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

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

[1]Cook Children's, [2]University of California San Francisco, [3]Children's National Hospital; [4]New York University Langone; [5]Children's Hospital Colorado; [6]Nicklaus Children's Hospital; [7]Children's Hospital of Chicago; [8]Oregon Health Sciences University; [9]Stoke Therapeutics

swallowtail
A DRAVET SYNDROME EXTENSION STUDY

BACKGROUND

- 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 unexpected 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

MECHANISM OF ACTION

- 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
  - *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

ACKNOWLEDGEMENTS

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STUDY DESIGN

- OLE study conducted at 18 sites in the US (NCT04740476) following participation in Single (SAD) or Multiple Ascending Dose (MAD) study, MONARCH (NCT04442295)
- Patients receive intrathecal (IT) doses of STK-001, once every 4 months and patients currently receive 30 mg per dose

PATIENT DEMOGRAPHICS

Demographics (N=44)	
Age at Screening, y	
Mean (SD)	11.2 (5.03)
Median (min, max)	13.0 (2, 19)
Age Group, N (%)	
2–12y	21 (47.7)
13y and older	23 (52.3)
Sex	
Female, n (%)	23 (52.3)
Male, n (%)	21 (47.7)
Race, N (%)*	
Asian	4 (9.09)
Black or African American	4 (9.09)
White	37 (84.1)
Prefer not to answer	3 (6.82)
Ethnicity, N (%)	
Not Hispanic/Latino	36 (81.8)

*Able to choose >1 option

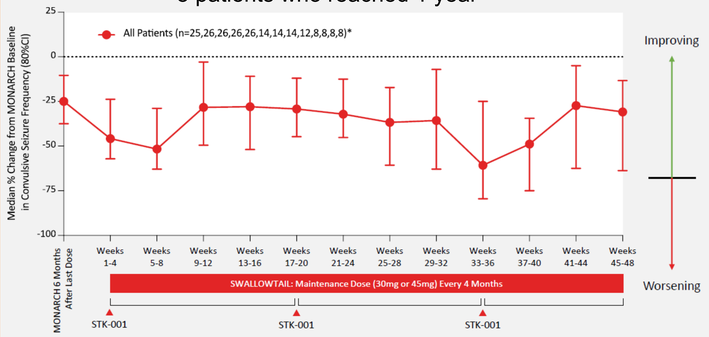
PATIENT EXPOSURE

Total STK-001 doses administered (N=44)	
10 mg	10
20 mg	14
30 mg	82
45 mg	36

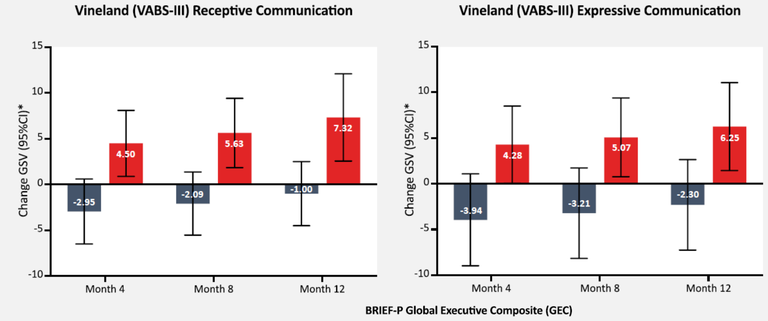
Data cutoff in SWALLOWTAIL: 24Mar2023

CLINICAL ASSESSMENTS*

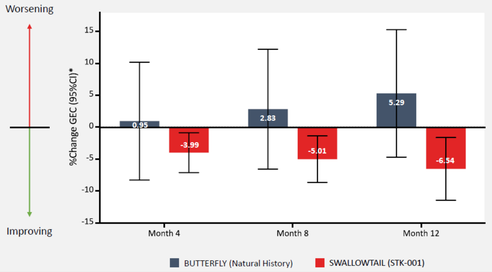
Durable reductions in convulsive seizure frequency were evident throughout the course of treatment, including among 8 patients who reached 1 year



Substantial improvements were evident in measures of cognition and behavior as assessed by the VABS-III and BRIEF-P



- Analysis of VABS-III data also indicated an improvement in Gross Motor function with mean change in GSV of +12.2 [3.09, 21.4] at Month 12 (not shown)
- Both Clinicians and Caregivers rated patient's overall condition improved on the Global Impression of Change (CGIC and CaGIC) scales with mean scores of 2.5 [1.92, 3.08] and 1.53 [0.893, 2.17] (not shown)



*Clinical assessment analyses included patients who completed treatment in MONARCH and received only doses of 30 mg or 45 mg in SWALLOWTAIL. Vineland Adaptive Behavior Scales-III (VABS-III) and Behavior Rating Inventory of Executive Function Preschool (BRIEF-P) data analyzed in mixed model repeated measures with AR(1) covariance structure. Baseline covariates in BUTTERFLY matched to SWALLOWTAIL. BUTTERFLY sample size: n=36 at screening and n=27 for VABS-III and n=30 for BRIEF-P at Month 12; SWALLOWTAIL sample size: n=24 for VABS-III and n=25 for BRIEF-P at screening; n=9 at Week 48 and n=5 at Week 64.
- GSV=Growth Scale Value; Brackets indicate 95% CI; Rating on CGIC and CaGIC ranges from 1=very much improved to 7=very much worse. A rating of 4=No change

PATIENT DISPOSITION

Assigned Cohort (MONARCH)	Enrolled (% total patients who completed MONARCH)	Ongoing
10 mg SAD*	5 (100)	3
20 mg SAD	4 (100)	3
30 mg SAD	7 (100)	6
45 mg SAD	5 (100)	5
20 mg MAD	4 (80.0)	3
30 mg MAD	14 (100)	13
45 mg MAD	5 (83.3)	5

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

SAFETY

Number (N (%)) of Patients with	2-12y N=21	13-18y N=23	Total N=44
TEAEs	16 (76.2)	22 (95.7)	38 (86.4)
TEAEs related to study drug (all mild or moderate)*	6 (28.6)	11 (47.8)	17 (38.6)
TEAEs related to CSF or study drug administration	6 (28.6)	13 (56.5)	19 (43.2)
≥Grade 3 TEAEs	1 (4.76)	0	1 (2.27)
≥Grade 3 TEAEs related to study drug	0	0	0
Serious TEAEs	3 (14.3)	2 (8.70)	5 (11.4)
Serious TEAE related to study drug	0	0	0

*Only Treatment-Related TEAE in >1 patient was CSF protein increased: 14/44 (31.8%) patients

TEAEs Reported in >10% Patients	
Preferred Term	**N (%)**
CSF protein increased	14 (31.8)
COVID-19	13 (29.5)
Post lumbar puncture syndrome	7 (15.9)
Pyrexia	7 (15.9)
Seizure	7 (15.9)
Upper respiratory tract infection	6 (13.6)
Headache	5 (11.4)
Nasal congestion	5 (11.4)
Puncture site pain	5 (11.4)

OVERALL SUMMARY

- 44 of 46 (95.7%) patients who completed MONARCH enrolled in SWALLOWTAIL, and 38 of 44 (86.4%) were ongoing in the study
- Patients received up to 7 doses of STK-001 ranging from 10 mg-45 mg/dose in SWALLOWTAIL
- Multiple doses of STK-001 up to 45 mg/dose given every 4 months IT were generally well tolerated
- Data indicated durable reductions in convulsive seizure frequency and substantial improvements in cognition and behavior over 12m