Stoke Therapeutics Announces MHRA Authorization to Initiate Phase 1/2a Clinical Trial of STK-001 for Dravet Syndrome in the United Kingdom

March 30, 2021

– New ADMIRAL study complements ongoing U.S. studies and marks first step in global expansion of clinical development of STK-001 –

– Study will evaluate safety and PK of multiple doses of STK-001 starting at 30mg; Enrollment and dosing anticipated to begin in 2H 2021 –

– STK-001 has the potential to be the first disease-modifying therapy to address the root cause of Dravet syndrome, a severe and progressive genetic epilepsy –

BEDFORD, Mass.--(BUSINESS WIRE)--Mar. 30, 2021-- Stoke Therapeutics, Inc. (Nasdaq: STOK), a biotechnology company dedicated to addressing the underlying cause of severe diseases by up-regulating protein expression with RNA-based medicines, today announced the authorization of its Clinical Trial Application (CTA) by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) to initiate a Phase 1/2a study (ADMIRAL) of STK-001 for the treatment of Dravet syndrome.

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, a severe and progressive genetic epilepsy characterized by frequent, prolonged and refractory seizures that usually begin within the first year of life. Dravet syndrome is classified as a developmental and epileptic encephalopathy resulting in developmental delay and cognitive impairment, in addition to seizure activity, that arise from the genetic mutation that causes the disease.

“We are making excellent progress with our ongoing studies of STK-001 in the U.S. The high level of interest from the Dravet community underscores the urgent need for new treatment options that go beyond seizure control,” said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. “The ADMIRAL study complements our U.S.-based MONARCH study, enabling the evaluation of higher dose levels of STK-001 and representing an initial step in the expansion of our global clinical development efforts. Together, we anticipate that these studies will generate a comprehensive set of data that will inform our future development plans. We look forward to working with the U.K. Dravet community – patients, families and healthcare providers – to add to our understanding of the potential for STK-001 to be the first disease-modifying therapy for Dravet syndrome.”

ADMIRAL is an open-label, multi-center, Phase 1/2a study designed to assess the safety and tolerability of multiple doses of up to 70mg of STK-001, as well as to characterize human pharmacokinetics. Secondary endpoints include change in seizure frequency and quality of life measures. The study is expected to enroll approximately 22 children and adolescents with Dravet syndrome across multiple clinical sites in the United Kingdom. Patient enrollment and dosing are expected to start in the second half of 2021.

“Current treatments for Dravet syndrome help us manage seizures, but some of the most devastating effects of the disease such as developmental and intellectual disabilities are not addressed by current therapies,” said Professor Helen Cross, Honorary Consultant in Paediatric Neurology at Great Ormond Street Hospital for Children NHS Foundation Trust. “There is great hope that a new approach, such as STK-001, that targets the root cause of the disease, may address the seizures as well as the myriad of devastating comorbidities that have impacts on patients and their families. I’m pleased to be helping lead the effort to bridge the treatment gap by conducting the first study of STK-001 in the U.K. as the lead investigator for the ADMIRAL study.”

MONARCH Phase 1/2a Clinical Trial is Ongoing in the United States

Enrollment of children and adolescents in the first two single ascending dose (SAD) cohorts (10mg and 20mg) is complete and enrollment and dosing in the third (30mg) SAD cohort is underway. Dosing above 30mg in this study remains on partial clinical hold with the U.S. Food and Drug Administration (FDA). Preliminary safety and pharmacokinetic data from the SAD portion of the MONARCH study are expected in the second half of 2021.

In addition, enrollment and dosing in the multiple ascending dose (MAD) portion of the MONARCH study is underway at the 20mg dose level. 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 STK-001

STK-001 is an investigational new medicine for the treatment of Dravet syndrome and is being evaluated in a Phase 1/2a clinical trial. 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 up-regulate $Na_V1.1$ 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 the Phase 1/2a MONARCH Clinical 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 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 human pharmacokinetics. A secondary objective is to assess the effect 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. Enrollment and dosing are ongoing in MONARCH and 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 the 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 human 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.

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 severe intellectual disabilities, severe developmental disabilities, motor impairment, speech impairment, autism, behavioral difficulties and sleep abnormalities. 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. Approximately 85% of those diagnosed with Dravet syndrome have a mutation of the *SCN1A* gene. Dravet syndrome affects approximately 35,000 people in the United States, Canada, Japan, Germany, France and the United Kingdom, and it is not concentrated in a particular geographic area or ethnic group.

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: enrollment in the ADMIRAL study and the study's ability to support our clinical development plans; our expectation about timing and execution of anticipated milestones; our ability to use ADMIRAL or MONARCH study data to advance the development of STK-001; the ability of STK-001 to treat the underlying causes of Dravet syndrome and the expected benefits thereof; and the ability of TANGO to design medicines to increase protein production and the expected benefits thereof. These forward-looking statements may be accompanied by such words as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "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. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: our ability to develop, obtain regulatory approval for and commercialize STK-001, any potential clinical candidate for OPA1 and future product candidates; the timing and results of preclinical studies and clinical trials; the risk that positive results in a clinical trial may not be replicated in subsequent trials or success in early stage clinical trials may not be predictive of results in later stage clinical trials; risks associated with clinical trials, including our ability to adequately manage clinical activities and activities in international jurisdictions; the risk that regulatory authorities may require additional information or further studies, or may fail to approve or may delay approval of our drug candidates; the occurrence of adverse safety events; failure to protect and enforce our intellectual property and other proprietary rights; risks associated with current and potential delays, work stoppages, or supply chain disruptions caused by the coronavirus pandemic; risks associated with current and potential future healthcare reforms; failure to comply with legal and regulatory requirements in the United States and abroad; and the other risks and uncertainties that are described in the Risk Factors section of our most recent annual or quarterly report and in other reports we have filed with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations and speak only as of the date of this press release. We do not undertake any obligation to publicly update any forward-looking statements.

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