MONARCH and ADMIRAL: Phase 1/2a Studies in US and UK Investigating Safety and Drug Exposure of STK-001, an Antisense Oligonucleotide (ASO), in Children and Adolescents with Dravet Syndrome (DS)

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DS is a severe and progressive epilepsy

- DS is characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year (y) of life
- DS includes comorbidities including intellectual disability, ataxia/motor abnormalities, behavioral problems, speech impairment, sleep disturbances, and a high risk for sudden unexpected death
- 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
- In DS, patients have one wild type copy and one mutated copy, resulting in half as much $Na_v1.1$ protein as needed to maintain health
- Upregulating $Na_v1.1$ protein may restore functioning neurons and prevent seizures and reduce non-seizure related comorbidities in DS

STK-001 may be the first disease-modifying therapy to address the genetic cause of DS

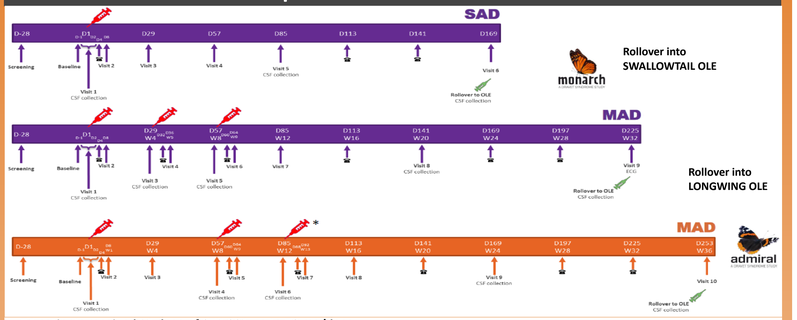
- STK-001 is an investigational antisense oligonucleotide designed to upregulate $Na_v1.1$ protein expression by leveraging the non-mutant (wild type) copy of *SCN1A* to restore physiological $Na_v1.1$ protein levels

Patients in MONARCH and ADMIRAL are treated with the best available medicines

Total: N=74	
Age at screening, y	
Mean (SD)	10.2 (5.05)
Median (min, max)	10.5 (2, 18)
Sex, n (%)	
Female	39 (52.7)
Male	35 (47.3)
Number of concomitant ASMs, n (%)	
≥3	60 (81.1)
≥4	37 (50.0)
Concomitant fenfluramine	36 (48.6)
Race, n (%)*	
Asian	4 (5.41)
Black or African American	4 (5.41)
White	66 (89.2)
Prefer not to answer	4 (5.41)
Ethnicity, n (%)	
Not Hispanic/Latino	64 (86.5)
Baseline convulsive seizure frequency per 28 days, Median (min,max)	
17.5 (1, 2335)	

*can answer in more than one category

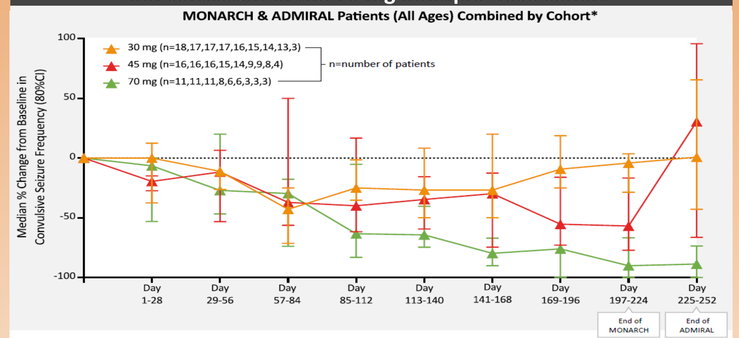
Patients receive up to 3 doses of STK-001 in MONARCH and ADMIRAL with option to rollover into an OLE



74 patients received ≥1 dose of STK-001 up to 70 mg/dose

*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).

Reductions in convulsive seizures were more substantial, sustained, and consistent in the 70 mg multiple-dose 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)

Acknowledgements

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Single and multiple doses of STK-001 up to 70 mg have been generally well-tolerated

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)

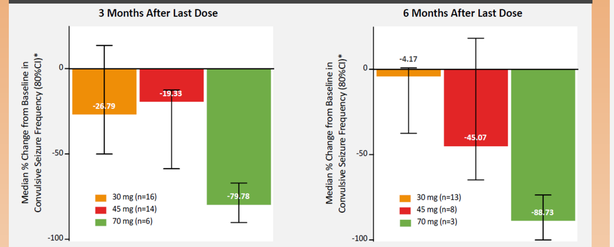
Safety data cutoffs: 12Apr2023 (ADMIRAL); 13Apr2023 (MONARCH)

- Most common TEAEs related to study drug were CSF protein elevations, vomiting, and irritability
- Most treatment-emergent AEs (TEAEs) were mild to moderate in severity; 1 fatal event of presumed Sudden Unexpected Death in Epilepsy (SUDEP) not related to study drug
- 1 patient with serious TEAEs related to study drug classified as Suspected Unexpected Serious Adverse Reactions (SUSARs) that the investigator attributed to STK-001. The patient completed the study. All other related TEAEs were non-serious/mild or moderate.

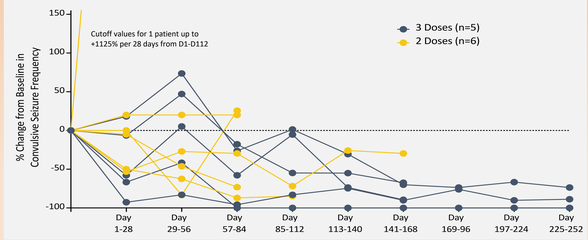
TEAEs in >10% by Preferred Term	n (%)
Post lumbar puncture syndrome	19 (25.7)
Vomiting	17 (23.0)
Seizure	16 (21.6)
Pyrexia	14 (18.9)
Upper respiratory tract infection	12 (16.2)
Irritability	11 (14.9)
Contusion	10 (13.5)
CSF protein increased	10 (13.5)
Rhinorrhea	10 (13.5)
Diarrhea	9 (12.2)
Nasopharyngitis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

- 38 (51.4%) had TEAEs related to CSF collection or study drug administration
- 26 (35.1%) had CSF protein values >50 mg/dL; no associated clinical manifestations

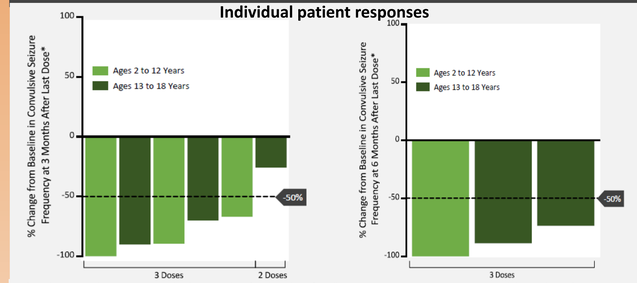
Median reductions in convulsive seizure frequency were 80% at 3 months and 89% at 6 months after last dose in 70 mg multiple-dose cohort



Patients treated with 2 or 3 doses of 70 mg experienced a differentiated pattern of response



All patients who received 3 doses of 70 mg achieved >50% reduction at 3 months and at 6 months 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.

Positive safety and efficacy data from patients treated in MONARCH and ADMIRAL support ongoing development of STK-001 for the treatment of DS

- Single and multiple doses of STK-001 up to 70 mg have been generally well-tolerated
- Substantial reductions in convulsive seizure frequency were observed in patients treated with STK-001 who have severe disease and are refractory to standard treatments
- The multiple dose 70 mg cohort showed the greatest reduction in convulsive seizure frequency, outperforming all prior dose groups
- Data suggest that STK-001 requires time to achieve a maximal clinical effect, consistent with the mechanism of action of STK-001
- Poster #1.279 reports effects of continuing treatment with STK-001 in the SWALLOWTAIL and LONGWING OLE studies