UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): September 21, 2021

Stoke Therapeutics, Inc.
(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-38938**	**47-1144582**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

45 Wiggins Ave **Bedford, Massachusetts**	**01730**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (781) 430-8200

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**STOK**	**Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On September 21, 2021, Stoke Therapeutics, Inc. (the "Company") announced positive safety, pharmacokinetic ("PK") and cerebrospinal fluid ("CSF") exposure data from a planned interim analysis of the multi-center, open-label Phase 1/2a MONARCH study of STK-001 in children and adolescents with Dravet syndrome. STK-001 is an investigational new medicine for the treatment of Dravet syndrome. The MONARCH study is a U.S. multi-center, Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet syndrome. The study is designed to evaluate single-ascending doses ("SAD") and multiple ascending doses ("MAD") of STK-001. The primary objectives for the study are to assess the safety and tolerability of STK-001, as well as to characterize blood PK and CSF exposure levels. A secondary objective is to assess the efficacy of STK-001 as measured by the percentage change from baseline in convulsive seizure frequency over a 12-week treatment period.

The interim analysis is based on data from 21 patients who were treated in the single 10 mg (n=5), 20mg (n=4), or 30mg (n=6) dose cohorts of STK-001 and who were followed for at least three months after their dose. Also included in this analysis were six patients from the 20mg MAD dose cohort, most of whom had received three monthly doses of STK-001.

Despite concomitant use of multiple anti-seizure medicines, patients enrolled in MONARCH had a high seizure burden. Patients had a median of 17 convulsive seizures during the 4-week screening period leading up to their first dose of STK-001. More than 85% (18/21) of patients were taking three or more concomitant anti-seizure medicines as maintenance therapy and 67% (14/21) were taking four or more concomitant medicines. The most commonly used anti-seizure medicines were clobazam (13/21, 62%) and fenfluramine (10/21, 48%).

Key findings from the MONARCH study interim analysis include:

- Single doses of STK-001 up to 30mg and multiple doses of STK-001 at 20mg were found to be well-tolerated with no safety concerns related to the drug.
- The most common treatment emergent adverse events ("TEAE") were headache, irritability, vomiting, seizure, and back pain.
- 3/21 (14%) of patients experienced a TEAE that was related to study drug. None of these patients were in the two higher dose groups (30mg single dose or 20mg multiple dose).
- 4/21 (19%) of patients had a treatment-emergent serious adverse event ("SAE"). There were no SAEs related to study drug.
- A dose proportional increase in study drug exposure was observed in plasma PK.
- CSF exposure was measurable up to 6 months following a single intrathecal ("IT") dose, indicating sustained exposure of STK-001 in the brain. A dose-proportional increase in CSF concentration was observed from 20mg to 30mg.
- Preliminary analyses of daily seizure diaries suggested a trend toward a reduction in median percent change from baseline in convulsive seizure frequency among patients treated with single doses of STK-001. This trend was more evident in the 2 to 12 year-old age group.
- Based on data available from 11 patients in the SAD cohorts (10mg, 20mg, 30mg), 8 out of 11 patients demonstrated a reduction in convulsive seizure frequency.

No patients discontinued study treatment and, at the time of the analysis, all patients who completed dosing in the SAD portion of MONARCH continued treatment in SWALLOWTAIL, an open label extension study designed to evaluate the long-term safety and tolerability of repeat doses of STK-001.

PK Model Findings

- A population pharmacokinetic model for intrathecal STK-001 was developed using non-human primate data and was scaled and adjusted using clinical data to predict STK-001 concentrations in plasma, CSF and brain in pediatric patients with Dravet syndrome.
- Data from the MONARCH study showed that STK-001 levels in plasma and CSF in patients treated with STK-001 correlated very well with model predictions, indicating that plasma and CSF levels observed in patients are good predictors of STK-001 brain levels in patients.
- Estimated pharmacologically active levels of STK-001 in the brain are conservatively defined as those that could result in a 2-fold increase in Nav1.1, which is anticipated to restore normal physiologic levels in patients' brain cells.

- Modeling of early clinical data suggests that 95% of patients are predicted to have pharmacologically active STK-001 brain levels following three doses of 30mg administered one month apart. Half of all patients are anticipated to remain at therapeutic levels for approximately 3 months after the last dose.

Clinical Progress Updates

- In September, the first patient was dosed in the 30mg MAD portion of the ongoing Phase 1/2a MONARCH study.
- In September, the first patient was dosed with STK-001 (30mg) in the Phase 1/2a ADMIRAL study of STK-001 for the treatment of children and adolescents with Dravet syndrome in the United Kingdom. This study complements the Company's ongoing MONARCH study by evaluating multiple doses of STK-001 up to 70mg.
- Following recent interactions with the U.S. Food and Drug Administration ("FDA") related to the partial clinical hold on higher dose levels in the MONARCH study, the FDA will allow the Company to add an additional higher dose level (45mg) to the SAD and MAD portions of the MONARCH study.
- The Company expects to provide greater detail on data from the MONARCH study at the American Epilepsy Society annual meeting December 3-7, 2021 in Chicago, IL.
- The company expects to share clinical data from multiple doses of 30mg in the second half of 2022.

A copy of the presentation regarding the data announcement is attached as Exhibit 99.1 to this Current Report on Form 8-K.

Cautionary Note Regarding Forward-Looking Statements

This report contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: the ability of STK-101 to treat Dravet syndrome and reduce seizures, the timing and expected progress of clinical trials, data readouts and presentations, and the timing or receipt of regulatory approval. Statements including words such as "plan," "will," "continue," "expect," or "ongoing" and statements in the future tense are forward-looking statements. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they do not fully materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Forward-looking statements are subject to risks and uncertainties that may cause the company's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to the Company's ability to advance its product candidates, obtain regulatory approval of and ultimately commercialize its product candidates, the timing and results of preclinical and clinical trials, the company's ability to fund development activities and achieve development goals, the company's ability to protect intellectual property and other risks and uncertainties described under the heading "Risk Factors" in documents the company files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and the Company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Presentation, dated as of September 2021.
104	Cover Page Interactive Data File (the cover page XBRL tags are embedded within the inline XBRL document).

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

STOKE THERAPEUTICS, INC.

Date: September 21, 2021

By: /s/ Stephen J. Tulipano
Stephen J. Tulipano
Chief Financial Officer

Exhibit 99.

MONARCH study in Dravet Syndrome
Interim Analysis

September 21, 2021

Agenda

- **Introduction**
  Eric Rojas, Head of Investor Relations

- **Disease Overview, Patient Need, and STK-001 Mechanism of Action**
  Edward M. Kaye, M.D., Chief Executive Officer

- **Phase 1/2a MONARCH Interim Analysis**
  Barry Ticho, M.D., Ph.D., Chief Medical Officer

- **Closing Remarks**
  Edward M. Kaye, M.D., Chief Executive Officer

- **Q&A**

Forward Looking Statements

This presentation has been prepared by Stoke Therapeutics, Inc. ("Stoke" or "our") for informational purposes only and not for any other purpose. Nothing contained in this presentation is, or should be construed as, a recommendation, promise or representation by the presenter or Stoke or any officer, director, employee, agent or advisor of Stoke. This presentation does not purport to be all-inclusive or to contain all of the information you may desire. Information provided in this presentation speaks only as of the date hereof. Stoke assumes no obligation to publicly update any information or forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments, subsequent events, or circumstances after the date hereof, or to reflect the occurrence of unanticipated events.

This presentation contains "forward-looking" statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: the ability of STK-001 to treat Dravet syndrome and reduce seizures, the timing and expected progress of clinical trials, data readouts, milestones and presentations, and the timing or receipt of regulatory approval. These forward-looking statements may be accompanied by such words as "anticipate," "believe," "could," "estimate," "expect," "intend," "likely," "may," "might," "plan," "potential," "possible," "will," "would," and other words and terms of similar meaning. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they do not fully materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Forward-looking statements are subject to risks and uncertainties that may cause the company's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to the Company's ability to advance its product candidates, obtain regulatory approval of and ultimately commercialize its product candidates, the timing and results of preclinical and clinical trials, the company's ability to fund development activities and achieve development goals, the company's ability to protect intellectual property and other risks and uncertainties described under the heading "Risk Factors" in documents the company files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and the Company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof. These statements are based on our current beliefs and expectations and speak only as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements.

By attending or receiving this presentation you acknowledge that you are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made; you will be solely responsible for your own assessment of the market and our market position; and that you will conduct your own analysis and be solely responsible for forming your own view of the potential future performance of Stoke.

Dravet Syndrome Disease Overview
STK-001 Mechanism of Action

Edward M. Kaye, M.D.
Chief Executive Officer

Dravet Syndrome: A Severe, Progressive Genetic Epilepsy

85%
of cases caused by a **HAPLOINSUFFICIENCY** of the *SCN1A* gene

RESULTS IN

50%
$Na_V1.1$ protein expression

1 out of 16,000
babies are born with Dravet syndrome

Up to 20%
of children and adolescents with Dravet syndrome die before adulthood, due to SUDEP[1], prolonged seizures, seizure-related accidents or infections

Seizures are not adequately controlled in **90%** of people with Dravet syndrome

~35,000
people affected in the U.S., Canada, Japan, Germany, France and the UK

Dravet syndrome is not concentrated in a particular geographic area or ethnic group

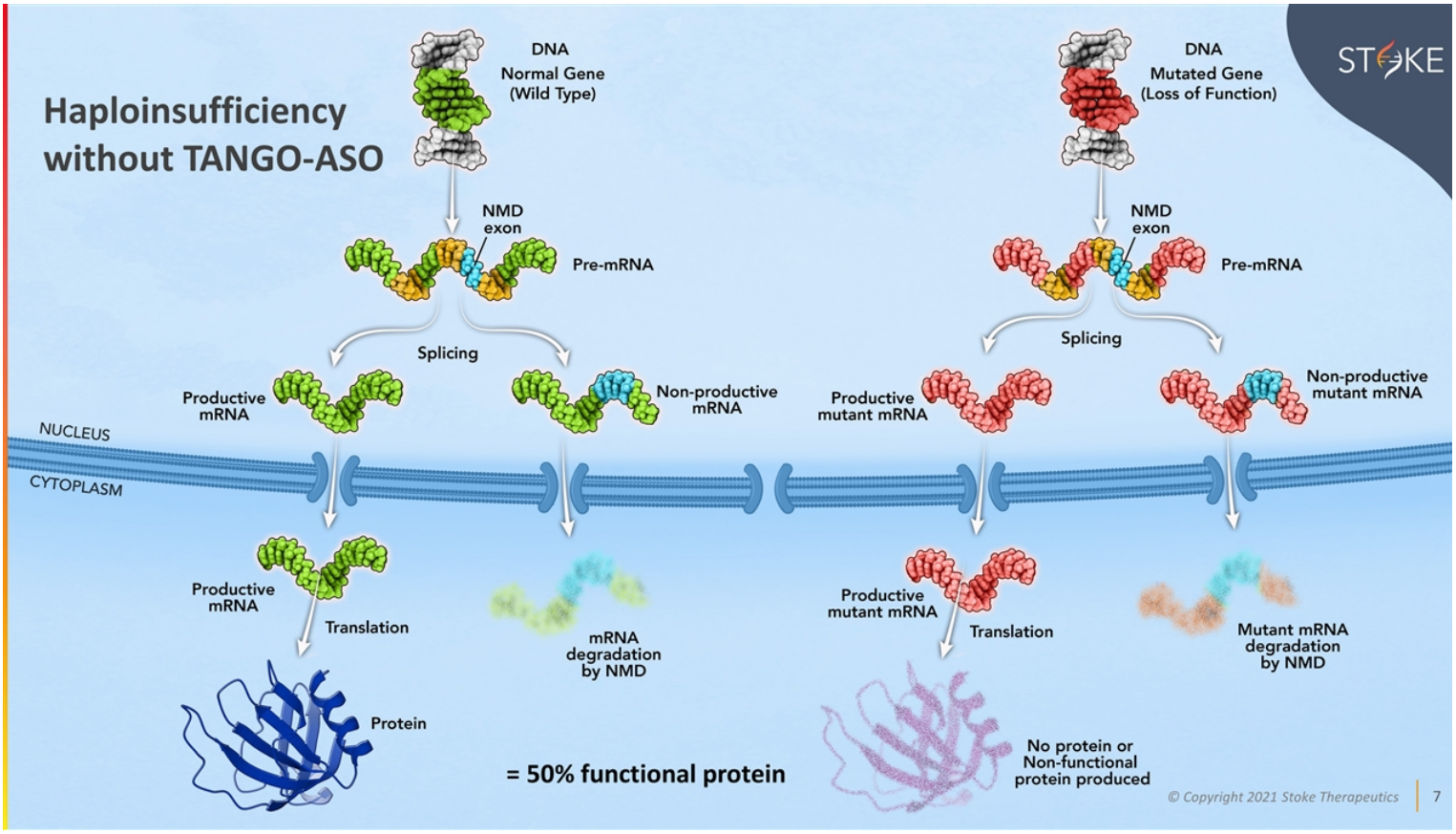
[1] Sudden Unexpected Death in Epilepsy

Sources: *2018 Health Advances Report*; Djémié et al., *Molecular Genetics & Genomic Medicine*, 2016; Lagae et al., *Developmental Medicine & Child Neurology*, 2017; Nabbout et al., *Orphanet Journal of Rare Diseases*, 2013

No Approved Disease-Modifying Therapies for Dravet Syndrome

Non-Seizure Comorbidities of Dravet Syndrome Are Not Addressed by Current Therapies

- Intellectual disability
- Developmental delays
- Movement and balance issues
- Language and speech disturbances
- Growth defects
- Sleep abnormalities
- Disruptions of the autonomic nervous system
- Mood disorders


Haploinsufficiency without TANGO-ASO
DNA
Normal Gene (Wild Type)
NMD exon
Pre-mRNA
Splicing
Productive mRNA
Non-productive mRNA
NUCLEUS
CYTOPLASM
Productive mRNA
Translation
Protein
mRNA degradation by NMD
= 50% functional protein
DNA
Mutated Gene (Loss of Function)
NMD exon
Pre-mRNA
Splicing
Productive mutant mRNA
Non-productive mutant mRNA
Productive mutant mRNA
Translation
No protein or Non-functional protein produced
Mutant mRNA degradation by NMD
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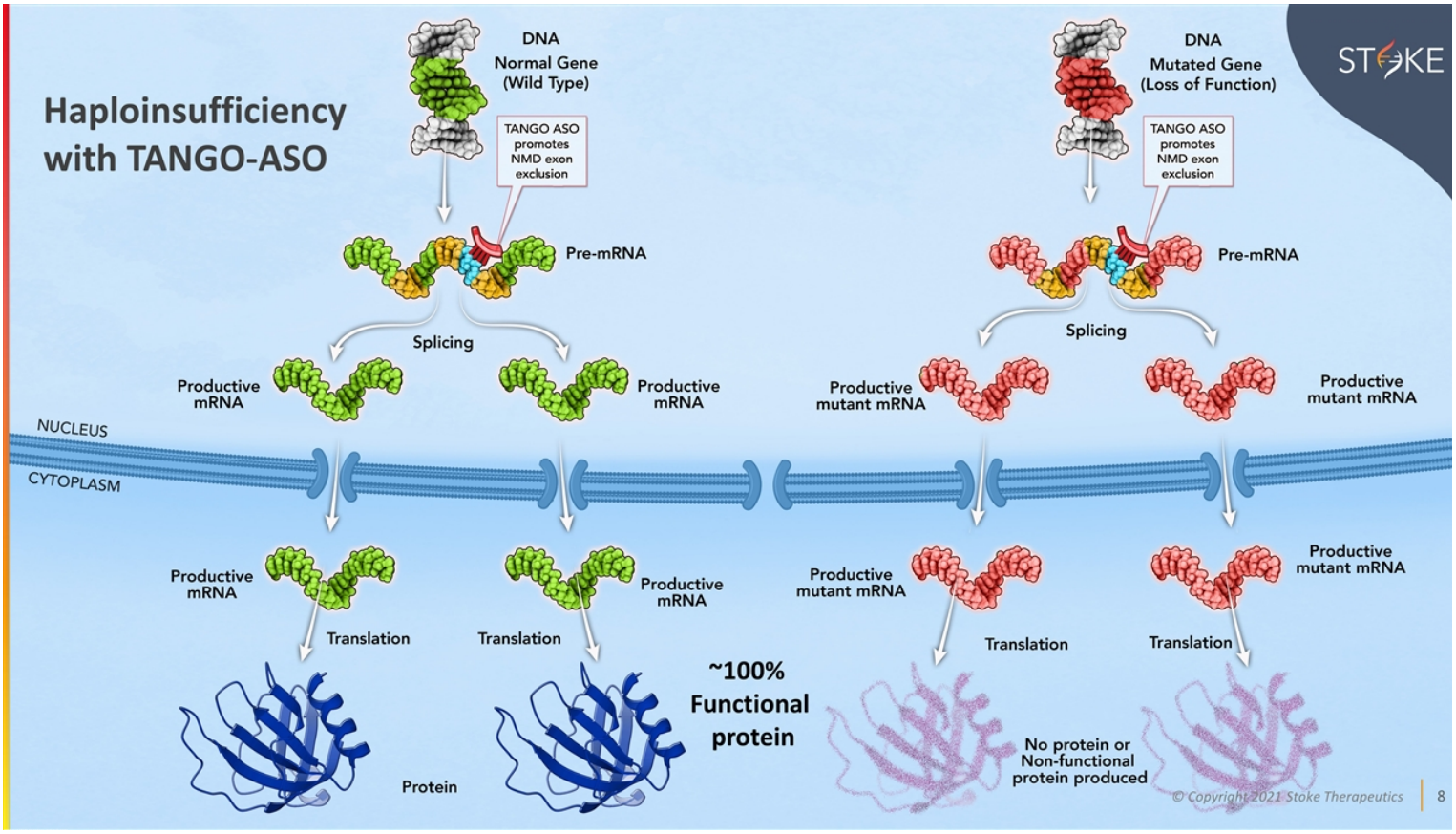


Studies of STK-001 Ongoing in the U.S. and UK

monarch
A DRAVET SYNDROME STUDY

Open-label evaluation of single and multiple ascending doses of STK-001 in the U.S.

- Interim results show single doses of STK-001 up to 30mg and multiple doses of 20mg were well-tolerated with no safety concerns related to the study drug
- First patient dosed in MAD portion at 30mg
- FDA will allow the evaluation of an additional higher dose level (45mg)

admiral
A DRAVET SYNDROME STUDY

Open-label evaluation of multiple ascending doses of STK-001 (up to 70mg) in the UK

- First patient dosed at 30mg

Phase 1/2a MONARCH Interim Analysis

Barry Ticho, M.D., Ph.D.
Chief Medical Officer

MONARCH Study Design and Objectives

Design:

- Multi-center, open-label, SAD and MAD study of STK-001 in patients with Dravet syndrome conducted in U.S.
- SAD: 3 cohorts (10 mg, 20mg, 30mg) with study drug administration at Day 1
- MAD: 2 cohorts (20mg, 30mg) with study drug administrations at Day 1, Week 4 (Day 29), and Week 8 (D57)
- All patients in SAD and MAD portion of study are followed for 6 months after last dose
- Study duration for each patient approximately 7 months (SAD) and 9 months (MAD)

Primary Objectives:

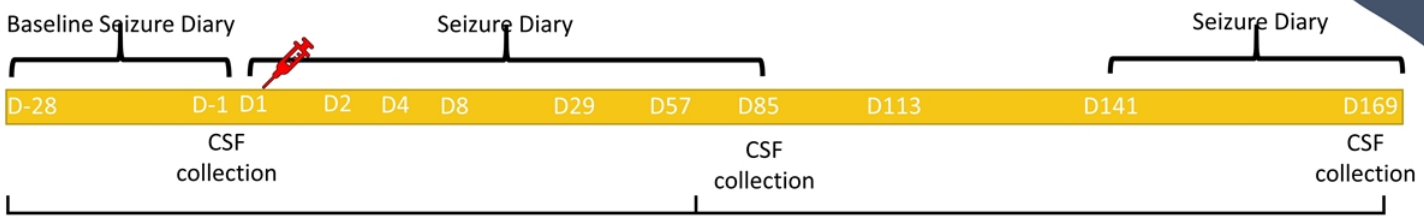
- Evaluate safety and tolerability of SAD and MAD of STK-001
- Determine pharmacokinetics (PK) of SAD and MAD of STK-001 in plasma and exposure in CSF

monarch
A DRAVET SYNDROME STUDY

Secondary Objectives:

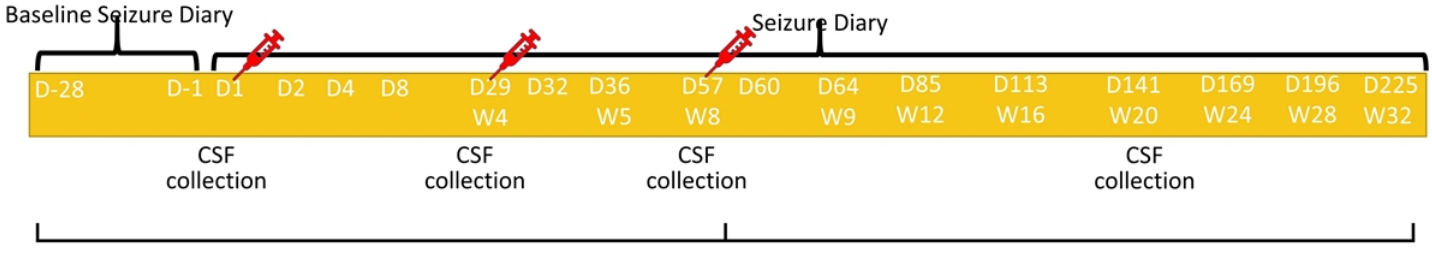
- Assess effect of SAD and MAD of STK-001:
  - As an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency
  - On overall clinical status and quality of life (not included in this interim analysis)

MONARCH SAD Study Assessments



AE monitoring, Physical Examination, Clinical laboratories, Plasma PK

MONARCH MAD Study Assessments



AE monitoring, Physical Examination, Clinical laboratories, Plasma PK

= Study Drug Administration

MONARCH Study Interim Analysis Included 21 Patients, All of Whom Had Severe Disease Despite Use of Anti-Seizure Medications

No patients withdrew from the study

Cohort A1
10mg SAD
(n=5)

Cohort A2
20mg SAD
(n=4)

Cohort A3
30mg SAD
(n=6)

Cohort B1
20mg MAD
(n=6)

Analysis conducted 3-months after the last patient was treated with 30mg (SAD)

All patients received ≥1 dose of STK-001

Age at Screening, years	
Median (min, max)	13.0 (2, 18)
Age of onset of first seizure type (months)	
Mean (SD)	4.85 (2.242)
Median (min, max)	4.00 (2.0, 11.0)
Observed baseline convulsive seizure frequency (per 28 days)	
Mean (SD)	54 (128.564)
Median (min, max)	17 (3.0, 591.0)
Number of concomitant anti-seizure medications as maintenance therapy	
85% (18/21) of patients used ≥3 concomitant anti-seizure medications; 66.7% (14/21) used ≥4	Most common medications were clobazam (61.9%) and fenfluramine (47.6%)

Single Doses of STK-001 up to 30mg and Multiple Doses of 20mg Were Well-Tolerated and No Safety Concerns Related to STK-001

- 3 of 21 (14.3%) patients experienced a TEAE related to study drug
  - None observed in 30mg SAD or 20mg MAD cohorts
- 4 of 21 (19.0%) patients had a treatment-emergent SAE
  - None related to study drug
- No new clinically significant neurologic exam findings emerged and no sign of lower extremity weakness
- No increase in seizures were identified in 1 hour EEG recorded ~24 hours post-dose
- No clinically significant changes in blood coagulation, liver function, or renal function parameters were observed

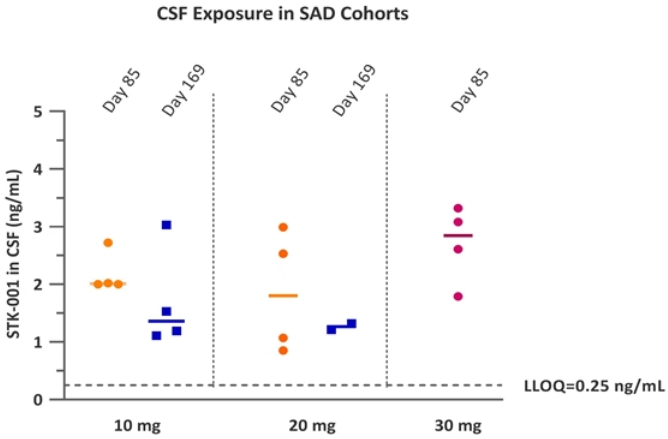
Increases in Plasma Exposure **and** Mean CSF Concentration Observed in Patients Who Received Doses From 10mg to 30mg

A dose-proportional increase in study drug exposure was observed in plasma PK

Dose (mg)	Plasma PK parameters	
	N	AUC_{last} (h*ng/mL) (Mean ± SD)
10	4	2450 ± 1690
20	4	6460 ± 2820
30	5	11600 ± 7110

- Mean group AUC_{last} increased 2.6- and 4.7-fold for dose increase of 2- and 3-fold, respectively

A dose-proportional increase in CSF concentration was observed from 20mg to 30mg

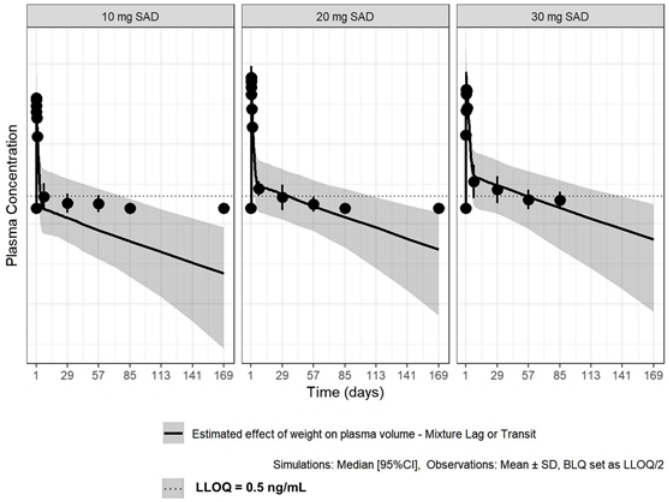


- STK-001 levels were detected in CSF to last collection i.e., Day 169 for 10 and 20 mg Cohorts, and Day 85 for 30 mg Cohort
- Measurable CSF Exposure up to 6 Months Post Single IT Dose Indicated Sustained Exposure in Brain

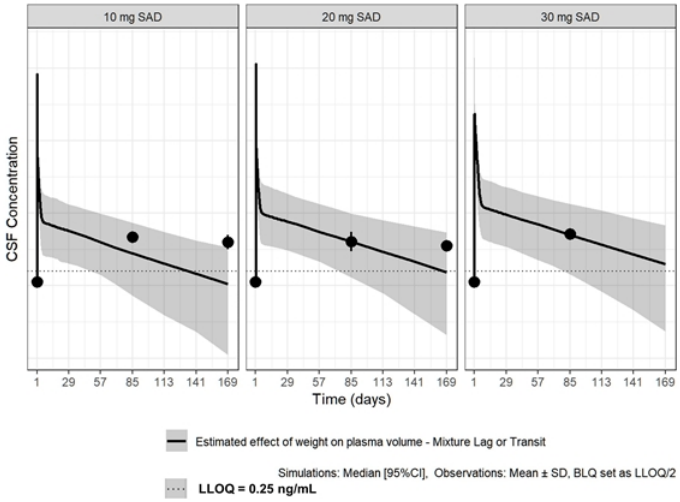
Note: AUC=Area Under the Curve; CSF=Cerebrospinal Fluid; IT=Intrathecal; LLOQ=Lower Limit of Quantification; PK=Pharmacokinetic; SAD=Single Ascending Dose

Observed Plasma and CSF Levels in Patients Correlated Well with Model Predictions

Comparison of PK Model Predictions
With Mean Observed **Plasma** Data



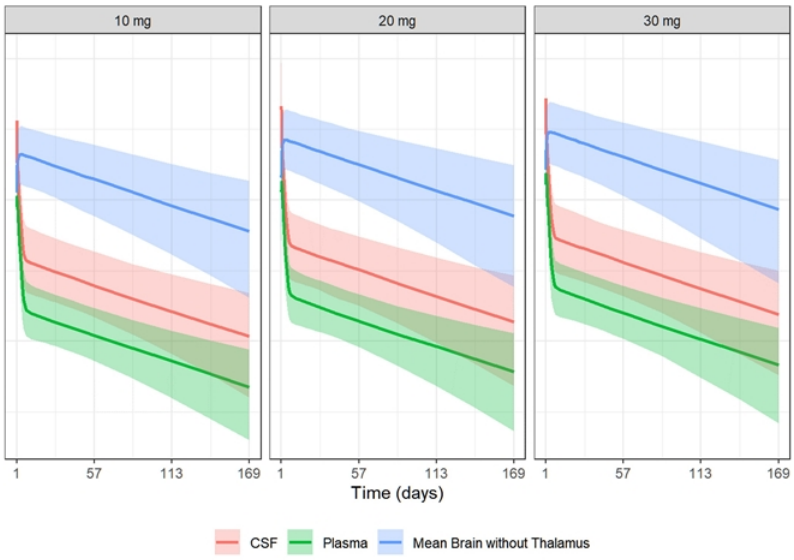
Comparison of PK Model Predictions
With Mean Observed **CSF** Data



Solid lines represent median and shaded areas represent 95% CI.
Black dots represent observed data from clinical trial

- CSF was drawn on Days 85 and 169 post single dose for STK-001 analyses

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

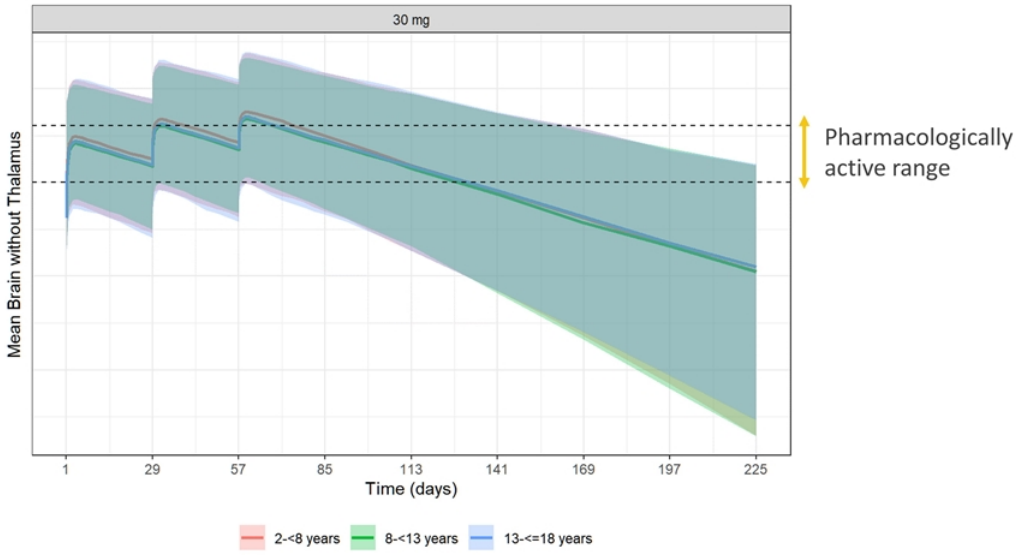


- Projected plasma, CSF, and brain levels were strongly correlated across time and dose groups following single IT STK-001 doses
- Therefore, CSF and/or plasma levels in MONARCH can be used to estimate STK-001 levels in brain

Note: Solid lines represent median and all shaded areas represent 95% CI

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

~50% of patients anticipated to remain at active levels approximately 3 months after their last dose



Pharmacologic effect likely lasts beyond timepoint when STK-001 brain concentration falls below minimum level

Secondary Endpoint: Trend Toward Seizure Reduction Observed

Based on data available from 11 patients in the SAD cohorts (10mg, 20mg, 30mg)

- 8/11 patients experienced a reduction in convulsive seizure frequency
- Trend more evident in patients 2 to 12 years old
- Patients in the study were taking multiple anti-seizure medicines: 85% on ≥3 and 67% ≥4
- Data being prepared for presentation at the American Epilepsy Society annual meeting in early December

Dravet Syndrome Program Continues to Progress

swallowtail
A DRAVET SYNDROME EXTENSION STUDY

All patients who have completed dosing in the SAD portion of MONARCH have continued treatment in SWALLOWTAIL

monarch
A DRAVET SYNDROME STUDY

First patient dosed in MONARCH MAD at 30mg

FDA will allow the evaluation of STK-001 up to 45mg in MONARCH

admiral
A DRAVET SYNDROME STUDY

First patient dosed at 30mg in ADMIRAL UK Study evaluating multiple doses up to 70mg

We expect to share clinical data from multiple doses of 30mg in the second half of 2022

Acknowledgements

Closing Remarks

Edward M. Kaye, M.D.
Chief Executive Officer

Overall Summary of MONARCH Interim Analysis Results

- Single doses of STK-001 up to 30mg and multiple doses of 20mg were well-tolerated and no safety concerns related to the study drug
- Interim analysis confirms our pre-clinical work and gives us greater understanding of dose levels that are likely to be pharmacologically active in patients
- Interim findings support the advancement of STK-001 as the first potentially disease-modifying treatment for patients with Dravet syndrome

2021 Milestones as of September 2021

1H2021	Initiate Swallowtail Open Label Extension (OLE) study of STK-001	✓
2H2021	Initiate MAD study of STK-001 (MONARCH) – COMPLETED IN 1H2021	✓
3Q2021	Preliminary safety, PK, CSF, and modeling data from SAD portion of MONARCH	✓
2H2021	Initiate MAD study of STK-001 in the U.K. (ADMIRAL)	✓
2H2021	Initiate ADOA natural history data collection	
YE2021	Identify a clinical candidate for the treatment of ADOA	
YE2021	Demonstrate *in vivo* proof of mechanism & safety for a third TANGO ASO program	

Q&A