Stoke Therapeutics Presents New Data That Demonstrate Tango Antisense Oligonucleotides (ASOs) Increase OPA1 Protein Production and Improve Mitochondrial Function in Cells Derived From Patients With Autosomal Dominant Optic Atrophy (ADOA)

May 4, 2021

– Results presented at ARVO annual meeting confirm earlier preclinical findings and support the Company's work to discover and develop the first potential disease modifying approach for the treatment of ADOA –

– ADOA is the most common inherited optic nerve disorder –

BEDFORD, Mass.--(BUSINESS WIRE)--May 4, 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 new preclinical data demonstrating in-vitro protein upregulation and improved mitochondrial function in OPA1 protein-deficient fibroblasts derived from patients with ADOA. OPA1 protein deficiency is the primary cause of ADOA and reduced OPA1 levels are associated with impaired mitochondrial function. The data will be presented today at The Association for Research in Vision and Ophthalmology (ARVO) 2021 Annual Meeting and at the American Society of Gene and Cell Therapy (ASGCT) Annual Meeting on Tuesday, May 11, 2021 from 8:00 AM – 10:00 AM Eastern.

"These findings are important because they offer the first evidence from patient cells that our TANGO approach can address the underlying cause of ADOA by upregulating OPA1 protein production and increasing mitochondrial function," said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. "ADOA represents a strong fit for Stoke's science and our strategy: targeting severe genetic diseases that are caused by protein deficiencies and that have limited, if any treatment options. A disease-modifying approach would represent a significant advancement in the treatment of this disease."

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. 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.

"By demonstrating an improvement in the mitochondrial function of patient cells across different OPA1 mutations, the data suggest that ASO mediated increase in OPA1 could be sufficient to slow or reduce disease progression in a mutation-independent manner," said Gene Liau, Ph.D., Chief Scientific Officer of Stoke Therapeutics.

The data presented today provide in-vitro proof-of-concept for TANGO ASOs in ADOA patient fibroblasts. Highlights from today's presentation include new data that demonstrate ADOA patient fibroblast cell lines treated with TANGO ASOs exhibit:

- Reduced non-productive exon inclusion and increased total OPA1 mRNA expression in three patient fibroblast cell lines with different mutations;
- Increased expression of multiple OPA1 protein isoforms by ~35% to 47%; and
- A dose-dependent improvement in mitochondrial bioenergetics.

Details of today's presentation are as follows:

Presentation Title: Antisense oligonucleotide mediated increase in OPA1 improves mitochondrial function in fibroblasts derived from patients with autosomal dominant optic atrophy (ADOA)

Session Date & Time: Tuesday, May 4, 2021; 2:15 p.m. – 3:45 p.m. E.T.

Session Title: Gene therapy in ocular diseases

Presenter: Aditya Venkatesh, Ph.D., Senior Scientist, Stoke Therapeutics

The presentation at ARVO is now available online on the Events and Presentations section of Stoke's website at https://investor.stoketherapeutics.com/.

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. Symptoms typically begin between the ages of 4 and 6 years old, affecting males and females equally. The severity of the condition by adolescence reflects the overall level of visual function to be expected throughout most of the individual's adult life. Roughly half of people with ADOA fail driving standards and up to 46% are registered as legally blind. ADOA is considered a haploinsufficiency disease, as most people living with ADOA have genetic mutations in the *OPA1* gene that result in only half the necessary OPA1 protein being produced. 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. 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.

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: preclinical data and study results regarding OPA1; our ability to develop TANGO ASOs to treat the underlying causes of ADOA and increase mitochondrial function; our ability to advance OPA1 as our next preclinical target; 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 any potential clinical candidate for OPA1; the timing and results of preclinical studies and clinical trials; the risk that positive results in a preclinical trial may not be replicated in subsequent trials or success in early stage preclinical trials may not be predictive of results in later stage trials; 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; 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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