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A Pharmacokinetic (PK) Model For STK-001, An Antisense Oligonucleotide (ASO), Based On Data From Non-Human Primates (NHP) Enables Dose Selection In Patients With Dravet Syndrome (DS)

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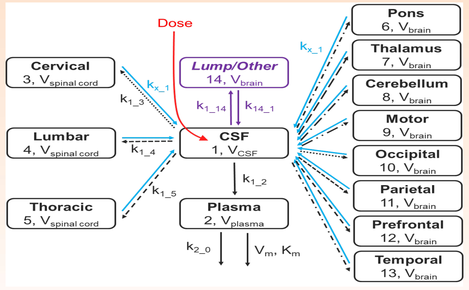
monarch — A DRAVET SYNDROME STUDY

1. Introduction

- DS is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year (y) of life, and is not adequately controlled by available therapies
- 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 $Na_V1.1$ levels following intrathecal (IT) dosing
- A 14-compartment NHP PK model for STK-001 was designed based on distribution from 95 NHPs following single or repeat IT doses
- PK in NHPs was characterized in CSF, plasma, 3 spinal cord regions, 8 brain regions, and a lump compartment (uncharacterized brain tissues)
- NHP model was scaled directly to predict PK in patients with DS aged from 2 to ≤18y based on CSF and brain volumes, transfer rates from and to CSF, age, and weight differences in target population
- Model was adapted to obtain better fits between simulated and observed profiles in plasma and CSF concentrations in patients from Phase 1/2a (MONARCH) study (NCT04442295) administered 1 or 3 IT doses of STK-001

2. Population PK Model



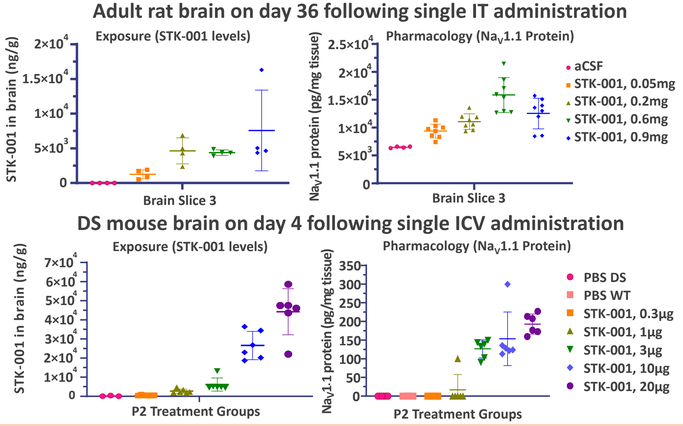
Km=Michaelis-Menten constant; ktr=transfer rate between depot compartment and CSF; k_{x_y}=transfer rate between compartment x to compartment y; V_x=distribution volume of compartment x. Red line=IT administration into CSF; dashed black lines=transfer from CSF to brain and spinal cord compartments with available concentrations; blue full lines=transfer from those brain and spinal cord compartments to CSF; purple lines=transfer between CSF and other brain tissues without available concentrations; full lines=transfer of STK-001 from CSF to plasma and to exit.

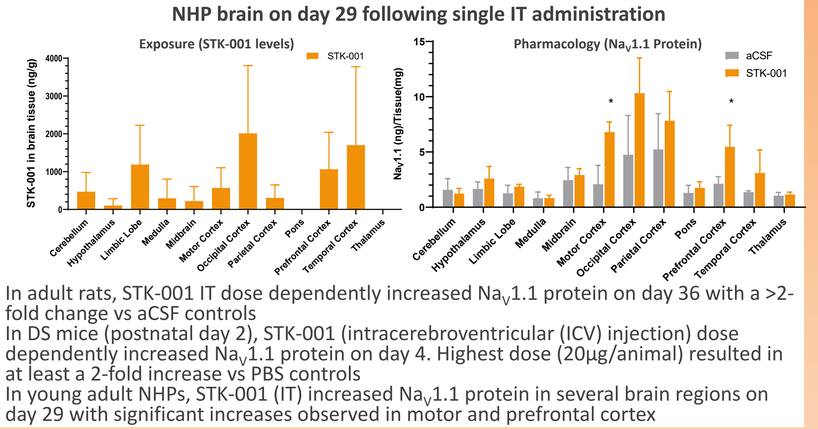
3. Predicted Human Safety Margins

Age	Compartment	Median [5th , 95th percentiles] Safety Margin (IT dose 45mg)	
		AUC0-8weeks	Cmax
2-<8y	Plasma	4.41 [2.0, 10.9]	8.14 [3.8, 17.0]
	CSF	8.95 [3.2, 25.8]	7.97 [3.2, 20.4]
	Brain	13.3 [3.0, 58.7]	11.7 [2.9, 49.1]
8-<13y	Plasma	7.51 [3.3, 18.4]	15.30 [7.2, 32.2]
	CSF	9.59 [3.4, 26.6]	8.91 [3.5, 20.7]
	Brain	13.9 [3.1, 64.8]	12.5 [2.9, 54.5]
13-≤18y	Plasma	10.20 [4.7, 23.8]	21.70[11.2, 42.6]
	CSF	10.30 [3.7, 27.7]	9.31 [3.7, 22.7]
	Brain	13.6 [3.0, 61.2]	12.4 [2.8, 50.0]

Predicted human safety margins following single IT dose of 45mg STK-001 are adequate. Based on no-observed adverse effect level exposures in NHP. AUC0-8w=area under the concentration-time curve from time 0 to 8 weeks; Cmax=maximum concentration

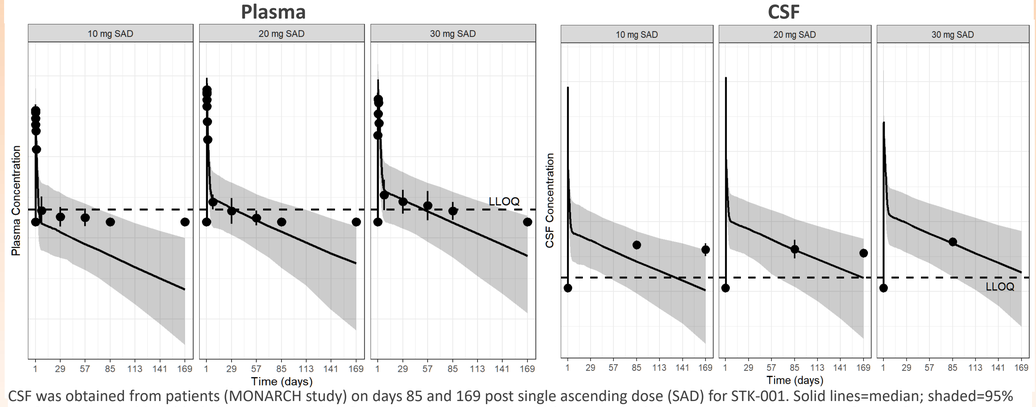
4. Non-Clinical Studies STK-001 Brain Pharmacologically Active Levels





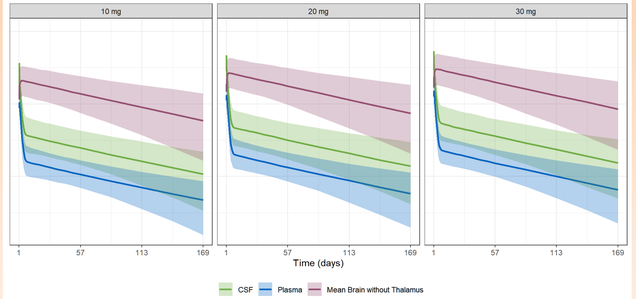
- In adult rats, STK-001 IT dose dependently increased $Na_V1.1$ protein on day 36 with a >2-fold change vs aCSF controls
- In DS mice (postnatal day 2), STK-001 (intracerebroventricular (ICV) injection) dose dependently increased $Na_V1.1$ protein on day 4. Highest dose (20µg/animal) resulted in at least a 2-fold increase vs PBS controls
- In young adult NHPs, STK-001 (IT) increased $Na_V1.1$ protein in several brain regions on day 29 with significant increases observed in motor and prefrontal cortex

5. Observed Plasma and CSF Levels in Patients are in Good Agreement with Model Predictions



CSF was obtained from patients (MONARCH study) on days 85 and 169 post single ascending dose (SAD) for STK-001. Solid lines=median; shaded=95% Confidence Interval (CI); black dots=observed data from clinical trial (n=4-7); whiskers=standard deviation; LLOQ=lower limit of quantification.

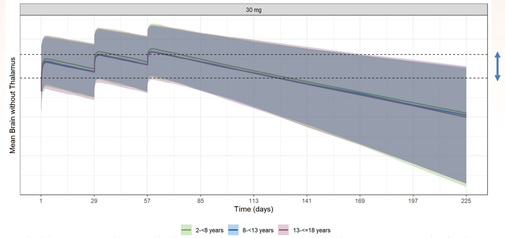
6. Steady State Plasma and CSF STK-001 Levels are Good Predictors of STK-001 Brain Levels in Patients



Solid lines=median; all shaded areas=95% CI. Thalamus not included due to significantly lower levels of measured STK-001 in NHPs

- Projected plasma, CSF, and brain levels were strongly correlated across time and dose groups following single IT STK-001 doses
- Therefore, CSF and/or plasma levels in MONARCH can be used to estimate STK-001 levels in patients' brain

7. 3 Doses of STK-001 (30mg) Given Monthly are Projected to Achieve Pharmacologically Active Brain Levels in 95% of Patients



Solid lines=median; all shaded areas=95% CI. Thalamus not included due to significantly lower levels of measured STK-001 in NHPs

Pharmacologically active range

- Approximately 50% of patients are anticipated to remain at pharmacologically active levels approximately 3 months after last dose
- Pharmacological effect likely lasts beyond timepoint when STK-001 brain concentration falls below minimum level

8. OVERALL SUMMARY

- Based on semi-mechanistic population PK model in NHPs, PK predictions in patients were made based on maturation and allometric scaling of NHP model after age and weight adjustment, and incorporation of observed plasma and CSF exposure data
- Model predictions correlated well with observed plasma and CSF levels of STK-001 in pediatric patients with DS
- CSF and/or plasma levels in MONARCH can be used to estimate STK-001 levels in brain
- In all age groups, anticipated tissue concentrations of STK-001 (45mg; current maximum dose in MONARCH) are predicted to keep safety margin ≥8-fold in plasma, CSF, and brain
- 3 doses of STK-001 (30mg) given monthly are projected to achieve pharmacologically active brain levels in >95% of patients
- Approximately 50% of patients are predicted to maintain greater than minimum pharmacologically active levels of STK-001 for approximately 3 months following 3rd monthly dose of 30mg

REFERENCES: Dravet C, et al. *Epilepsia.* 2011;52:3-9; 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.

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A DRAVET SYNDROME STUDY

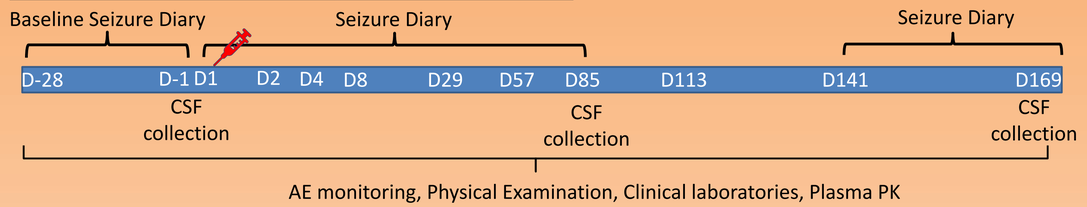
MONARCH Key Study Criteria

Inclusion CRITERIA
- 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

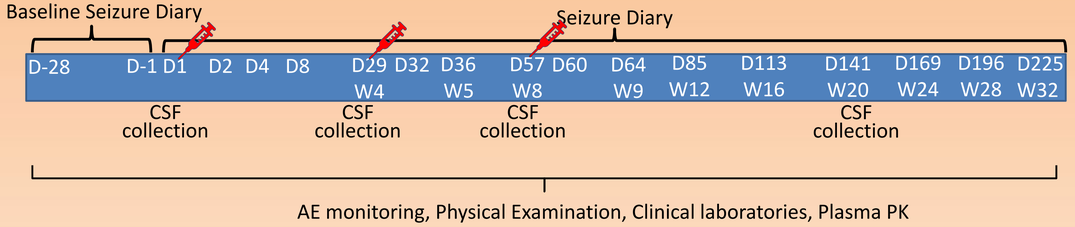
EXCLUSION CRITERIA
- Known pathogenic mutation in another gene that causes epilepsy
- Currently being treated with an anti-epileptic drug acting primarily as a sodium channel blocker, as maintenance treatment
- Clinically significant unstable medical condition(s) other than epilepsy
- Clinically relevant 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 patient at risk, influence study results, or affect patient's ability to participate

MONARCH SAD Study Assessments

The currently planned maximum dose in MONARCH study is 45mg



MONARCH MAD Study Assessments



= Study Drug Administration

MONARCH Study Design

Protocol Amendment v3.0	
Open-label, Single and Multiple Ascending Doses (SAD and MAD) of STK-001 in 2–18-year-olds (y) (NCT04442295)	
Duration	7-9 months / patient
# patients	<70
Sites	Approximately 20 in US
Cohorts	Each dose cohort enrolls 4 patients, with option for 6 more for safety evaluation • SAD at 10, 20, and 30mg • MAD at 20 and 30mg every 28 days for 3 doses
Dosing	• Dose escalation based on safety and tolerability assessed by Safety Team (with external reviewers) • Dosing begins in 13- to 18y cohorts, with internal safety team approving dosing in 2- to 12y
Data cutoff was after 4th patient in Cohort A3 (30mg) completed Visit 5 (Day 85). All included in analysis received ≥1 dose of STK-001.	

Predicted Safety Margins Based on NHP Data

Age	Single IT Dose (mg)	Median [5th , 95th percentiles]					
		Plasma		CSF		Brain	
		AUC0-8w	Cmax	AUC0-8w	Cmax	AUC0-8w	Cmax
2 - <8y	10	20.2[9.63, 46.7]	36.7[17.8, 73.8]	38.1[14.5, 116]	35.2[15.3, 92.8]	59.5[13.8, 257]	52.8[13.0, 213]
	20	10.1[4.46, 23.4]	18.3[8.39, 38.1]	20.5[7.16, 56.5]	18.7[7.16, 47.8]	27.9[6.69, 134]	24.8[6.42, 114]
	30	6.91[3.06, 16.8]	11.9[5.59, 25.5]	13.7[4.75, 37.5]	12.2[5.01, 30.4]	19.5[3.83, 84.9]	17.2[3.82, 70.9]
	45	4.41[2.03, 10.9]	8.14[3.77, 17.0]	8.95[3.24, 25.8]	7.97[3.18, 20.4]	13.3[3.04, 58.7]	11.7[2.90, 49.1]
8 - <13y	10	33.5[14.5, 79.9]	67.1[32.8, 154]	41.6[14.2, 119]	37.5[15.5, 101]	60.6[12.7, 265]	50.8[11.9, 228]
	20	16.9[7.55, 39.0]	34.7[15.3, 73.7]	21.8[7.93, 63.6]	20.5[8.27, 51.8]	30.9[6.73, 137]	28.0[6.22, 122]
	30	11.0[4.99, 25.4]	23.0[10.9, 46.0]	14.4[5.28, 40.8]	13.1[5.54, 32.7]	19.0[4.59, 84.7]	16.8[4.31, 75.4]
	45	7.51[3.32, 18.4]	15.3[7.15, 32.2]	9.59[3.40, 26.6]	8.91[3.53, 20.7]	13.9[3.11, 64.8]	12.5[2.92, 54.5]
13 - ≤18y	10	46.2[21.5, 106]	99.1[49.1, 203]	42.6[15.5, 137]	39.5[15.5, 107]	63.9[14.2, 287]	56.7[13.6, 241]
	20	22.8[10.3, 50.6]	50.3[24.0, 98.6]	23.5[8.01, 62.2]	21.0[8.25, 50.8]	30.3[6.01, 138]	27.9[5.86, 119]
	30	15.2[7.08, 35.8]	33.2[16.3, 66.9]	15.9[4.93, 40.2]	14.1[5.03, 32.8]	20.5[4.42, 85.4]	18.0[3.90, 75.4]
	45	10.2[4.74, 23.8]	21.7[11.2, 42.6]	10.3[3.69, 27.7]	9.31[3.74, 22.7]	13.6[2.98, 61.2]	12.4[2.76, 50.0]

Predicted safety margins following single IT dose based on no-observed adverse effect level exposures in NHPs.
AUC0-8w=area under the plasma concentration-time curve from time 0 -8 weeks; Cmax=maximum concentration.

More Information

To find out more: MONARCHstudy.com. By contacting us, your patient is under no obligation to take part in the study. For MONARCH clinical, please see poster 2.405.