Stoke Therapeutics Receives Authorization to Initiate a Phase 1/2 Study of STK-002 for Autosomal Dominant Optic Atrophy (ADOA) in the United Kingdom

April 25, 2023

– Company advancing second TANGO ASO into the clinic –

– STK-002 has the potential to be the first disease-modifying therapy to address the root cause of ADOA, the most common inherited optic nerve disorder –

BEDFORD, Mass.--(BUSINESS WIRE)--Apr. 25, 2023-- 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 authorization of its Clinical Trial Application (CTA) by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) to initiate a Phase 1/2 study (OSPREY) of STK-002 for the treatment of autosomal dominant optic atrophy (ADOA), the most common inherited optic nerve disorder.

ADOA is a rare disease that causes progressive and irreversible vision loss in both eyes starting in the first decade of life. An estimated 65% to 90% of cases are caused by mutations in the *OPA1* gene, most of which lead to a haploinsufficiency, resulting in 50% OPA1 protein expression and disease manifestation. There are currently no approved treatments for ADOA.

STK-002 is a proprietary antisense oligonucleotide (ASO) being developed by Stoke as the first potential disease-modifying therapy to address the genetic cause of ADOA. STK-002 is designed to restore OPA1 protein expression by upregulating protein production from the non-mutant (wild-type) copy of the *OPA1* gene. By doing this, the company hopes to slow or even stop vision loss in patients with ADOA.

"We are advancing a second TANGO ASO into the clinic which speaks to the potential of our unique approach to treat the underlying cause of a variety of genetic diseases, particularly of the central nervous system and the eye," said Barry Ticho, M.D., Ph.D., Chief Medical Officer of Stoke Therapeutics. "As we look to initiate the clinical studies of STK-002, our ongoing natural history study called FALCON is progressing well and will provide important information about the progression of this disease, which often leads to legal blindness. We look forward to working with the ADOA community as we prepare to start the first clinical study of STK-002 in early 2024."

The OSPREY study is a Phase 1/2 open-label study of children and adults ages 6 to 55 who have an established diagnosis of ADOA and have evidence of a genetic mutation in the *OPA1* gene. The primary objectives for the study are to assess the safety and tolerability of single ascending doses of STK-002, as well as to determine the exposure in serum. A secondary objective is to assess efficacy following intravitreal (IVT) administration of STK-002 in one eye of each patient as measured by changes in visual function and ocular structure as well as quality of life in patients with ADOA. Enrollment and dosing are anticipated to begin in early 2024.

About Autosomal Dominant Optic Atrophy (ADOA)
Autosomal dominant optic atrophy (ADOA) is the most common inherited optic nerve disorder. It is a rare disease that causes progressive and irreversible vision loss in both eyes starting in the first decade of life. Severity can vary and the rate of vision loss can be difficult to predict. Roughly half of people with ADOA fail driving standards and approximately 50% are registered as legally blind. More than 400 *OPA1* mutations have been reported in people diagnosed with ADOA. Currently there is no approved treatment for people living with ADOA. ADOA affects approximately one in 30,000 people globally with a higher incidence in Denmark of one in 10,000 due to a founder effect.

About STK-002
STK-002 is a proprietary antisense oligonucleotide (ASO) in preclinical development for the treatment of Autosomal Dominant Optic Atrophy (ADOA). Approximately 80% of individuals with ADOA experience symptoms before age 10, typically beginning between the ages of 4 and 6. Stoke believes that STK-002 has the potential to be the first disease-modifying therapy for people living with ADOA. An estimated 65% to 90% of cases are caused by mutations in the *OPA1* gene, most of which lead to a haploinsufficiency resulting in 50% OPA1 protein expression and disease manifestation. STK-002 is designed to upregulate OPA1 protein expression by leveraging the non-mutant (wild-type) copy of the *OPA1* gene to restore OPA1 protein expression with the aim to stop or slow vision loss in patients with ADOA. Stoke has generated preclinical data demonstrating proof-of-mechanism and proof-of-concept for STK-002. STK-002 has been granted orphan drug designation by the FDA as a potential new treatment for ADOA and the company has received authorization of its CTA from the MHRA.

About the Phase 1/2 OSPREY Study (United Kingdom)
The OSPREY study is a Phase 1/2 open-label study of children and adults ages 6 to 55 who have an established diagnosis of ADOA and have evidence of a genetic mutation in the *OPA1* gene. The primary objectives for the study are to assess the safety and tolerability of single ascending doses of STK-002, as well as to determine the exposure in blood A secondary objective is to assess efficacy following intravitreal (IVT) administration of STK-002 in one eye of each patient as measured by changes in visual function and ocular structure as well as quality of life in patients with ADOA. Enrollment and dosing are anticipated to begin in early 2024.

About the FALCON Study
FALCON is a multicenter, prospective natural history study of people ages 8 to 60 who have an established clinical diagnosis of ADOA that is caused by a heterozygous *OPA1* gene variant. No investigational medications or other treatments will be provided. The study is expected to enroll approximately 45 patients across 10 sites in the U.S., U.K., Italy and Denmark. Patients will undergo assessments at baseline, 6 months, 12 months, 18 months, and 24 months. There will be no additional follow-up period. For more information about enrolling in the study, please email Falconstudy@medpace.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, resulting in disease. 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 functional (or wild-type) genes produce more protein. TANGO aims to restore missing proteins by increasing – or stoking – protein output from healthy genes, thus compensating for the mutant 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 upregulating protein expression with RNA-based medicines. Using Stoke's proprietary TANGO (Targeted Augmentation of Nuclear Gene Output) approach, Stoke is developing antisense oligonucleotides (ASOs) to selectively restore protein levels. Stoke'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. Stoke is pursuing the development of STK-002 for the treatment of 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 its 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 Stoke 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-002 to treat the underlying causes of ADOA and reduce or stop vision loss, and the timing and expected progress of clinical trials for STK-002. 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 prove incorrect or do not fully materialize, could cause our results to differ materially from those expressed or implied by such forward-looking statements, including, but not limited to, risks and uncertainties related to: the Company's ability to advance, obtain regulatory approval of, and ultimately commercialize its product candidates; the timing of data readouts and interim and final results of preclinical and clinical trials; positive results in a clinical trial may not be replicated in subsequent trials or successes in early stage clinical trials may not be predictive of results in later stage trials; preliminary interim data readouts of ongoing trials may show results that change when such trials are completed; the Company's ability to fund development activities and achieve development goals to the end of 2025; the Company's ability to protect its intellectual property; the direct and indirect impacts of the ongoing COVID-19 pandemic and its variants on the Company's business; and other risks and uncertainties described under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2022, its quarterly reports on Form 10-Q, and the other 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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Stoke Media & Investor Contacts:
Dawn Kalmar
Chief Communications Officer
dkalmar@stoketherapeutics.com
781-303-8302

Eric Rojas
Vice President, Investor Relations
IR@stoketherapeutics.com
617-312-2754

Source: Stoke Therapeutics, Inc.