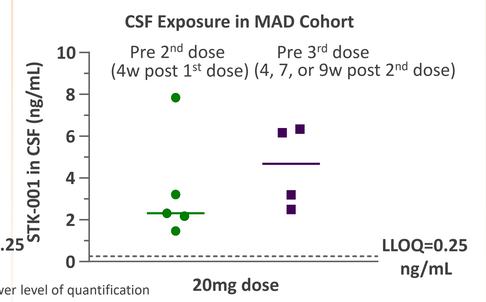
	SAD			MAD	Total
	A1 (10mg)	A2 (20mg)	A3 (30mg)	B1 (20mg)	
Age at Screening, y					
n	5	4	7	6	22
Mean (SD)	11.2 (5.89)	10.8 (5.19)	9.1 (5.90)	13.7 (5.13)	11.1 (5.46)
Median (min, max)	13.0 (2, 18)	10.0 (6, 17)	10.0 (2, 16)	16.0 (4, 17)	13.0 (2, 18)
Age Group, n (%)					
2–12y	2 (40)	2 (50)	4 (57.1)	2 (33.3)	10 (45.5)
13–18y	3 (60)	2 (50)	3 (42.9)	4 (66.7)	12 (54.5)
# patients (all ages) with TEAEs (treatment-emergent adverse effects)					
TEAEs, n (%)	4 (80.0)	4 (100.0)	7 (100.0)	6 (100.0)	21 (95.5)
TEAEs related to study drug, n (%)	2 (40.0)	1 (25.0)	0	1 (16.7)	4 (18.2)
≥Grade 3 TEAEs, n (%)	0	1 (25.0)	1 (14.3)	1 (16.7)	3 (13.6)
≥Grade 3 TEAEs related to study drug, n (%)	0	0	0	0	0
Serious TEAEs, n (%)	1 (20.0)	1 (25.0)	1 (14.3)	2 (33.3)	5 (22.7)
Serious TEAEs related to study drug, n (%)	0	0	0	0	0
TEAEs leading to study withdrawal or death, n (%)	0	0	0	0	0

Most Common TEAEs	# Patients
Headache	7
Vomiting	6
Seizure	5
Irritability	4
Back pain	3
Fall	3
Pyrexia	3

- No new clinically significant weakness reported on physical exam
- No increase in seizures identified in 1 hour EEG recorded ~24 hours post-dose
- No clinically significant changes in laboratories assessed as related to study drug

PLASMA PK AND CSF EXPOSURE





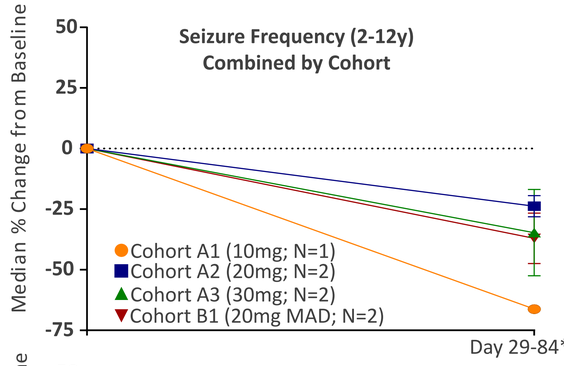
*Lower level of quantification

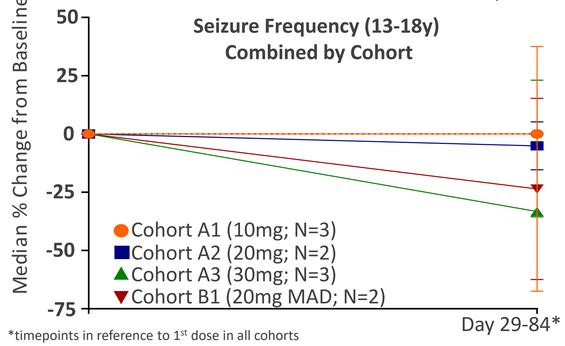
Dose (mg)	Plasma PK parameters	
	n	AUC_{last} (h*ng/mL) (mean ± SD)
SAD 10	4	2450 ± 1690
SAD 20	4	6460 ± 2820
SAD 30	7	15300 ± 12100
MAD 20 (dose 1)	6	4450 ± 3110

- Plasma AUC_{last} was similar for the 20mg SAD cohort and 1st dose in the 20mg MAD cohort
- STK-001 CSF levels detected to last collection, day 169 for 10 and 20mg, and day 85 for 30mg
- Overall, mean CSF concentration at day 85 increased from 10 to 30mg
- 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

SEIZURE FREQUENCY

Observed baseline convulsive seizure frequency/28 days	
Mean (SD)	51.41 (131.4)
Median (min, max)	16 (1.0, 630.0)
# concomitant anti-seizure medications as maintenance therapy	
90.9% patients used ≥3 concomitant anti-seizure medications; 72.7% used ≥4	Most common medications were clobazam (68.2%) and fenfluramine (54.5%)





*timepoints in reference to 1st dose in all cohorts

Cohort A1: excludes patient with incorrect dosing; Cohort A3: excludes patients meeting minimum seizure count during observation but not during defined baseline; Cohort B1: excludes patients who received only 2 doses prior to D84

OVERALL SUMMARY

- Patients in this study have severe disease
- Interim data show that single doses of STK-001 up to 30mg and multiple doses of 20mg were well-tolerated, and there were no safety concerns related to study drug
- Dose-dependent increases in plasma exposure and CSF concentration were observed
- Seizures were reduced in 12 of 17 (70.6%), including all 2-12y patients, at days 29-84 vs baseline period

REFERENCES: Dravet C, et al. *Epilepsia.* 2011;52:3-9; Harkin LA, et al. *Brain.* 2007;130:843-852; Kluckova D, et al. *Sci Rep*. 2020;10:10288; Escayg A, Goldin AL. *Epilepsia*. 2010;51(9):1650-1658.

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MONARCH KEY STUDY CRITERIA

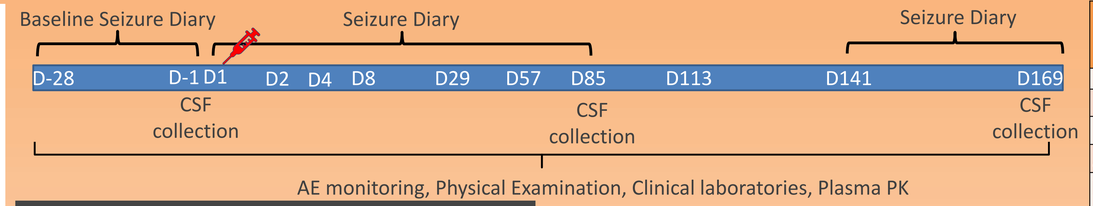
Inclusion Criteria

- Clinical diagnosis of DS with:
  - Onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic), which are often prolonged and triggered by hyperthermia
  - No history of causal MRI lesion
  - No other known etiology
  - Normal development at seizure onset
- Documented pathogenic, likely pathogenic variant, or variant of uncertain significance in *SCN1A*
- ≥2 prior treatments for epilepsy that lacked adequate seizure control or had to be discontinued due to adverse events
- ≥1 anti-epileptic drug (and any other interventions for epilepsy) at stable dose for ≥4 weeks

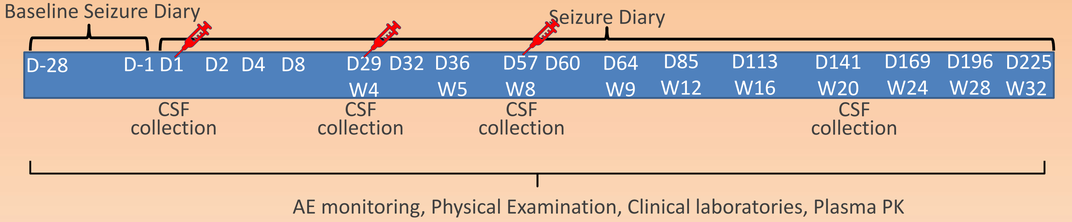
Exclusion Criteria

- Known pathogenic mutation in another gene that causes epilepsy
- Currently being treated with an anti-epileptic drug acting primarily as a sodium channel blocker, as maintenance treatment
- Clinically significant unstable medical condition(s) other than epilepsy
- Clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or dosing on day 1, other than epilepsy
- Any other significant disease or disorder, in the investigator's opinion, that may put patient at risk, influence study results, or affect patient's ability to participate

MONARCH SAD STUDY ASSESSMENTS



MONARCH MAD STUDY ASSESSMENTS

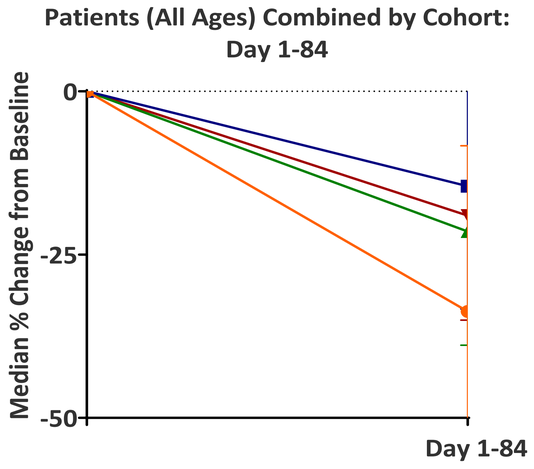


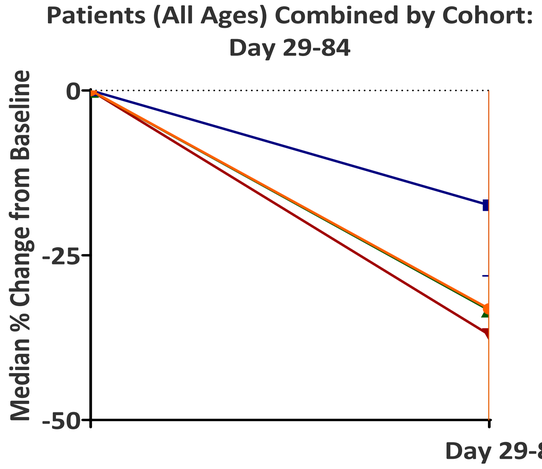
= Study Drug Administration

DEMOGRAPHICS

	SAD			MAD	Total n=22
	A1 (10mg)	A2 (20mg)	A3 (30mg)	B1 (20mg)	
Gender					
Female, n (%)	3 (60)	1 (25)	4 (57.1)	3 (50)	11 (50.0)
Race, n (%)					
Asian	1 (20)	0	0	0	1 (4.5)
Black or African American	0	1 (25)	1 (14.3)	0	2 (9.1)
White	4 (80)	3 (75)	6 (85.7)	6 (100)	19 (86.4)
Prefer not to answer	0	1 (25)	0	0	1 (4.5)
Ethnicity, n (%)					
Hispanic/Latino	2 (40)	1 (25)	0	1 (16.7)	4 (18.2)
Not Hispanic/Latino	3 (60)	3 (75)	7 (100)	5 (83.3)	18 (81.8)

SEIZURE FREQUENCY (timepoints in reference to first dose in all cohorts)





- Cohort A1 (10mg; N=4, Excludes patient with incorrect dosing)
- Cohort A2 (20mg; N=4)
- Cohort A3 (30mg; N=5, Excludes patients meeting minimum seizures during observation but not during defined baseline)
- Cohort B1 (20mg; N=4, Excludes patients who received only 2 doses prior to D84)

ACKNOWLEDGEMENTS

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