Stoke Therapeutics Announces Positive Interim Safety, PK and CSF Exposure Data from the Phase 1/2a MONARCH Study of STK-001 in Children and Adolescents with Dravet Syndrome

September 21, 2021

– Results show that 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 –

– A trend toward a reduction in convulsive seizure frequency was observed among patients treated with single doses of STK-001 –

– >95% of patients anticipated to achieve pharmacologically active levels of STK-001 with three monthly doses of 30mg –

– Complementary Phase 1/2a studies ongoing; First patients dosed in the 30mg multiple ascending dose (MAD) cohorts of MONARCH in the U.S. and ADMIRAL in the UK –

– FDA will allow the evaluation of an additional higher dose level (45mg) in the MONARCH study –

– Management will host a webinar and conference call for analysts and investors at 8:30 a.m. Eastern Time today –

BEDFORD, Mass.--(BUSINESS WIRE)--Sep. 21, 2021-- Stoke Therapeutics, Inc. (Nasdaq: STOK), a biotechnology company dedicated to addressing the underlying cause of severe diseases by upregulating protein expression with RNA-based medicines, today 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. As part of today's announcement, the company is providing several updates on the clinical progress of STK-001. Management will host a webinar and conference call today at 8:30 a.m. Eastern Time.

Dravet syndrome is a severe and progressive genetic epilepsy characterized by frequent, prolonged and refractory seizures, beginning within the first year of life. Complications of the disease often contribute to poor quality of life for patients and their caregivers. Stoke believes that STK-001, a proprietary antisense oligonucleotide (ASO), has the potential to be the first disease-modifying therapy to address the genetic cause of Dravet syndrome.

"Dravet syndrome is a devastating disease that is difficult to treat. Despite available anti-seizure medicines, seizures are not adequately controlled for more than 90% of patients, contributing to poor quality of life," said Barry Ticho, M.D., Ph.D., Chief Medical Officer of Stoke Therapeutics. "The initial positive safety data from MONARCH are highly encouraging and we now have greater clarity on the dose levels that are likely to be pharmacologically active in patients. Although based on an open-label study of a small number of patients, we saw an early trend toward a reduction in convulsive seizure frequency, which is remarkable considering the amount of concomitant medicines used and the relatively low single dose levels of STK-001 evaluated. We look forward to continuing our two ongoing studies as we work to identify a dose level that has the potential to maximize efficacy while minimizing treatment frequency for patients with Dravet syndrome."

Study Design
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 10mg (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 last 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 study 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 six 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 a patient's 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 three 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.
- The Company expects to share clinical data from multiple doses of 30mg in the second half of 2022.

Stoke Webinar and Conference Call for Analysts and Investors
Stoke will host a webinar and conference call for analysts and investors at 8:30 a.m. Eastern Time on Tuesday, September 21, 2021, to present the interim data from the Phase 1/2a MONARCH study of STK-001. To participate in the call, please dial (866) 996-7187, or (270) 215-9492 for international callers and provide conference ID number 1568363. The webinar will be broadcast live on the Investors & Media section of Stoke's website at https://investor.stoketherapeutics.com/ and can be accessed by following this Link. An archived replay of the webinar will be available for at least 30 days following the event.

About Dravet Syndrome
Dravet syndrome is a severe and progressive genetic epilepsy characterized by frequent, prolonged and refractory seizures, beginning within the first year of life. Dravet syndrome is difficult to treat and has a poor long-term prognosis. Complications of the disease often contribute to a poor quality of life for patients and their caregivers. The effects of the disease go beyond seizures and often include intellectual disability, developmental delays, movement and balance issues, language and speech disturbances, growth defects, sleep abnormalities, disruptions of the autonomic nervous system and mood disorders. The disease is classified as a developmental and epileptic encephalopathy due to the developmental delays and cognitive impairment associated with the disease. Compared with the general epilepsy population, people living with Dravet syndrome have a higher risk of sudden unexpected death in epilepsy, or SUDEP. There are no approved disease modifying therapies for people living with Dravet syndrome. One out of 16,000 babies are born with Dravet syndrome, which is not concentrated in a particular geographic area or ethnic group.

About STK-001
STK-001 is an investigational new medicine for the treatment of Dravet syndrome that is currently being evaluated in ongoing clinical trials. Stoke believes that STK-001, a proprietary antisense oligonucleotide (ASO), has the potential to be the first disease-modifying therapy to address the genetic cause of Dravet syndrome. STK-001 is designed to upregulate $Na_V1.1$ protein expression by leveraging the non-mutant (wild-type) copy of the *SCN1A* gene to restore physiological $Na_V1.1$ levels, thereby reducing both occurrence of seizures and significant non-seizure comorbidities. Stoke has generated preclinical data demonstrating proof-of-mechanism and proof-of-concept for STK-001. STK-001 has been granted orphan drug designation by the FDA as a potential new treatment for Dravet syndrome.

About Phase 1/2a MONARCH Study (United States)
The MONARCH study is a Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet

syndrome and have evidence of a pathogenic genetic mutation in the *SCN1A* gene. The primary objectives for the study are to assess the safety and tolerability of STK-001, as well as to characterize blood pharmacokinetics. A secondary objective is to assess the efficacy as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency over a 12-week treatment period. Stoke also intends to measure non-seizure aspects of the disease, such as quality of life, as secondary endpoints. Stoke plans to enroll approximately 48 patients in the study across 20 sites in the United States. Additional information about the MONARCH study can be found at https://www.monarchstudy.com/.

Patients who participated in the MONARCH study are eligible to continue treatment in SWALLOWTAIL, an open label extension (OLE) study designed to evaluate the long-term safety and tolerability of repeat doses of STK-001. Enrollment and dosing in SWALLOWTAIL are underway.

About Phase 1/2a ADMIRAL Study (United Kingdom)
The ADMIRAL study is a Phase 1/2a open-label study of children and adolescents ages 2 to <18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study are to assess the safety and tolerability of multiple doses of STK-001, as well as to characterize blood pharmacokinetics. A secondary objective is to assess the effect of multiple doses of STK-001 as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency over a 24-week treatment period. Stoke also intends to measure non-seizure aspects of the disease, such as overall clinical status and quality of life, as secondary endpoints. Stoke plans to enroll approximately 22 patients in the study across multiple sites in the United Kingdom. Additional information about the ADMIRAL study can be found at https://www.admiralstudy.com.

About TANGO
TANGO (Targeted Augmentation of Nuclear Gene Output) is Stoke's proprietary research platform. Stoke's initial application for this technology are diseases in which one copy of a gene functions normally and the other is mutated, also called haploinsufficiencies. In these cases, the mutated gene does not produce its share of protein, so the body does not function normally. Using the TANGO approach and a deep understanding of RNA science, Stoke researchers design antisense oligonucleotides (ASOs) that bind to pre-mRNA and help the target genes produce more protein. TANGO aims to restore missing proteins by increasing – or stoking – protein output from healthy genes, thus compensating for the non-functioning copy of the gene.

About Stoke Therapeutics
Stoke Therapeutics (Nasdaq: STOK), is a biotechnology company dedicated to addressing the underlying cause of severe diseases by up-regulating protein expression with RNA-based medicines. Using the Company's proprietary TANGO (Targeted Augmentation of Nuclear Gene Output) approach, Stoke is developing antisense oligonucleotides (ASOs) to selectively restore protein levels. The Company's first compound, STK-001, is in clinical testing for the treatment of Dravet syndrome, a severe and progressive genetic epilepsy. Dravet syndrome is one of many diseases caused by a haploinsufficiency, in which a loss of ~50% of normal protein levels leads to disease. The Company is pursuing treatment for a second haploinsufficient disease, autosomal dominant optic atrophy (ADOA), the most common inherited optic nerve disorder. Stoke's initial focus is haploinsufficiencies and diseases of the central nervous system and the eye, although proof of concept has been demonstrated in other organs, tissues, and systems, supporting the Company's belief in the broad potential for its proprietary approach. Stoke is headquartered in Bedford, Massachusetts with offices in Cambridge, Massachusetts. For more information, visit https://www.stoketherapeutics.com/ or follow the Company on Twitter at @StokeTx.

Cautionary Note Regarding Forward-Looking Statements
This press release 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.

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