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MONARCH and ADMIRAL Interim Analyses: Phase 1/2a Studies Investigating Safety and Drug Exposure of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

Linda Laux[1], J Helen Cross[2], Joseph Sullivan[3], Archana Desurkar[4], Andreas Brunklaus[5], Colin Roberts[6], John M Schreiber[7], Scott Perry[8], Orrin Devinsky[9], Matt Lallas[10], Steven Phillips[11], Javier Avendaño[12], Charlene Brathwaite[12], Carrie Condon[12], Jessie Lynch[12], Meena[12], James Stutely[12], Nancy Wyant[12], Kimberly A Parkerson[12], Barry Ticho[12]

[1]Ann & Robert H Lurie Children's Hospital of Chicago; [2]Great Ormond Street Hospital for Children, London; [3]UCSF, [4]Sheffield Children's, Sheffield; [5]Royal Hospital for Children, Glasgow; [6]OHSU; [7]Children's National Hospital, [8]Cook Children's, [9]NYU Langone Health, [10]NeuroNetwork Partners, [11]Mary Bridge Children's; [12]Stoke Therapeutics

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% of 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

- The proprietary TANGO (Targeted Augmentation of Nuclear Gene Output) 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
- 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 (See Figure 1 in QR code)
  - *SCN1A* is transcribed into pre-messenger RNA (pre-mRNA) that is spliced to generate productive mRNA (which is translated into $Na_v1.1$ protein) and non-productive mRNA due to the inclusion of an exon that leads to nonsense-mediated mRNA decay (NMD)
  - TANGO ASOs bind to specific stretches of *SCN1A* pre-mRNA to prevent the inclusion of the non-productive exon thereby increasing productive mRNA level
  - Increased level of productive mRNA from the functional gene copy increases $Na_v1.1$ protein production restoring it 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

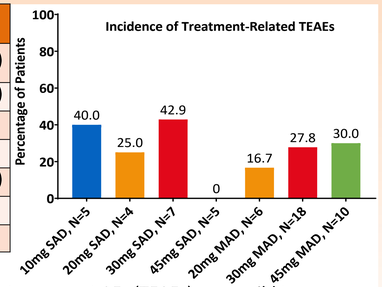
DEMOGRAPHICS

	10mg SAD	20mg SAD	30mg SAD	45mg SAD	20mg MAD	30mg MAD	45mg MAD	Total
N	5	4	7	5	6	18	10	55
Age at Screening, y								
Mean (SD)	11.2 (5.89)	10.8 (5.19)	9.1 (5.90)	11.0 (5.52)	13.7 (5.13)	9.2 (5.35)	10.9 (3.63)	10.5 (5.08)
Median (min, max)	13.0 (2, 18)	10.0 (6, 17)	10.0 (2, 16)	13.0 (4, 18)	16.0 (4, 17)	8.5 (2, 18)	13.0 (4, 15)	13.0 (2, 18)
Age Group, n (%)								
2 to 12 years	2 (40.0)	2 (50.0)	4 (57.1)	2 (40.0)	2 (33.3)	11 (61.1)	4 (40.0)	27 (49.1)
13 to <18 years	3 (60.0)	2 (50.0)	3 (42.9)	3 (60.0)	4 (66.7)	7 (38.9)	6 (60.0)	28 (50.9)
Sex								
Female, n (%)	3 (60.0)	1 (25.0)	4 (57.1)	3 (60.0)	3 (50.0)	10 (55.5)	4 (40.0)	28 (50.9)
Race, n (%)(*)								
Asian	1 (20.0)	0	0	3 (60.0)	0	0	0	4 (7.2)
Black or African American	0	1 (25.0)	2 (28.6)	0	0	1 (5.6)	0	4 (7.2)
White	4 (80.0)	3 (75.0)	6 (85.7)	4 (80.0)	6 (100.0)	16 (88.9)	9 (90.0)	48 (87.2)
Ethnicity, n (%)								
Hispanic/Latino	2 (40.0)	1 (25.0)	0	0	1 (16.7)	3 (16.7)	1 (10.0)	8 (14.5)
Number of Concomitant Anti-Seizure Medications								
≥3	4 (80.0)	4 (100.0)	5 (71.4)	5 (100.0)	6 (100.0)	13 (72.2)	6 (60.0)	43 (78.1)
≥4	3 (60.0)	4 (100.0)	5 (71.4)	2 (40.0)	3 (50.0)	8 (44.4)	3 (30.0)	28 (50.9)

(*) No or multiple selections for race may be entered; Demographics data cutoff was 11Aug2022; All single ascending doses (SAD) and 20mg multiple ascending doses (MAD) cohorts are from MONARCH only; 30 and 45mg MAD cohorts combined MONARCH and ADMIRAL; All received ≥1 STK-001 dose

SAFETY

Patients n (%)	2-12y n=27	13-18y n=28	Total N=55
TEAEs	26 (96.3)	27 (96.4)	53 (96.4)
TEAEs related to study drug	4 (14.8)	11 (39.3)	15 (27.3)
≥Grade 3 TEAEs	5 (18.5)	4 (14.3)	9 (16.4)
≥Grade 3 TEAEs related to study drug	0	0	0
Serious TEAEs	5 (18.5)	7 (25.0)	12 (21.8)
Serious TEAEs related to study drug	0	0	0
TEAEs leading to death	0	1 (3.6)	1 (1.8)

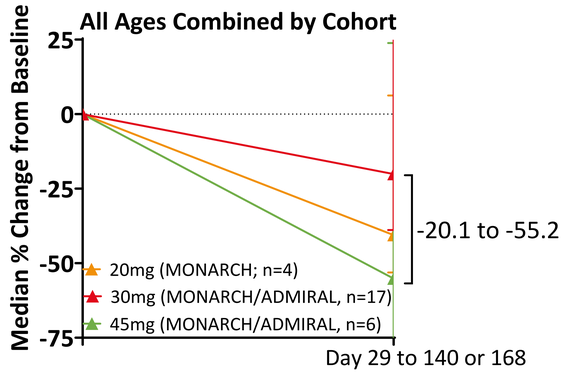


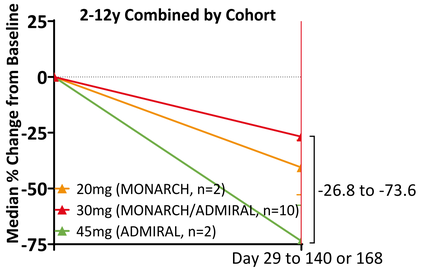
TEAEs in >10% by Preferred Term	n (%)
Vomiting	15 (27.3)
Headache	14 (25.5)
Seizure	13 (23.6)
Irritability	9 (16.4)
Pyrexia	9 (16.4)
Rhinorrhea	8 (14.5)
Contusion	7 (12.7)
COVID-19	6 (10.9)
Diarrhea	6 (10.9)
Nasopharyngitis	6 (10.9)
Post lumbar puncture syndrome	6 (10.9)
Upper respiratory tract infection	6 (10.9)

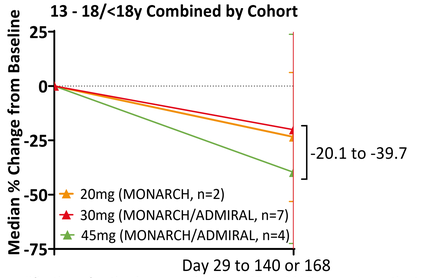
- Most treatment-emergent AEs (TEAEs) were mild to moderate; 1 fatal event (SUDEP) and 1 life-threatening event (near drowning), neither related to study drug
- All TEAEs related to study drug were non-serious and mild or moderate
- 33 (60.0%) patents experienced TEAEs related to CSF or study drug administration procedure
- No new significant neurological exam findings or lower extremity weakness emerged related to study drug
- 5 patients had TEAEs of CSF protein increase and 1 patient had TEAE of proteinuria assessed as related to study drug
- No other clinically significant laboratory changes related to study drug were reported as AEs

Safety data cutoff was 11Aug2022

CONVULSIVE SEIZURE FREQUENCY IN MAD

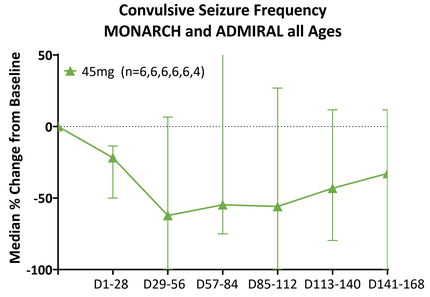


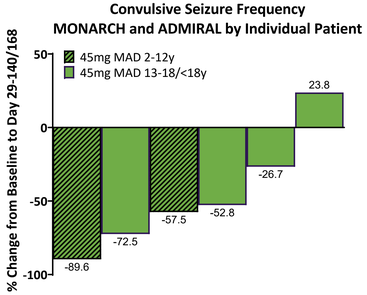




- Observed baseline convulsive seizure frequency / 28 days ranged from 10.0 to 53.9 across MAD cohorts (n=27)
- Median reductions from baseline in convulsive seizure frequency of 55.2% (45mg, n=6), 20.1% (30mg, n=17), 40.6% (20mg, n=4) were observed in patients treated with 3 doses of STK-001 as measured from Day 29 after their 1st dose to 3 months after receiving their last dose
- Similar seizure reduction was observed among patients taking or not taking concomitant fenfluramine

20mg MAD: excludes patients who received 3rd dose with delay; 30mg MAD: excludes patient with early modification of anti-seizure medications; 45mg MAD: excludes patients without sufficient seizure diary data to date; Seizure Frequency data cutoff was 11Aug2022





OVERALL SUMMARY

- 55 children and adolescents with DS received ≥1 dose of STK-001 up to 45mg/dose
- STK-001 was well-tolerated and overall potential benefit-risk remains favorable in single and multiple doses up to 45mg
- 74.1% (20/27) of patients treated with 3 doses of STK-001 (20mg, 30mg or 45mg) experienced a reduction from baseline in convulsive seizure frequency and 55.2% median reduction was observed in patients treated with 45mg
- The seizure reductions observed were more evident at the highest dose and in younger patients and occurred on top of a background of standard anti-seizure medications, including fenfluramine

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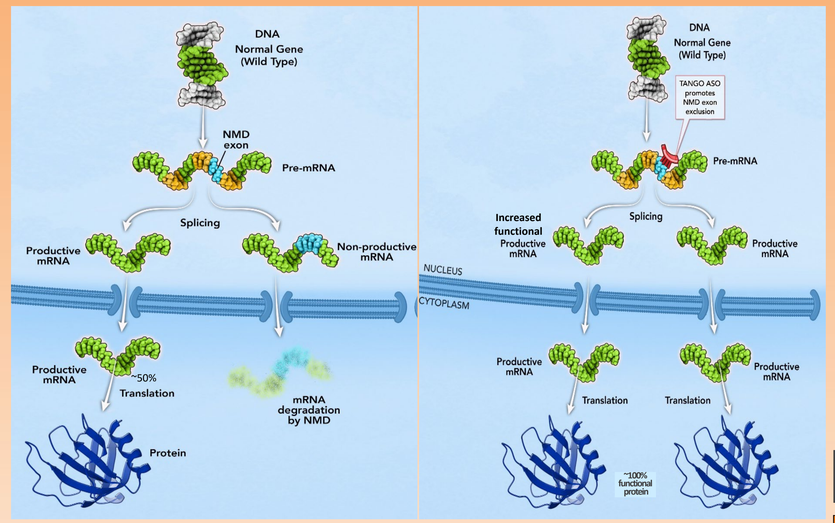
FIGURE 1. TANGO PLATFORM IN DS



KEY STUDY CRITERIA (Both Studies)

Inclusion Criteria

- Clinical diagnosis of DS with:
  - Onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic)
  - 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

STUDY OBJECTIVES (Both Studies)

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]

MONARCH STUDY DESIGN

Open-label, Single and Multiple Ascending Doses (SAD and MAD) of STK-001 in 2 to 18y (NCT04442295)

Duration	7-9m / patient
# patients	<70
Sites	Approximately 20 in US
Cohorts	Each dose cohort enrolls 4 patients, with option to dose up to 6 additional patients per cohort for safety evaluation • SAD at 10, 20, 30, and 45mg • MAD at 20, 30, and 45mg on Days 1, 29, and 57

- Dose escalation based on safety and tolerability assessed by Safety Committee (with external reviewers)
- Dosing begins in 13 to 18y age group

ADMIRAL STUDY DESIGN

Open-Label, MAD of STK-001 in 2 to <18y (EudraCT Number 2020-006016-24)

Duration	10-12m / patient
# patients	≤60
Sites	Approximately 5-7 in UK
Cohorts	Each dose cohort enrolls 4 patients, with option to dose up to 6 additional patients per cohort for safety evaluation • MAD at 30, 45 and 70mg on Days 1, 57, and 85

MONARCH: PATIENT DISPOSITION FOR PLASMA PK AND CSF EXPOSURE

Data Cut: Plasma (26Apr2022) CSF (16Aug2022)

	Bioanalysis		Plasma PK (N)
Dose (SAD)	**Plasma (N)**	**CSF (N)**	
10mg	5*	5*	20*
20mg	4	4	
30mg	7	7	
45mg	4	5	
Dose (MAD)	**Plasma (N)**	**CSF (N)**	
20mg	6**	6**	22
30mg	14	14	
45mg	2	6	

*PK analyses was not conducted for 1 patient (10mg); administered incorrect dose
**One patient deceased/did not complete EOS/D169

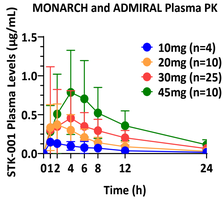
ADMIRAL: PATIENT DISPOSITION FOR PLASMA PK AND CSF EXPOSURE

Data Cut: Plasma (29Mar2022) CSF (06Aug2022)

	Bioanalysis*		Plasma PK Analyses (N)
Dose	**Plasma (N)**	**CSF (N)**	
30mg	4	4	8
45mg	4	4	

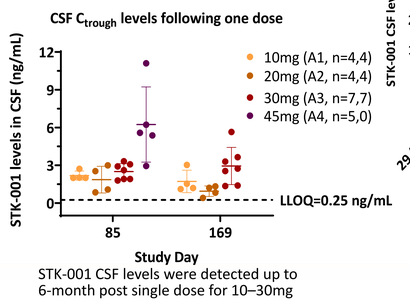
* The number of patient samples at each time point varied

PLASMA PK

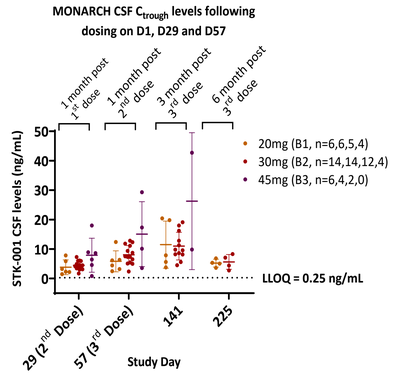


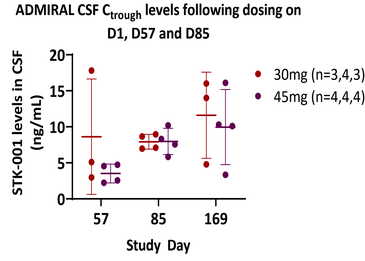
A dose dependent increase in C_{max} and AUC_{last} was observed with dose increase

CSF EXPOSURE



STK-001 CSF levels were detected up to 6-month post single dose for 10–30mg





Following repeat dosing, CSF STK-001 accumulation was observed. C_{trough} levels are related to brain levels, therefore brain accumulation is expected at this dosing regimen.

ACKNOWLEDGEMENTS

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MORE INFORMATION

To find out more: MONARCHstudy.com or Admiralstudy.com. By contacting us, your patient is under no obligation to take part in the study.

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MONARCH SAD, MAD and ADMIRAL STUDY ASSESSMENTS