MONARCH and ADMIRAL Interim Analyses: Open-label, Phase 1/2a Studies in US and UK Investigating STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

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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
  - 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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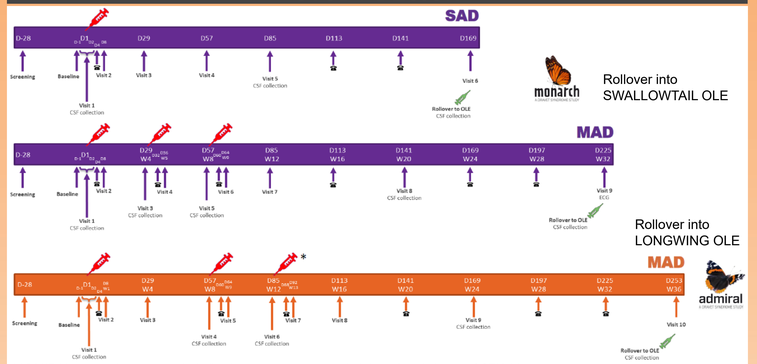
STUDY DESIGN



*ADMIRAL protocol was amended allowing investigators to administer 2 or 3 doses of STK-001 (70 mg) before patients would be eligible to enroll in LONGWING open label extension (OLE).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Total, n (%) N=74
Age at Screening, y	
Mean (SD)	10.2 (5.05)
Median (min, max)	10.5 (2, 18)
Sex	
Female	39 (52.7)
Male	35 (47.3)
Number of Concomitant ASMs	
≥3	60 (81.1)
≥4	37 (50.0)
Concomitant Fenfluramine	36 (48.6)
Baseline Convulsive Seizure Frequency/28 days Median (min/max)	
17.5 (1, 2335)	

Data cutoffs: 12Apr2023 and 21Jun2023 (ADMIRAL); 13Apr2023 (MONARCH). ASMs: Antiseizure medications

SUMMARY

- STK-001 remains the first potential medicine in the clinic to treat the underlying cause of DS
- 74 patients with DS received ≥1 dose of STK-001 up to 70 mg/dose
- Enrolled patients had severe disease and were refractory to standard treatments
- Single and multiple doses of STK-001 up to 70 mg were generally well tolerated
- Patients treated with 2 or 3 initial doses of 70 mg experienced substantial and sustained reductions in convulsive seizure frequency, outperforming all prior dose groups
- These data continue to support future development and progression to Phase 3 pending end of study data.

SAFETY

Patients n (%)	2-12y n=40	13-18y n=34	Total N=74
TEAEs	38 (95.0)	32 (94.1)	70 (94.6)
TEAEs related to study drug	9 (22.5)	15 (44.1)	24 (32.4)
≥Grade 3 TEAEs	7 (17.5)	5 (14.7)	12 (16.2)
≥Grade 3 TEAEs related to study drug	0	1 (2.94)	1 (1.35)
Serious TEAEs	7 (17.5)	8 (23.5)	15 (20.3)
Serious TEAEs related to study drug	0	1 (2.94)	1 (1.35)
TEAEs leading to death	0	1 (2.94)	1 (1.35)

Safety data cutoffs: 12Apr2023 (ADMIRAL); 13Apr2023 (MONARCH)

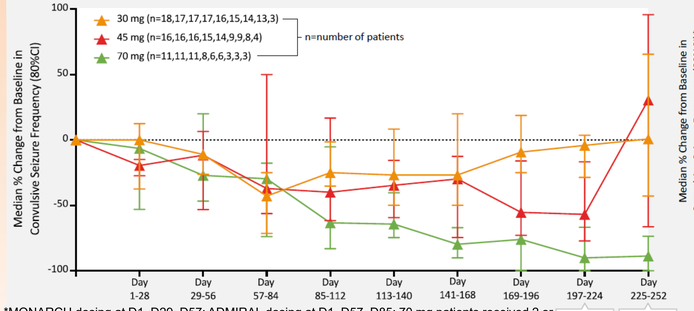
TEAEs in >10% by Preferred Term	n (%)
Post lumbar puncture syndrome	19 (25.7)
Vomiting	17 (23.0)
Seizure	16 (21.6)
Pyrexia	14 (18.9)
Upper respiratory tract infection	12 (16.2)
Irritability	11 (14.9)
Contusion	10 (13.5)
CSF protein increased	10 (13.5)
Rhinorrhea	10 (13.5)
Diarrhea	9 (12.2)
Nasopharyngitis	9 (12.2)
Procedural vomiting	8 (10.8)

- Most treatment-emergent AEs (TEAEs) were mild to moderate; 1 fatal event (SUDEP) not related to study drug
- 24 (32.4%) patients with TEAEs related to study drug
  - Most common TEAEs related to study drug were CSF protein elevations, vomiting, and irritability
  - 1 (1.4%) patient with serious TEAEs related to study drug; 1 (1.4%) patient with suspected unexpected serious adverse reactions (SUSARs); all other related TEAEs were non-serious/mild or moderate
- 38 (51.4%) patients experienced TEAEs related to CSF or study drug administration procedure
- 26 (35.1%) patients with CSF protein value >50 mg/dL; no associated clinical manifestations

CONVULSIVE SEIZURE FREQUENCY IN 30 MG TO 70 MG MAD

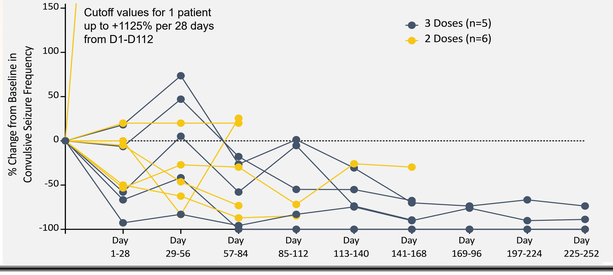
Reductions in convulsive seizures reductions were more substantial, sustained, and consistent in the 70 mg cohort

MONARCH & ADMIRAL Patients (All Ages) Combined by Cohort*

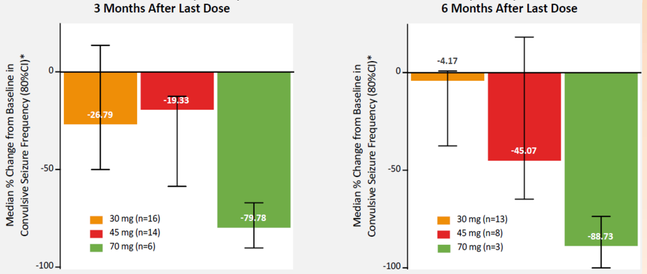


*MONARCH dosing at D1, D29, D57; ADMIRAL dosing at D1, D57, D85; 70 mg patients received 2 or 3 doses; MONARCH ends D224, ADMIRAL ends D252. Seizure data cut: 12Apr2023 and 21Jun2023 (ADMIRAL); 13Apr2023 (MONARCH)

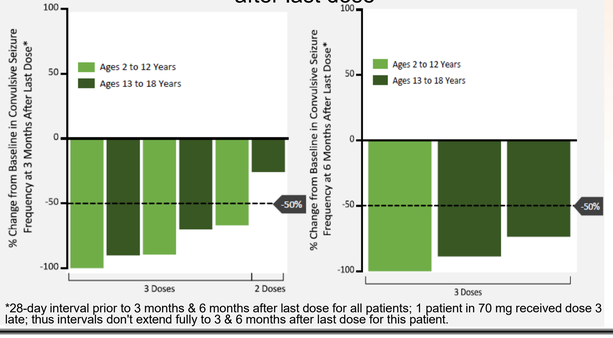
70 mg MAD (ADMIRAL)*



Median reductions after last dose for 70 mg cohort were 80% at 3 months (n=6) and 89% at 6 months (n=3)



All patients who received 3 initial doses of 70 mg achieved >50% reduction at 3 months (n=5) and at 6 months (n=3) after last dose



*28-day interval prior to 3 months & 6 months after last dose for all patients; 1 patient in 70 mg received dose 3 late; thus intervals don't extend fully to 3 & 6 months after last dose for this patient.