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# SWALLOWTAIL: An Open-Label Extension (OLE) Study for Patients with Dravet Syndrome (DS) who Previously Participated in Studies of STK-001

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swallowtail
A DRAVET SYNDROME EXTENSION STUDY

## INTRODUCTION

- Dravet syndrome (DS) is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year of life
- Available therapies do not adequately control seizures in 90% of DS patients, and they do not address other comorbidities of the disease, including intellectual disability, ataxia/motor abnormalities, behavioral problems, speech impairment, sleep disturbances, and a high risk for sudden unexpected death
- Complications of the disease 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, prevent seizures, and reduce non-seizure related comorbidities in DS

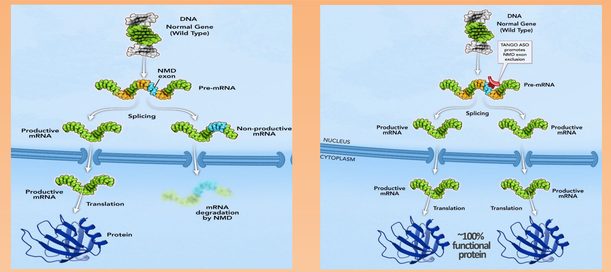
## STK-001

- STK-001 is an investigational proprietary antisense oligonucleotide (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 (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
- 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 (**Figure 1**)
- STK-001 may be the first disease-modifying therapy to address the genetic cause of DS by upregulating $Na_V1.1$ protein levels

## 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.

## FIGURE 1. TANGO PLATFORM IN DS




## 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)
- Each patient (up to 70) receives 3 intrathecal (IT) doses of STK-001, once every 4 months; Total duration 15 months /patient
- Patients receive the same dose level they received in MONARCH, or the dose recommended by the SMC; highest dose may not exceed the highest dose allowed in MONARCH (currently 30mg)
- Purpose: Gather additional information on long-term safety and tolerability of repeat doses of STK-001
- Study Design (**Figure 2**):
  - Screening/Baseline Assessments Evaluate: safety, neurodevelopment, adaptive behavior, gait, executive function, electroencephalogram (EEG), seizure frequency
  - Patients are admitted to hospital on day of dosing of intrathecal STK-001 and discharged after completing post-dose assessments
  - Week 16 and Week 32 Assessments: Same as baseline

## STUDY POPULATION

**Key Inclusion Criteria**

- ≥2.5 years of age
- Must have completed dosing with STK-001 and the MONARCH end of study (EOS) 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

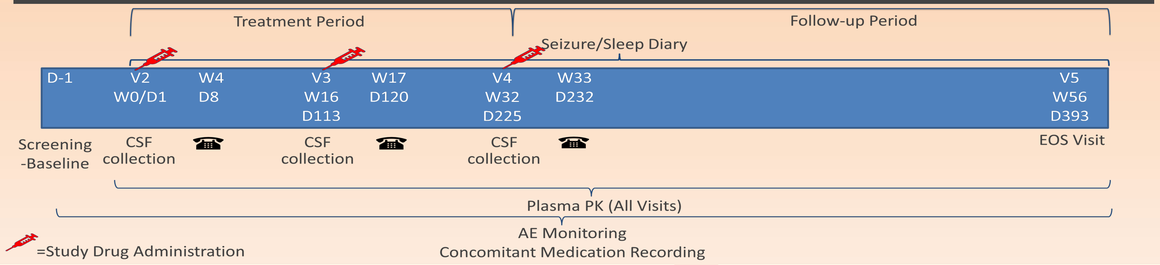
**Key Exclusion Criteria**

- 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

## STUDY ASSESSMENTS

| | |
|---|---|
| **Primary Outcome Measures** | |
| Safety and tolerability | Adverse events (AEs) and treatment emergent AEs (TEAEs) |
| | Vital signs and physical examination |
| | Electrocardiogram (ECG) |
| | Laboratories |
| | Immunogenicity parameters |
| **Secondary Outcome Measures** | |
| Pharmacokinetics (PK) | STK-001 plasma concentrations |
| CSF | STK-001 CSF concentrations |
| Seizure frequency | % change in convulsive seizures (via paper diary) |
| Clinical status | Caregiver and Clinical Global Impression of Change |
| Quality of life | EQ-5D-Y: assesses mobility, looking after self, doing usual activities, pain, and feelings |
| **Exploratory Outcome Measures** | |
| Neurodevelopmental (BSID-III/WPPSI-IV), Adaptive Behavior (VABS-III), Executive Function (BRIEF-P), Gait (Gillette FAQ), total seizure frequency, EEG parameters | |

## FIGURE 2. STUDY DESIGN




## DEMOGRAPHICS, DOSES ADMINISTERED, AND TEAEs (AS OF 8Oct21)

| Demographics (N=13) | |
|---|---|
| Age at screening, years | |
| Mean (SD) | 12 (4.862) |
| Median (min, max) | 13 (2,18) |
| Gender, n (%) | |
| Female | 7 (54) |
| Race, n (%), may select more than 1 option | |
| Asian | 1 (7.7) |
| Black or African American | 2 (15.0) |
| White | 11 (85.0) |
| Prefer not to answer | 1 (7.7) |
| Ethnicity, n (%) | |
| Hispanic/Latinx | 3 (23) |
| Not Hispanic/Latinx | 10 (77) |

| MONARCH enrolled patients (N=13) | |
|---|---|
| SAD 10mg | 5 (38.5) |
| SAD 20mg | 4 (30.8) |
| SAD 30mg* | 4 (30.8) |

*1 patient enrolled; not dosed as of 8OCT21

| Total STK-001 doses administered (n=12)** | |
|---|---|
| 10mg | 11 |
| 20mg | 6 |
| 30mg | 3 |

**4 patients received 2 doses and 1 patient received 3 doses of 10mg; 2 patients received 2 doses of 20mg

| TEAEs (n=12) | n (%) |
|---|---|
| Patients with ≥1 TEAE | 6 (37.5) |
| Total TEAEs | 16 |
| Related to study drug | 0 (0) |
| Serious TEAEs | 0 (0) |
| ≥Grade 3 (Severe) | 0 (0) |
| Grade 2 (Moderate) | 1 (6.3) |
| Grade 1 (Mild) | 15 (93.8) |
| Leading to study withdrawal | 0 (0) |

| Most common TEAEs | n (%) |
|---|---|
| Headache | 3 (18.8) |
| COVID-19 | 2 (12.5) |
| All other TEAEs*** | 1 each (6.3) |

***astigmatism, back pain, eyelid myoclonus, gastroesophageal reflux disease, hypermetropia, influenza-like illness, post-procedural contusion, procedural headache, rash, seizure, urinary incontinence

## SUMMARY

- **Multiple doses, up to 30mg, of STK-001 were well tolerated with no safety concerns**
- **Dosing IT every 4 months appears to be well tolerated**
- **No patients discontinued treatment**
- **SWALLOWTAIL will provide valuable information on safety of long-term use of STK-001 along with preliminary effects on seizures and cognition**

## ACKNOWLEDGMENTS

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## 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.