1.134

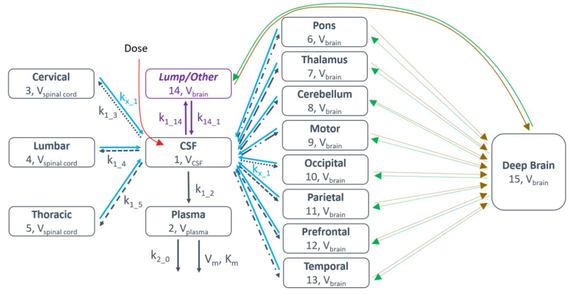
Utilization of a Pharmacokinetic (PK) Model for STK-001 in Patients with Dravet Syndrome (DS) To Predict Pharmacologically Active Doses in Clinic

Meena[1], Susovan Mohapatra[1], Yanyan Cui[1], , Barry Ticho[1], Olivier Barriere[2], Nathalie H Gosselin[2]
[1]Stoke Therapeutics; [2]Certara USA, Inc.

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.
- 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 in epilepsy (SUDEP).
- 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.
- 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 15-compartment NHP PK model for STK-001 was developed based on 3499 measurable PK observations in different biological matrices from total 141 NHPs following a single or repeat IT doses with data up to 365 days.
- PK in NHPs was characterized in CSF, plasma, 3 spinal cord regions, 8 brain regions. A lump compartment (uncharacterized brain tissues) and deep brain compartment were added to capture the full dynamics of the system.
- 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 studies. (MONARCH) study administered 1 or 3 IT doses of STK-001, Phase 1/2 (ADMIRAL) study administered 3 IT doses of STK-001 and OLE (SWALLOWTAIL) with every 4 months dosing.

2. Schematic of population PK model in NHP



CSF=cerebrospinal fluid; IT=intrathecal; Km=Michaelis-Menten constant; kx_y=transfer rate between compartment x to compartment y; NHP=nonhuman primate; PK=pharmacokinetic; Vx= distribution volume of compartment x
Note: Red line represents the IT administration into CSF; dashed black lines represent the transfer from CSF to the brain and spinal cord compartments with available concentrations, blue solid lines represent the transfer from those brain and spinal cord compartments to CSF, purple lines are the transfer between CSF and other brain tissues without available concentrations, brown lines are the transfer from all brain compartments to the deep brain tissues and green lines are the transfer from the deep brain tissues back to the brain compartments. The solid black lines represent the transfer of STK-001 from CSF to plasma and to the exit.

3. Ongoing clinical trials of STK-001 for DS

Phase 1/2	monarch STK-001-DS-101	admiral STK-001-DS-102
Design	Evaluation of STK-001 (up to 45 mg*)	Evaluation of STK-001 (up to 70 mg)
Status	MAD @45 mg: Dosing ongoing	MAD @70 mg: Dosing ongoing
Target Enrollment	~90	Up to 60
Primary Endpoint	Safety and tolerability of SAD and MAD dose levels	Safety and tolerability of MAD dose levels
	Characterize human plasma PK and cerebrospinal fluid (CSF) drug exposure	
Secondary Endpoint	Change in seizure frequency, overall clinical status, and quality of life	
Open-Label Extension (OLE)	swallowtail STK-001-DS-501	Longwing STK-001-DS-502

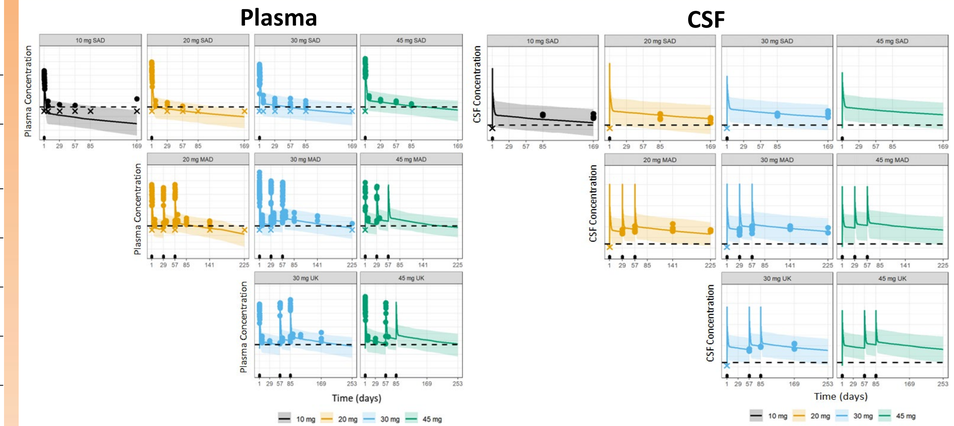
*Doses >45 mg remain on FDA partial clinical hold

4. Number of pediatric patients with DS-model development

Study	Cohorts	2 – 12 years old (N=24, 49.0%)	13 – 18 years old (N=25, 51.0%)	Overall (N=49)
STK-001-DS-101 N=41	10 mg SAD[a]	1 (3.7%)	3 (9.4%)	4 (6.8%)
	20 mg SAD	2 (7.4%)	2 (6.3%)	4 (6.8%)
	30 mg SAD	4 (14.8%)	3 (9.4%)	7 (11.9%)
	45 mg SAD	2 (7.4%)	2 (6.3%)	4 (6.8%)
	20 mg MAD	2 (7.4%)	4 (12.5%)	6 (10.2%)
	30 mg MAD	9 (33.3%)	5 (15.6%)	14 (23.7%)
	45 mg MAD	0 (0%)	2 (6.3%)	2 (3.4%)
STK-001-DS-501[b] N=10	10 mg OLE	1 (3.7%)	3 (9.4%)	4 (6.8%)
	20 mg OLE	2 (7.4%)	2 (6.3%)	4 (6.8%)
	30 mg OLE	0 (0%)	2 (6.3%)	2 (3.4%)
STK-001-DS-102 N=8	30 mg UK	2 (7.4%)	2 (6.3%)	4 (6.8%)
	45 mg UK	2 (7.4%)	2 (6.3%)	4 (6.8%)

MAD= multiple ascending dose; N= number of patients; OLE= open-label extension; SAD= single ascending dose
[a] one patient received incorrect dose level at Dose 1 and therefore this patient was excluded for model development, but PK data collected was retained for model validation.
[b] The plasma and CSF data from this study is not shown in this poster.

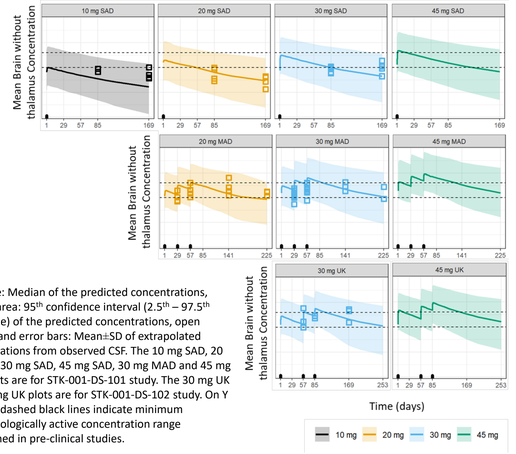
5. Overlay of the model predictions and observed concentrations (Phase 1/2)



There was a good agreement between the model predictions and observed plasma (n=613) and CSF (n=75) concentrations* from 49 patients

Solid line: median of the predicted concentrations, shaded area: 95th confidence interval (2.5th – 97.5th percentile) of the predicted concentrations, Dots and Crosses (x) represent individual measurable and BLQ concentrations (set to half of LLOQ), respectively. The 10 mg SAD, 20 mg SAD, 30 mg SAD, 45 mg SAD, 30 mg MAD, and 45 mg MAD plots are for STK-001-DS-101 study. Two patients that received 20 mg dose in MAD had deviations (delayed dosing), therefore that data was excluded from these plots. The 30 mg UK and 45 mg UK plots are for STK-001-DS-102 study. * These data points included the data from SWALLOWTAIL study.

6. Overlay of the model predictions and extrapolated concentrations in brain from observed CSF (Phase 1/2)



Solid line: Median of the predicted concentrations, Shaded area: 95th confidence interval (2.5th – 97.5th percentile) of the predicted concentrations, open squares and error bars: Mean±SD of extrapolated concentrations from observed CSF. The 10 mg SAD, 20 mg SAD, 30 mg SAD, 45 mg SAD, 30 mg MAD and 45 mg MAD plots are for STK-001-DS-101 study. The 30 mg UK and 45 mg UK plots are for STK-001-DS-102 study. On Y axis, the dashed black lines indicate minimum pharmacologically active concentration range determined in pre-clinical studies.

7. Overall summary

- A semi-mechanistic 15 compartment population PK model of STK-001 was developed based on NHP PK data obtained after a single or repeat IT doses.
- NHP PK model was scaled 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.
- Human PK model was further updated with PK data collected in patients with DS after single or multiple IT administration of 10 mg, 20 mg, 30 mg or 45 mg of STK-001 in Phase 1/2 and OLE studies.
- There was a good agreement between the model predictions and observed plasma and CSF concentrations.
- The brain STK-001 levels in patients with DS were extrapolated based on CSF trough concentrations and were mostly within 95th CI of model simulations.
- The median simulated and extrapolated human brain concentrations in most patients following 3 monthly doses at 20 mg and 30 mg dose, are within the minimum pharmacologically active concentration range determined in preclinical studies.

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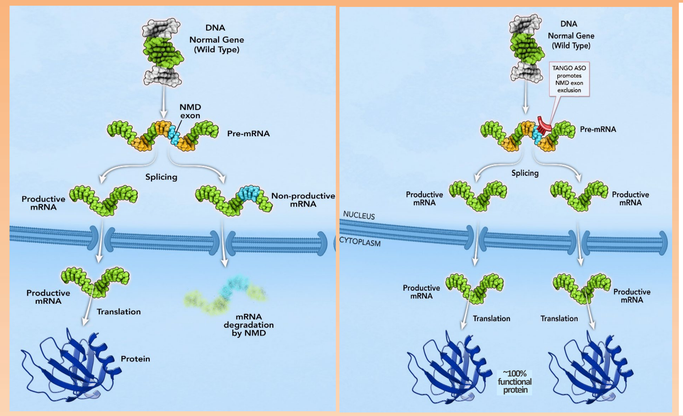
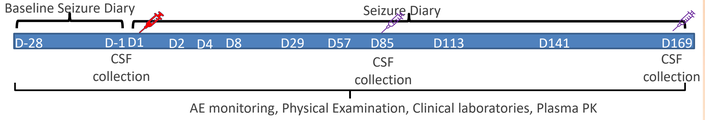
admiral A DRAVET SYNDROME STUDY · monarch A DRAVET SYNDROME STUDY · swallowtail A DRAVET SYNDROME EXTENSION STUDY

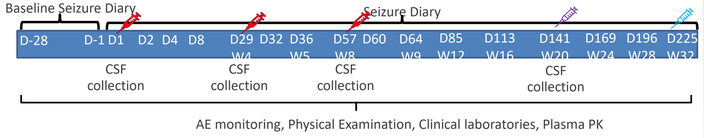
1. Tango Platform In DS



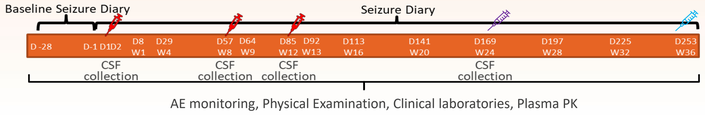
2. MONARCH SAD Study Assessments



3. MONARCH MAD Study Assessments



4. ADMIRAL MAD Study Assessments



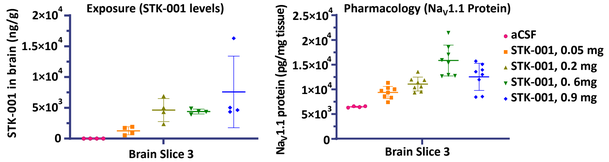
= Study Drug Administration + CSF collection

= CSF collection

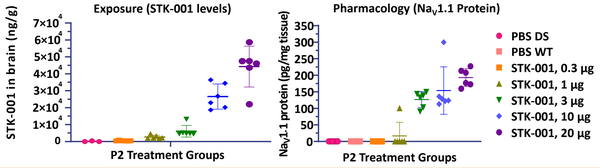
= CSF collection on 1st visit of open-label extension study with rollover on same day

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

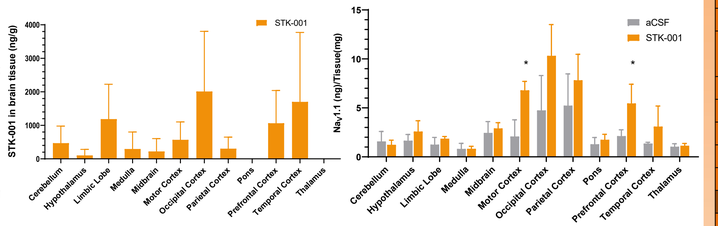
Adult rat brain on day 36 following single Intrathecal administration



DS mouse brain on day 4 following single Intracerebroventricular administration

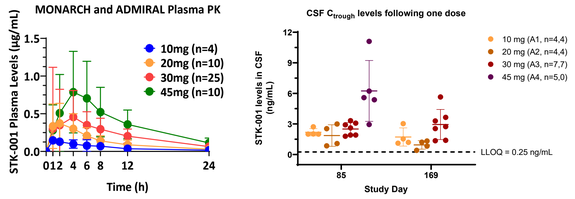


NHP brain on day 29 following single Intrathecal administration



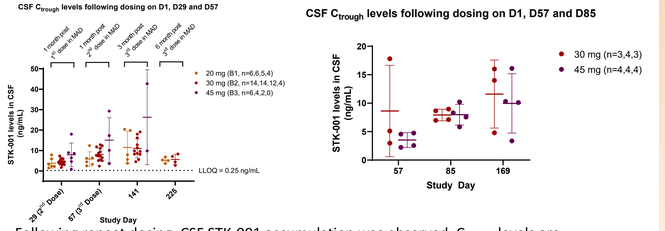
- In adult rats, STK-001 IT dose dependently increased $Na_V1.1$ protein on day 36 with a >2-fold change vs aCSF controls
- In DS mice (postnatal day 2), STK-001 (intracerebroventricular (ICV) injection) dose dependently increased $Na_V1.1$ protein on day 4. Highest dose (20µg/animal) resulted in at 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

6. Plasma PK and CSF Exposure in STK-001 Treated DS Patients



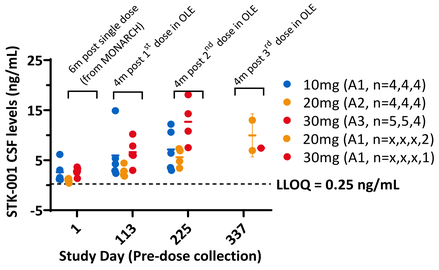
A dose dependent increase in C_{max} and AUC_{last} was observed with dose increase

STK-001 CSF levels were detected up to 6-month post single dose for 10–30 mg

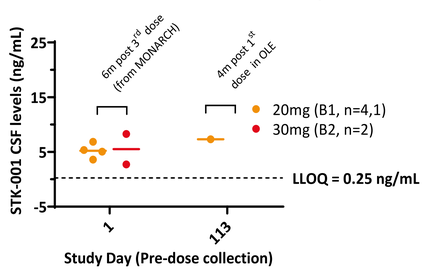


Following repeat dosing, CSF STK-001 accumulation was observed. C_{trough} levels are related to brain levels, therefore brain accumulation is expected at this dosing regimen.

Patients from SAD rolled into OLE



Patients from MAD rolled into OLE Study



- Pre-dose STK-001 plasma levels (not shown) were near lower limit of quantification (LLOQ) indicating no accumulation at this regimen
- Mean STK-001 CSF levels at 6m post single dose (SAD end of study) were lower than those at 6m-post 3m doses (MAD end of study)
- Dose-dependent increase in CSF C_{trough} levels was observed from 20 mg – 30 mg across all cohorts
- Following every 4m dosing, slight STK-001 accumulation in CSF was observed for 10 – 30 mg for 3 doses though not significant to Cmax. STK-001 CSF C_{trough} levels can predict brain concentration (See poster 1.134).

7. MONARCH/ADMIRAL: Patient Disposition for Plasma PK and CSF Exposure

MONARCH

Data Cut: Plasma (26Apr2022) CSF (16Aug2022)

	Bioanalysis		Plasma PK Analyses (N)
Dose (SAD)	Plasma (N)	CSF (N)	
10 mg	5*	5*	20*
20 mg	4	4	
30 mg	7	7	
45 mg	4	5	
Dose (MAD)	**Plasma (N)**	**CSF (N)**	
20 mg	6**	6**	22
30 mg	14	14	
45 mg	2	6	

ADMIRAL

Data Cut: Plasma (29Mar2022) CSF (06Aug2022)

	Bioanalysis***		Plasma PK Analyses (N)
Dose	Plasma (N)	CSF (N)	
30 mg	4	4	8
45 mg	4	4	

*PK analyses was not conducted for 1 patient (10 mg); administered incorrect dose
**One patient deceased/did not complete EOS/D169
***The number of patient samples at each time point varied

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.

More Information

To find out more: MONARCHstudy.com or Admiralstudy.com. By contacting us, your patient is under no obligation to take part in the study.

Acknowledgements

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