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SWALLOWTAIL: An Open-Label Extension (OLE) Study for Children and Adolescents with Dravet Syndrome (DS) who Previously Participated in a Study of Antisense Oligonucleotide (ASO) STK-001

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

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swallowtail
A DRAVET SYNDROME EXTENSION STUDY

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 sudden unexplained death
- 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

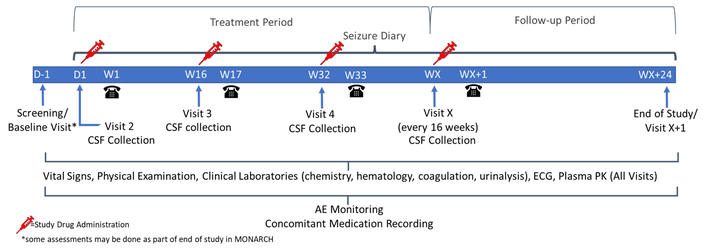
STK-001

- 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

STUDY DESIGN AND ASSESSMENTS

- OLE study conducted at 18 sites in the US (NCT04740476) following participation in Single (SAD) or Multiple Ascending Dose (MAD) study, MONARCH (NCT04442295; **See poster 1.227)**
- Each patient initially receives 3 intrathecal (IT) doses of STK-001, once every 4 months (m) with study duration approximately 15m; patients may continue treatment beyond 3 doses, every 4m until end of study
- Patients receive the same dose level they received in MONARCH, or the dose recommended by the Safety Monitoring Committee; highest dose may not exceed 30mg/dose

Outcome Measures Included in this Analysis	
Safety and tolerability	Treatment emergent AEs (TEAEs)
Pharmacokinetics (PK)	STK-001 plasma concentrations
Cerebrospinal Fluid (CSF)	STK-001 CSF concentrations



DEMOGRAPHICS, DISPOSITION AND EXPOSURE

Demographics (N=24)	
Age at Screening, y	
Mean (SD)	11.7 (4.93)
Median (min, max)	13.0 (2, 18)
Age Group, N (%)	
2–12y	9 (37.5)
13–18y	15 (62.5)
Sex	
Female, n (%)	13 (54.2)
Race, N (%)*	
Asian	2 (8.3)
Black or African American	3 (12.5)
White	19 (79.2)
Prefer not to answer	2 (8.3)
Ethnicity, N (%)	
Not Hispanic/Latino	20 (83.3)

Data cutoff: 11Jul2022

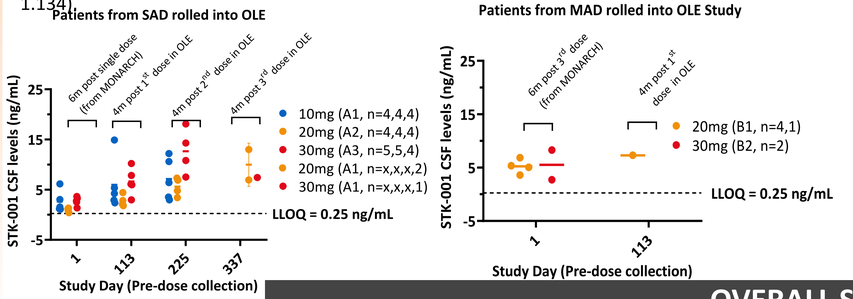
Total STK-001 doses administered (N=24)	
10mg	10
20mg	14
30mg	32
45mg	8

Patient Disposition		
Assigned Cohort (MONARCH)	Enrolled (% total patients who completed MONARCH)	Ongoing
10mg SAD*	5 (100.0)	3
20mg SAD	4 (100.0)	3
30mg SAD	7 (100.0)	7
45mg SAD	2 (100.0)	2
20mg MAD	4 (80.00)	4
30mg MAD	2 (100.0)	2

*1 patient in 10mg SAD cohort received an incorrect STK-001 dose in MONARCH but received 3 correct doses in SWALLOWTAIL

PLASMA PK AND CSF EXPOSURE

- Pre-dose STK-001 plasma levels (not shown) were near lower limit of quantification (LLOQ) indicating no accumulation at this regimen
- Mean STK-001 CSF levels at 6m post single dose (SAD end of study) were lower than those at 6m-post 3m doses (MAD end of study)
- Dose-dependent increase in CSF C_{trough} levels was observed from 20mg – 30mg across all cohorts
- After every 4m dosing, slight STK-001 accumulation in CSF was observed for 10 – 30mg for 3 doses though not significant to C_{max}. STK-001 CSF C_{trough} levels can predict brain concentration (See poster 1.134).



SAFETY

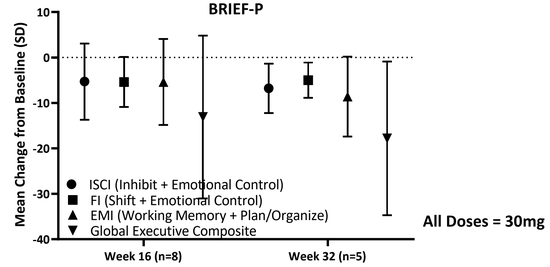
Number (N (%)) of Patients with	2-12y N=9	13-18y N=15	Total N=24
TEAEs	8 (88.9)	11 (73.3)	19 (79.2)
TEAE related to study drug (all mild or moderate)	1 (11.1)	3 (20.0)	4 (16.7)
TEAE related to CSF or study drug administration (all mild)	1 (11.1)	7 (46.7)	8 (33.3)
≥Grade 3 TEAE	1 (11.1)	0	1 (4.2)
≥Grade 3 TEAE related to study drug	0	0	0
Serious TEAE	2 (22.20)*	0	2 (8.30)
Serious TEAE related to study drug	0	0	0

*2 patients experienced 6 serious TEAEs: COVID-19 (2), status epilepticus (3), and respiratory failure; all resolved

TEAEs Reported in >1 Patient	
Preferred Term	N (%)
COVID-19	9 (37.5)
Nasal congestion	5 (20.8)
Post lumbar puncture syndrome	5 (20.8)
Pyrexia	4 (16.7)
Diarrhea	3 (12.5)
Puncture site pain	3 (12.5)
Headache	2 (8.30)
Status epilepticus	2 (8.30)
Viral infection	2 (8.30)
Vomiting	2 (8.30)

Treatment-Related TEAEs	
Preferred Term	N (%)
CSF protein increased	1 (4.2)
Irritability	1 (4.2)
Pain in extremity	1 (4.2)
Somnolence	1 (4.2)

BRIEF-P



Similar changes were not observed in BRIEF-P assessment in the BUTTERFLY Natural History Study (See poster #1.228)

OVERALL SUMMARY

- 24 of 25 (96%) patients who completed MONARCH enrolled in SWALLOWTAIL
- Patients received up to 5 doses of STK-001 ranging from 10mg – 45mg/dose in SWALLOWTAIL
- Multiple doses of STK-001 up to 45mg/dose given every 4m IT appear to be well tolerated
- Following every 4m dosing at 10 – 30mg for 3 doses, low CSF C_{trough} levels do not add significantly to C_{max} (predicted maximum STK-001 concentration in CSF). CSF C_{trough} levels indicate potential for every 4-6m dosing.
- A trend toward improvement in non-seizure measures of disease has been observed among a small group of evaluable patients in SWALLOWTAIL. Results support long-term use of STK-001 in patients with DS.

ACKNOWLEDGEMENTS

This study is supported by Stoke Therapeutics. We thank investigators, health care providers, research staff, patients, and caregivers who participated.

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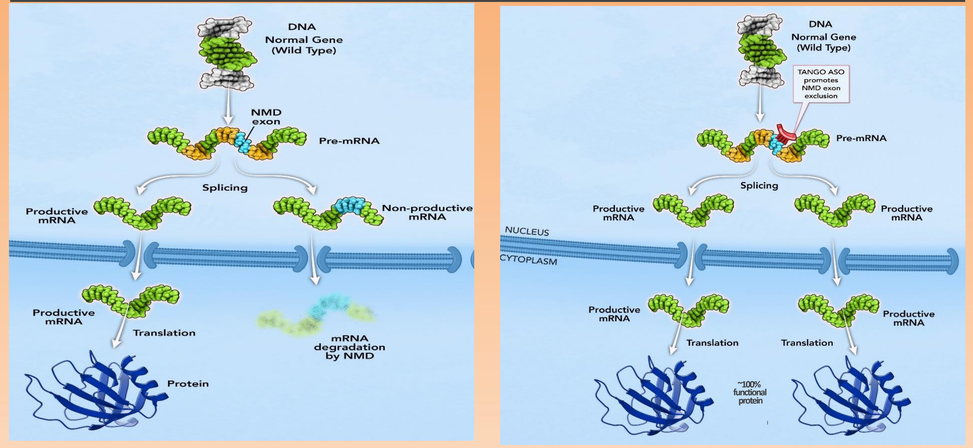
swallowtail
A DRAVET SYNDROME EXTENSION STUDY

FIGURE 1. TANGO PLATFORM IN DS



STUDY POPULATION

Key Inclusion Criteria

- ≥2.5 years of age
- Must have completed dosing with STK-001 and the MONARCH end of study visit, with an acceptable safety profile per investigator judgment
- Must have completed MONARCH within 4 weeks of starting participation in this study, unless approved by Sponsor

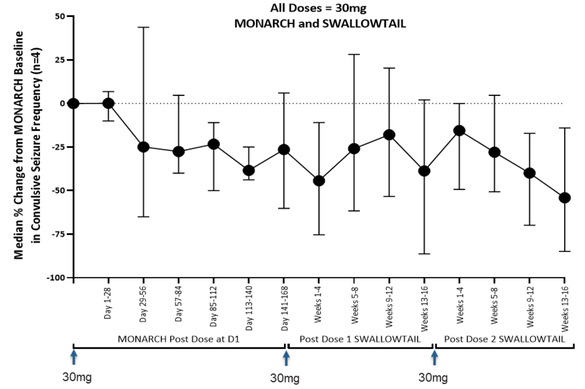
Key Exclusion Criteria

- Met any withdrawal criteria in MONARCH
- 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 4 weeks prior to screening or dosing on day 1, other than epilepsy
- Clinically significant abnormal laboratory values at baseline
- Any other significant disease or disorder, in investigator's opinion, that may put patient at risk, influence study results, or affect patient's ability to participate
- Been treated (or is being treated) with an investigational product (other than STK-001) since participating in MONARCH

STK-001 DOSES ADMINISTERED

Patient Exposure (N=24)						
Assigned Dose Cohort (MONARCH)	Administered Dose Level (SWALLOWTAIL)	1st Dose	2nd Dose	3rd Dose	4th Dose	5th Dose
10mg SAD*	10mg	5	5			
	20mg			4	1	
	30mg			1	2	1
	45mg					1
20mg SAD	20mg	4	4			
	30mg			4	1	
	45mg				1	
30mg SAD	30mg	7	5	4		
	45mg			1		
45mg SAD	45mg	2				
20mg MAD	20mg	1				
	30mg	3	2			
	45mg		2	1		
30mg MAD	30mg	2				

CONVULSIVE SEIZURE FREQUENCY



No exclusions for AED modification

REFERENCES

Dravet C, et al. *Epilepsia.* 2011;52(suppl 2):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; Wengert E, et al. *AES* 2020.

MORE INFORMATION

To find out more about Stoke Therapeutics, please visit www.stoketherapeutics.com.
By contacting us, your patient is under no obligation to take part in the study.