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

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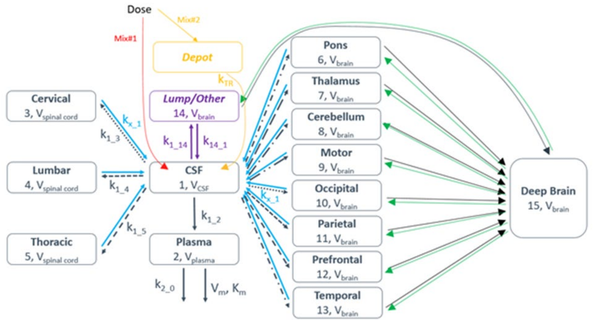
1. Introduction

- DS is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year (y) of life.
- 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. $Na_V1.1$ protein is primarily expressed in brain.
- STK-001 is an antisense oligonucleotide designed to upregulate $Na_V1.1$ protein expression following intrathecal (IT) dosing.
- A 15-compartment NHP (non-human primate) PK model for STK-001 was developed based on 3793 measurable PK observations in CSF (cerebrospinal fluid), plasma, 3 spinal cord regions and 8 brain regions from total 141 NHPs (cynomolgus monkeys) following a single or repeat IT doses with data up to 365 days. 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 two Phase 1/2a studies and one OLE study.
- Non-clinical PK/PD (pharmacokinetic/pharmacodynamic) studies informed minimum pharmacologically active levels range in brain to elicit desired pharmacology.
- Human PK model was used to guide the dosing regimens and evaluate exposure-seizure reduction relationship in clinic.

2. Schematic of population PK model in patients with DS



CSF=cerebrospinal fluid; Km= Michaelis-Menten constant; DS=Dravet syndrome; ktr= transfer rate between depot compartment and CSF; k_{x_y}= transfer rate between compartment x to compartment y; PK=pharmacokinetic; V_x= distribution volume of compartment x
Note: Red and orange line represents the IT administration into CSF or depot compartment respectively (Mix#1 and Mix#2 model); orange line also represents the transfer from depot compartment to CSF; dashed black lines represent the transfer from CSF to the brain and spinal cord compartments with available concentrations, blue full 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 full 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 1/2a	monarch STK-001-DS-101	admiral STK-001-DS-102
Design	Evaluation of STK-001*	Evaluation of STK-001 (up to 70 mg)
Status	• SAD: Dosing completed, up to 70 mg dose • MAD: Dosing completed up to 45 mg dose (Dosing on Day 1, Day 29 and Day 57)	• MAD: dosing completed, (Dosing on Day 1, Day 57 and Day 85)
Total number of patients	62	19
Primary Endpoint	Safety and tolerability of SAD and MAD dose levels	Safety and tolerability of MAD dose levels
	Characterize human plasma PK and 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

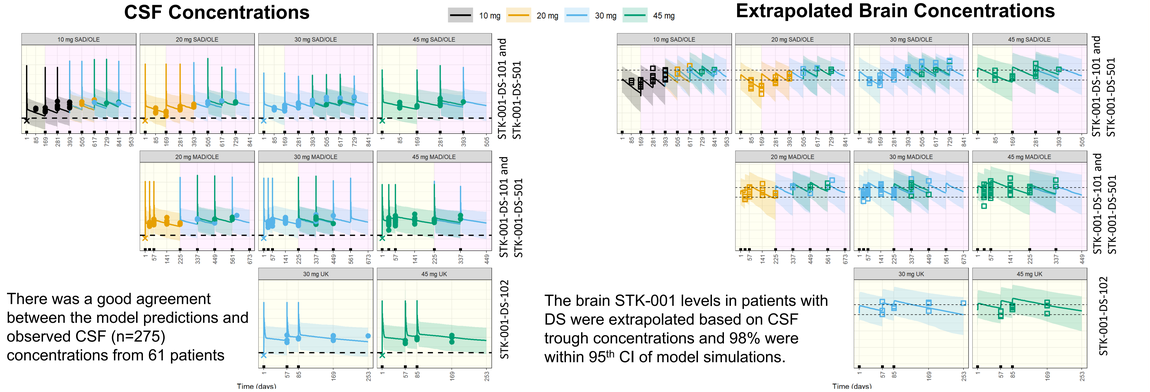
MAD = multiple ascending dose; N = number of patients; OLE = open-label extension; SAD = single ascending dose
*Doses >45 mg in MAD remain on FDA partial clinical hold
**Swallowtail dose level limited to 30 mg, Longwing dose level limited to 45 mg

4. Number of pediatric patients with DS-model development

Study	Cohorts	2 – 12 years old (N=40, 55.6%)	13 – 18 years old (N=32, 44.4%)
STK-001-DS-101 N= 53	10 mg SAD	2 (5.00%)	3 (9.38%)
	20 mg SAD	2 (5.00%)	2 (6.25%)
	30 mg SAD	4 (10.0%)	3 (9.38%)
	45 mg SAD	2 (5.00%)	3 (9.38%)
	20 mg MAD	2 (5.00%)	4 (12.5%)
	30 mg MAD	9 (22.5%)	5 (15.6%)
	45 mg MAD	8 (20.0%)	4 (12.5%)
STK-001-DS-501 N=43	10 mg OLE	2 (5.00%)	3 (9.38%)
	20 mg OLE	2 (5.00%)	3 (9.38%)
	30 mg OLE	9 (22.5%)	10 (31.5%)
	45 mg OLE	8 (20.0%)	6 (18.8%)
STK-001-DS-102 N=19	30 mg UK	2 (5.00%)	2 (6.25%)
	45 mg UK	2 (5.00%)	2 (6.25%)
	70 mg UK*	7 (17.5%)	4 (12.5%)

* Only plasma samples were available at 70 mg in Study STK-001-DS-102

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

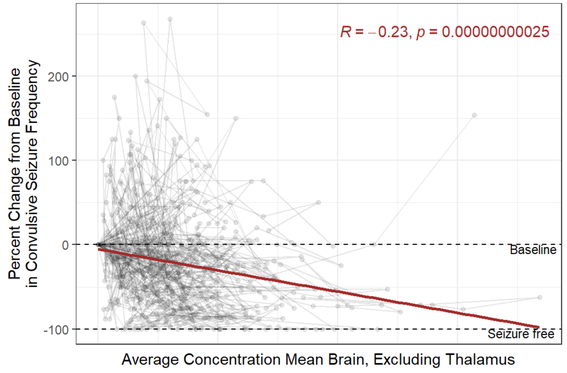


There was a good agreement between the model predictions and observed CSF (n=275) concentrations from 61 patients

The brain STK-001 levels in patients with DS were extrapolated based on CSF trough concentrations and 98% were within 95th CI of model simulations.

Solid line: Median of the predicted concentrations, Shaded area: 95th confidence interval (CI) (2.5th – 97.5th percentile) of the predicted concentrations. Dots and open squares represent individual measurable CSF and extrapolated brain concentrations, respectively. The cross represents BLQ concentration set to half of LLOQ (lower limit of quantification). Two dotted lines on the extrapolated brain concentrations graphs represent minimum pharmacologically active levels range estimated based on non-clinical PK/PD studies in mouse, rat and monkey. The Y-axis is plotted in log scale.

6. Overall Exposure-Seizure Relationship Across Studies



- All available seizure data was pooled from two Phase 1/2a and one OLE study.
- Seizures were measured as a count (% change from baseline) over various time intervals. The smallest resolution is 28 days.
- $C_{average}$ (AUC/time interval) concentration is simulated based on rich profiles and on posterior Bayes parameters (i.e., predictions at each day) over a period of 28 days.
- Significant negative trend for exposure-seizure correlation was observed based on simulated brain C_{avg} (R=-0.23, p <0.001)

7. Conclusions

- There was a good agreement between the human PK model predictions and observed plasma (not shown here) and CSF concentrations in DS patients treated with STK-001.
- The brain STK-001 levels in patients with DS were extrapolated based on CSF trough concentrations and 98% of the observations were within 95th CI of model simulations.
- The STK-001 PK model in DS patients helped in selecting the dosing regimen in Phase 1/2a and OLE studies based on the minimum pharmacologically active concentrations in brain that were determined from preclinical PK/PD studies.
- Exposure-seizure relationship evaluated based on two Phase 1/2a studies and one OLE study showed significant negative trend based on simulated brain C_{avg} (R=-0.23, p <0.001) demonstrating that higher STK-001 brain exposure leads to higher reduction in seizure frequency.
- The high confidence in the STK-001 PK model in patients with DS will help in identifying the optimal dosing regimen for a Phase 3 study.

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