Safety and Pharmacokinetics of Antisense Oligonucleotide STK-001 in Children and Adolescents with Dravet Syndrome: Design of the Open-Label Phase 1/2a MONARCH Study

Javier Avendaño[1], Linda Laux[2], Charlene Brathwaite[1], James Stutely[1], Nancy Wyant[1], Kimberly A. Parkerson[1], Barry Ticho[1]

[1]Stoke Therapeutics, Bedford, MA, [2]Anne & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

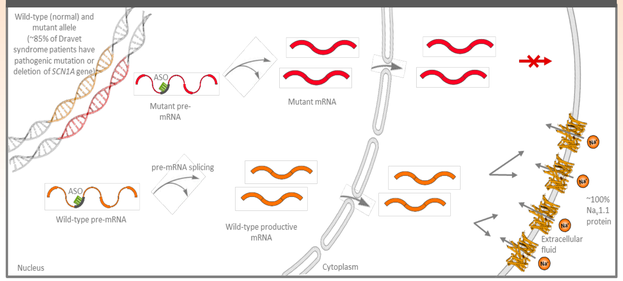
INTRODUCTION

- Dravet syndrome (DS) is a severe and progressive genetic developmental encephalopathy characterized by frequent, prolonged, and refractory seizures, beginning in the first year of life
- Available therapies do not adequately control seizures in 90% of DS patients, and they do not address other aspects of the disease, including cognitive regression or developmental stagnation, ataxia, speech impairment, sleep disturbances, and an increased risk of sudden unexpected death in epilepsy
- 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 ($Na_V1.1$)
- Upregulating the insufficient $Na_V1.1$ may restore functioning neurons and 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 $Na_V1.1$ levels
- The proprietary TANGO platform aims to increase protein production from the healthy copy of a gene (**Figure 1**)
  - In DS, patients have one functional gene copy (orange) and one mutated copy (red), 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
  - Synthesized ASOs (green) bind to specific stretches of pre-mRNA, reducing the synthesis of non-productive mRNA and increasing the synthesis of productive mRNA
  - The increased levels of productive mRNA from the functional gene copy increase protein production, thereby restoring the target protein to near normal levels
- STK-001 may be a first-in-class, disease-modifying (or precision medicine) for DS

Figure 1. Transformative potential of TANGO technology in DS



Source: Escayg and Goldin, *Epilepsia* 2010; Stoke data based on preclinical studies to date

STUDY DESIGN

- Phase 1/2a open-label, 2-part study conducted at approximately 20 sites in the United States (NCT04442295)

Item	Proposed Amendment v3.0
Cohorts	Single and Multiple Ascending Doses
Study duration	7-9 months / patient
Number of patients	<70

- Each dose cohort enrolls up to 4 patients, with an option to dose up to 6 additional patients per cohort for safety evaluation:
  - Single ascending dose (SAD) at doses of 10, 20, and 30 mg
  - Multiple ascending doses (MAD) up to 30 mg
- Dosing above 30 mg in this study remains on FDA partial clinical hold
- Dose escalation is based on safety and tolerability assessment by the Safety Monitoring Committee (including external reviewers)
- In each cohort dosing begins in 13- to 18-year-olds, with an internal safety team approving dosing in younger patients (2-12 years)
- Study visits include the following (**Figure 2**):
  - Screening visit
  - 4-week observation period:
    - No change to current anticonvulsant therapy, ketogenic diet, or vagal nerve stimulator settings
    - Caregivers track child's seizure frequency during this period
  - Baseline visit:
    - Blood and urine analyses
    - Quality of life, neurological, and general pediatric assessments
  - Inpatient treatment period: patients are admitted on the day of dosing and discharged after completing postdose assessments
    - All patients will receive intrathecal administration of STK-001
  - 6-month follow-up period
- Patients who complete the study will have the option to receive STK-001 in an open-label extension study if they meet enrollment criteria

Get more information

To find out more about the MONARCH study, please visit the following website:

MONARCHstudy.com

By contacting us, your patient is under no obligation to take part in the study

Study Population

Inclusion Criteria

- Aged 2-18 years
- DS 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) at a stable dose for ≥4 weeks

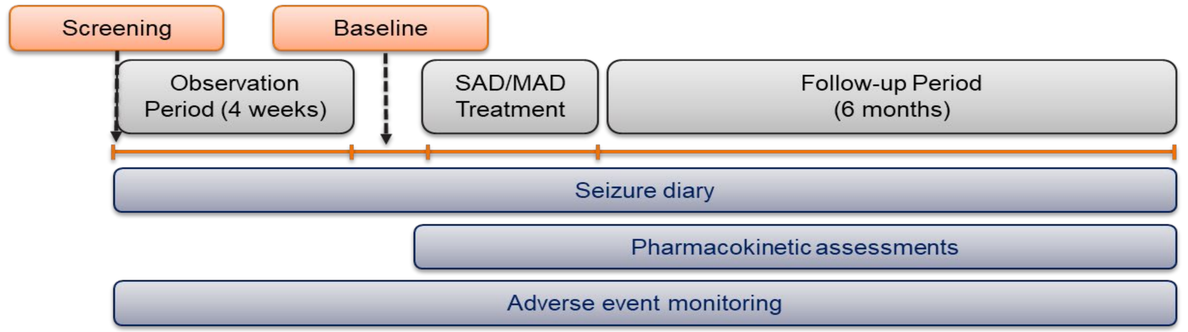
Exclusion Criteria

- 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 the patient at risk, influence the study results, or affect the patient's ability to participate in the study

Study Assessments

Primary Outcome Measures	
Safety assessments	• Adverse events
Pharmacokinetics	• Plasma concentrations of STK-001
Cerebral spinal fluid (CSF)	• STK-001 levels
Secondary Outcome Measures	
Seizure frequency	• Measured by paper diary
Clinical status (caregiver)	• Caregiver Global Impression of Change (CaGIC): 7-level scale from very much improved to very much worse
Clinical Status (clinician)	• Clinical Global Impression of Change (CGIC) : 7-level scale from very much improved to very much worse
Quality of life	• EQ-5D-Y (patients ≥8 years will complete themselves [Self Complete version] if able): scale 0-100

Figure 2. Study design



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.

ACKNOWLEDGMENTS

Stoke Therapeutics thanks the investigators, health care providers, research staff, patients, and caregivers who participate in this trial. Medical writing support was provided by Michelle McDermott, PharmD, supported by Stoke Therapeutics.