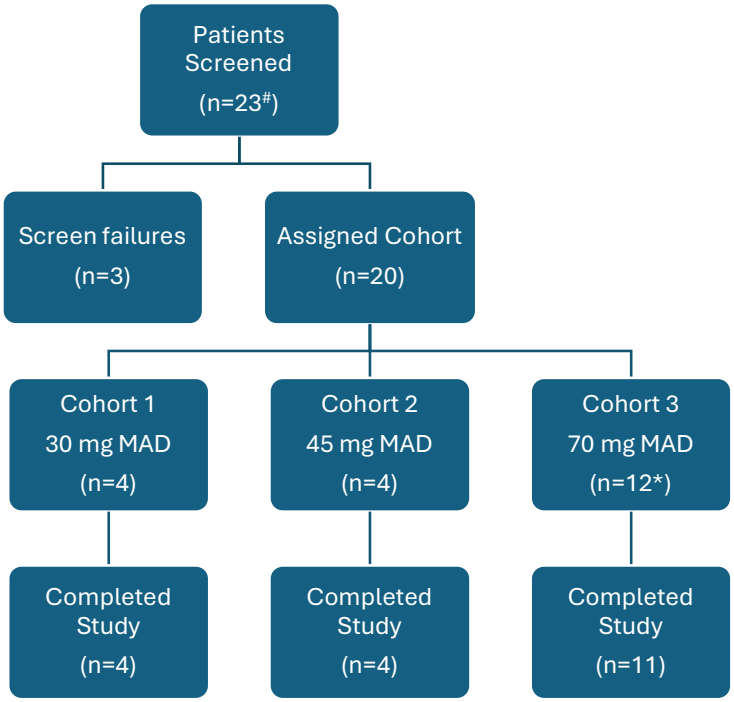
Clinical Trial Results

Study Title: An open-label study to investigate the safety and pharmacokinetics of multiple ascending doses of antisense oligonucleotide STK-001 in children and adolescents with Dravet syndrome

Study Number: STK-001-DS-102 (ADMIRAL)

Patient Disposition:

- Safety set (n=19) includes all patients who received ≥ 1 dose of STK-001
    - Data cutoff 12Dec2023 (End of Study)



#22 unique patients

*1 patient withdrew prior to dosing

Patient Demographics

	MAD			Overall
	Cohort 1 (30 mg)	Cohort 2 (45 mg)	Cohort 3 (70 mg)	
Age at Screening, years				
N	4	4	11	19
Mean (SD)	9.3 (6.18)	9.8 (5.12)	9.2 (5.67)	9.3 (5.35)
Median (min, max)	8.5 (4, 16)	10.0 (4, 15)	6.0 (3, 17)	7.0 (3, 17)
Age Group, n (%)				
2 to 12 years	2 (50.0)	2 (50.0)	7 (63.6)	11 (57.9)
13 to <18 years	2 (50.0)	2 (50.0)	4 (36.4)	8 (42.1)
Sex				
Female, n (%)	2 (50.0)	2 (50.0)	6 (54.5)	10 (52.6)
Male, n (%)	2 (50.0)	2 (50.0)	5 (45.5)	9 (47.4)
Race, n (%)(*)				
White	4 (100.0)	4 (100.0)	11 (100.0)	19 (100.0)
Ethnicity, n (%)				
Not Hispanic/Latino	4 (100)	4 (100)	10 (90.9)	18 (94.7)
Prefer not to answer	0 (0.0)	0 (0.0)	1 (9.1)	1 (5.3)

(*) multiple selections for race may be entered

Primary Outcome Measure: Safety and Tolerability

TEAE Summary by Age

(Safety Set, N=19)

Number of patients with:	Age 2 to 12 N=11	Age 13 to 18 N=8	Total N=19
TEAEs, n (%)	11 (100)	8 (100)	19 (100)
TEAE related to study drug, n (%)	4 (36.4)	4 (50.0)	8 (42.1)
TEAE related to CSF or study drug administration, n (%)	3 (27.3)	5 (62.5)	8 (42.1)
≥Grade 3 TEAE, n (%)	1 (9.1)	2 (25.0)	3 (15.8)
≥Grade 3 TEAE related to study drug, n (%)	0 (0.0)	1 (12.5)	1 (5.3)
Serious TEAE, n (%)	3 (27.3)	3 (37.5)	6 (31.6)
Serious TEAE related to study drug, n (%)	0 (0.0)	1 (12.5)	1 (5.3)
Potential DLT, n (%)	0 (0.0)	1 (12.5)	1 (5.3)
TEAE leading to study drug discontinuation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to study withdrawal, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

Primary Outcome Measure: Safety and Tolerability

TEAEs Reported in >10% of Patients by Preferred Term (PT)

(Safety Set, N=19)

- 19 of 19 (100%) patients experienced ≥1 TEAE

Preferred Term	**Total N=19 n (%)**
Vomiting	7 (36.8)
Pyrexia	6 (31.6)
Influenza like illness	5 (26.3)
Procedural vomiting	5 (26.3)
Upper respiratory tract infection	5 (26.3)
Contusion	4 (21.1)
Nasopharyngitis	4 (21.1)
Respiratory tract infection viral	4 (21.1)
Seizure	4 (21.1)
Cough	3 (15.8)
COVID-19	3 (15.8)
CSF protein increased	3 (15.8)
Diarrhea	3 (15.8)
Fall	3 (15.8)
Rhinorrhea	3 (15.8)
Bradycardia	2 (10.5)
Epistaxis	2 (10.5)
Head injury	2 (10.5)
Lower respiratory tract infection	2 (10.5)
Menstruation irregular	2 (10.5)
Procedural pain	2 (10.5)
Rash maculo-papular	2 (10.5)
Tonsillitis	2 (10.5)
Tremor	2 (10.5)
Varicella	2 (10.5)

Primary Outcome Measures: Plasma PK Parameters and CSF Concentrations

PK Parameters and CSF Concentrations for ISRCTN Submission

Table 1 Summary of Plasma STK-001 Parameters

Cohort	Dose (mg)	Dosing Day	Summary	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	T_{last} (h)	Term_$t_{1/2}$ (h)
1	30	1	N	4	4	4	4	4	4	2
			Mean	360	5.50	9560	9580	22.3	882	726
			SD	124	1.91	3010	3010	1.43	572	29.0
			CV%	34.3	34.8	31.5	31.4	6.4	64.8	4.0
			Min	187	4.00	7430	7450	20.8	168	705
			Median	398	5.00	8480	8510	22.5	1010	726
			Max	459	8.00	13900	13900	23.6	1340	746
		57	N	4	4	2	0	0	4	0
			Mean	460	4.50	30800	NC	NC	672	NC
			SD	145	2.52	13000	NC	NC	0.00	NC
			CV%	31.5	55.9	42.4	NC	NC	0.0	NC
			Min	259	2.00	21500	NC	NC	672	NC
			Median	496	4.00	30800	NC	NC	672	NC
			Max	589	8.00	40000	NC	NC	672	NC
		85	N	3	3	3	0	0	3	1
			Mean	521	5.33	31900	NC	NC	3360	1580
			SD	384	3.06	7670	NC	NC	1160	NC
			CV%	73.7	57.3	24.1	NC	NC	34.6	NC
			Min	262	2.00	26100	NC	NC	2020	1580
			Median	339	6.00	29000	NC	NC	4030	1580
			Max	963	8.00	40600	NC	NC	4030	1580
2	45	1	N	4	4	4	3	3	4	2
			Mean	928	7.00	16700	18900	22.1	1340	1090
			SD	576	4.16	7050	6780	2.69	0.00	312
			CV%	62.1	59.5	42.2	35.8	12.2	0.0	28.5
			Min	313	2.00	10200	11800	20.2	1340	873
			Median	890	7.00	15700	19700	20.8	1340	1090
			Max	1620	12.0	25300	25300	25.2	1340	1310
		57	N	4	4	4	0	0	4	0
			Mean	1010	4.00	43500	NC	NC	672	NC
			SD	701	1.63	20800	NC	NC	0.00	NC
			CV%	69.4	40.8	47.9	NC	NC	0.0	NC
			Min	329	2.00	20500	NC	NC	672	NC
			Median	911	4.00	46000	NC	NC	672	NC
			Max	1890	6.00	61600	NC	NC	672	NC
		85	N	4	4	4	0	0	4	4

Cohort	Dose (mg)	Dosing Day	Summary	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$t_{1/2}$ (h)	T_{last} (h)	Term_$t_{1/2}$ (h)
			Mean	1160	4.50	52600	NC	NC	3530	2000
			SD	866	2.52	18400	NC	NC	1010	606
			CV%	74.3	55.9	35.0	NC	NC	28.6	30.3
			Min	536	2.00	34300	NC	NC	2020	1590
			Median	842	4.00	53400	NC	NC	4030	1770
			Max	2440	8.00	69400	NC	NC	4030	2880
3	70	1	N	11	11	11	10	10	11	5
			Mean	1530	5.36	30100	28800	21.2	1340	1330
			SD	1350	2.98	10400	9770	1.22	0.00	222
			CV%	88.8	55.5	34.5	33.9	5.8	0.0	16.6
			Min	625	1.00	15800	15900	19.2	1340	1080
			Median	1090	6.00	28700	28600	21.2	1340	1370
			Max	5370	12.0	47900	47900	23.6	1340	1580
		57	N	10	10	10	0	0	10	0
			Mean	1400	5.00	80600	NC	NC	672	NC
			SD	1010	2.71	33600	NC	NC	0.00	NC
			CV%	72.6	54.2	41.7	NC	NC	0.0	NC
			Min	463	2.00	21300	NC	NC	672	NC
			Median	1170	4.00	85200	NC	NC	672	NC
			Max	3960	8.00	139000	NC	NC	672	NC
		85	N	5	5	4	0	0	5	5
			Mean	1560	4.80	93200	NC	NC	4030	2020
			SD	1250	2.28	69400	NC	NC	0.00	760
			CV%	80.0	47.5	74.4	NC	NC	0.0	37.6
			Min	283	2.00	33000	NC	NC	4030	1480
			Median	1110	4.00	92600	NC	NC	4030	1730
			Max	2970	8.00	155000	NC	NC	4030	3350

NC = Not calculated.

Note: Because of limited PK collection time points on dosing Day 57 and Day 85, limited PK parameters were calculated. $t_{1/2}$ was calculated using data up to 168 hours and Term_$t_{1/2}$ was calculated using data beyond 168 hours. The PK parameter for six patients in the 70 mg/cohort 3 who received two doses were summarized in table 2.

Primary Outcome Measures: Plasma PK Parameters and CSF Concentrations

Table 2 Summary of Plasma STK-001 Parameters for Subjects Administered 2 Doses in the 70 mg Dose Cohort

Cohort	Dose (mg)	Dosing Day	Summary	C_{max} (ng/mL)	T_{max} (h)	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	T_{last} (h)	Term_$t_{1/2}$ (h)
3	70	57	N	6	6	6	NC	6	6
			Mean	987	6.00	81600	NC	4370	1710
			SD	261	3.10	23800	NC	823	460
			CV%	26.5	51.6	29.1	NC	18.8	26.9
			Min	542	2.00	54600	NC	2690	1100
			Median	1080	8.00	75000	NC	4700	1780
			Max	1210	8.00	115000	NC	4700	2260

NC = Not calculated.
Note: Term_$t_{1/2}$ was calculated using data beyond 168 hours and associated λ_z was used to calculate the terminal phase parameters.

LIST OF ABBREVIATIONS (in order of appearance)

C_{max}	Maximum observed plasma concentration
T_{max}	Time to reach C_{max}
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
$t_{1/2}$	Elimination half-life
T_{last}	Time of last measurable observed concentration
Term_$t_{1/2}$	Terminal half-life

Primary Outcome Measures: Plasma PK Parameters and CSF Concentrations

Table 3 Summary of CSF STK-001 Concentrations

			Study Day			
			1	57	85	169
Cohort	Dose (mg)	Summary	Concentration (ng/mL)			
1	30	N	3	3	4	3
		Mean	0.00	8.63	7.93	11.6
		SD	0.00	8.01	1.02	5.98
		CV%	NC	92.9	12.9	51.6
		Min	0.00	2.98	6.98	4.79
		Median	0.00	5.10	7.89	14.0
		Max	0.00	17.8	8.95	16.0
2	45	N	4	4	4	4
		Mean	0.00	3.52	7.98	9.96
		SD	0.00	1.31	1.81	5.21
		CV%	NC	37.2	22.7	52.3
		Min	0.00	2.23	5.83	3.35
		Median	0.00	3.56	7.94	10.2
		Max	0.00	4.74	10.2	16.1
3	70	N	11	11	9	4
		Mean	0.00	8.07	9.75	12.2
		SD	0.00	14.7	7.34	7.18
		CV%	NC	182.5	75.3	59.1
		Min	0.00	0.00	3.66	6.57
		Median	0.00	2.85	5.71	9.68
		Max	0.00	51.9	23.4	22.7

NC = Not calculated.

Note: Concentrations considered aberrant and scientifically not plausible, and concentrations above the quantification limit were excluded from summary statistics. Days 1, 57 and 85 were dosing days. CSF was collected prior to dosing.

The concentrations for six patients in the 70 mg/cohort 3 who received two doses were summarized in table 4.

Table 4 Summary of CSF STK-001 Concentrations for Subjects Administered 2 Doses in the 70 mg Dose Cohort

			Study Day
			169
Cohort	Dose (mg)	Summary	Concentration (ng/mL)
3	70	N	6
		Mean	15.8
		SD	11.7
		CV%	74.1
		Min	6.06
		Median	12.2
		Max	36.6

Note: Last dosing occurred on Day 57.

ADA/Immunogenicity

- In the Admiral study (Phase 1/2a, STK-001-DS-102), 129 samples from 20 subjects (1 screen fail) were analyzed. There were no confirmed ADA positive results in Admiral study.