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ADMIRAL: A UK Study of the Safety and Pharmacokinetics of Antisense Oligonucleotide STK-001 in Children and Adolescents with Dravet Syndrome (DS)

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A DRAVET SYNDROME STUDY

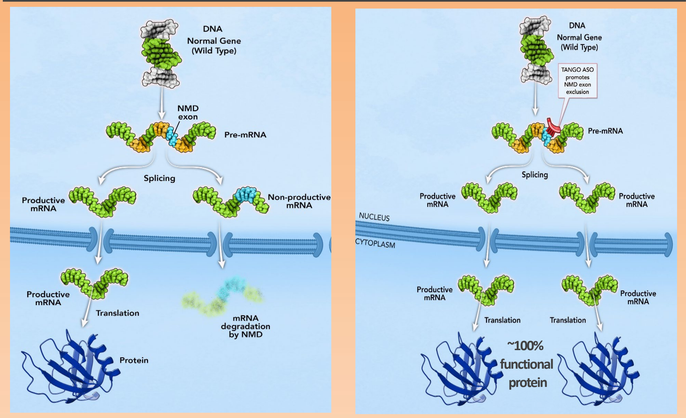
INTRODUCTION

- 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 and thereby 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 copy of a gene (**Figure 1**)
  - 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). **Figure 1** shows the mechanism of action of STK-001 on functional pre-mRNA
  - 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
- STK-001 has the potential to be the first disease-modifying therapy to address the genetic cause of DS by upregulating $Na_v1.1$ protein levels

FIGURE 1. TANGO PLATFORM IN DS



STUDY DESIGN

Item	Proposed
Cohorts	Multiple Ascending Dose levels, up to 70mg
Study duration	40-48 weeks / patient
Number of patients	Up to 60

- Phase 1/2a open-label study will be conducted at approximately 5-7 sites in the UK (ClinicalTrialsRegister.eu, EudraCT Number 2020-006016-24)
- Each dose cohort are enrolling up to 4 patients, with an option to dose up to 6 additional patients per cohort for safety evaluation
- Dose escalation is based on safety assessment by the Safety Monitoring Committee (led by independent external reviewer)
- Dosing begins in each cohort in 13- to <18-year-olds, with the safety monitoring committee approving dosing in younger patients (≥2- to 12-years-old)
- Study includes (**Figure 2**):
  - Screening visit
  - 4-week observation period:
    - No change to current anti-epileptic therapy, ketogenic diet, or vagal nerve stimulator settings for at least 4 weeks prior
    - Caregivers track child's seizure frequency
  - Baseline visit:
    - Blood and urine analyses
    - Quality of life, neurological, and general pediatric assessments
  - Inpatient treatment period:
    - Patients are admitted to hospital on day of dosing and discharged after completing post-dose assessments
    - All patients receive intrathecal (IT) STK-001 administration
  - 6-month follow-up
- Patients who complete the study will have the option to receive STK-001 in an Open-Label Extension study if they meet enrollment criteria

STUDY POPULATION

Key Inclusion Criteria

- Aged 2 to <18 years at screening
- Clinical diagnosis of DS with:
  - 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 for epilepsy) at stable dose for ≥4 weeks

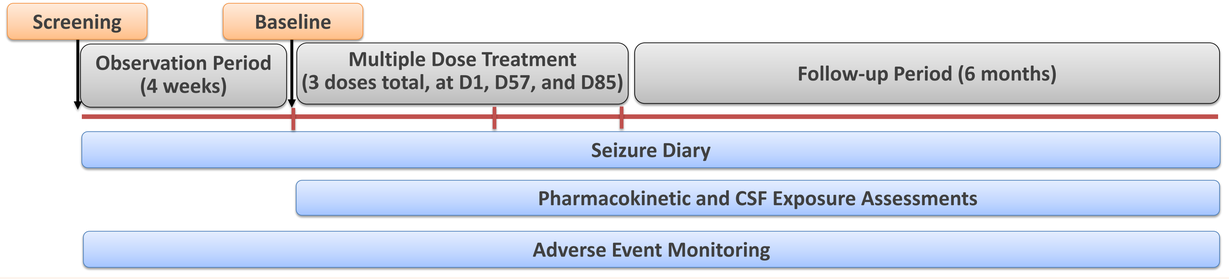
Key Exclusion Criteria

- 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 other than epilepsy in the 4 weeks prior to screening through prior to dosing on day 1
- 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 ASSESSMENTS

Primary Outcome Measures	
Safety	Adverse events
Pharmacokinetics	Plasma concentrations of STK-001
Cerebrospinal Fluid Exposure (CSF)	CSF concentrations of STK-001
Secondary Outcome Measures	
Seizure Frequency	Measured by paper diary
Clinical Status (Caregiver)	Caregiver Global Impression of Change (CaGI-C): 7-level scale from very much improved to very much worse
Clinical Status (clinician)	Clinical Global Impression of Change (CGI-C): 7-level scale from very much improved to very much worse
Quality of Life (Proxy or Self-Complete, if able)	EQ-5D-Y: assesses dimensions of mobility, looking after myself, doing usual activities, having pain or discomfort, and feeling worried, sad, or unhappy

FIGURE 2. STUDY FLOW DESIGN



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MORE INFORMATION

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