Stoke Therapeutics Presents Preclinical Data That Demonstrate In-Vitro and In-Vivo Target Engagement and Protein Upregulation in OPA1 Protein Deficiency, the Primary Cause of the Most Common Inherited Optic Nerve Disorder

May 12, 2020

First in-vivo proof-of-concept for TANGO antisense oligonucleotides in an ocular disease

Results presented at the American Society of Gene and Cell Therapy Annual Meeting further validate the company's mutation-independent approach to amplifying protein expression to treat severe genetic diseases

BEDFORD, Mass.--(BUSINESS WIRE)--May 12, 2020-- Stoke Therapeutics, Inc., (Nasdaq: STOK), a biotechnology company pioneering a new way to treat the underlying cause of genetic diseases by precisely upregulating protein expression, today announced new preclinical data demonstrating in-vitro and in-vivo target engagement and protein upregulation in *OPA1* protein-deficient cells. *OPA1* protein deficiency is the primary cause of autosomal dominant optic atrophy (ADOA), the most common inherited optic nerve disorder. This is the first proof-of-concept data for TANGO antisense oligonucleotides (ASOs) in an ocular disease. The results further validate the company's mutation-independent approach to amplifying protein expression to treat severe genetic diseases. These data will be presented today in a virtual poster session at the American Society of Gene and Cell Therapy (ASGCT) 2020 Annual Meeting.

"These data provide early evidence of the potential to address the underlying cause of autosomal dominant optic atrophy, an optic nerve disorder that causes progressive and irreversible vision loss starting in the first decade of a child's life. There are currently no approved treatments for ADOA," said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. "Our TANGO technology represents a unique, mutation-independent approach to treating the underlying cause of a variety of genetic diseases, particularly in the central nervous system and the eye. The ADOA program is one of several under consideration for future prioritization, and we look forward to nominating a second product candidate later this year."

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.

The data presented today demonstrate in-vitro and in-vivo proof-of-concept for TANGO ASOs in an ocular disease. Highlights from today's presentation include:

- Dose-dependent decreases in non-productive *OPA1* mRNA and increases in *OPA1* protein expression were observed in-vitro and in-vivo.
- An increase in *OPA1* protein expression to approximately 75% of wild-type levels was observed in an *OPA1* haploinsufficient (*OPA1* +/-) cell line.
- In-vivo increases in *O*PA1protein levels in the retina of wild-type rabbits were observed and the test ASO was well tolerated for up to 15 days after intravitreal injection.

Details of today's presentation are as follows:

Presentation Title: Antisense oligonucleotide mediated increase of *OPA1* expression using TANGO technology for treatment of autosomal dominant optic atrophy

Session Date & Time: Tuesday, May 12, 2020; 5:30 p.m. – 6:30 p.m. E.T.

Session Title: Oligonucleotide Therapeutics

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

Poster Number: 1593

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

About Autosomal Dominant Optic Atrophy

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, 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.

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 pioneering a new way to treat the underlying causes of severe genetic diseases by precisely upregulating protein expression to restore target proteins to near normal levels. Stoke aims to develop the first precision medicine platform to target the underlying cause of a broad spectrum of genetic diseases caused by haploinsufficiencies. 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: Stoke's ability to precisely upregulate protein expression in OPA1 protein-deficient cells; Stoke's ability to treat the underlying cause of ADOA; and Stoke's ability to use preclinical data to advance the development of TANGO ASOs to treat ocular disease. Statements including words such as "plan," "continue," "expect," "target," 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 Stoke's actual activities or results to differ significantly from those expressed in any forward-looking statement, including without limitation risks and uncertainties related to Stoke's ability to develop, obtain regulatory approval for and commercialize TANGO ASOs to treat ocular disease; the impact of the COVID-19 pandemic on Stoke's operations and the U.S. and world economies; the timing and results of preclinical studies; the timing for nominating a second product candidate; risks associated with potential delays, work stoppages, or supply chain disruptions caused by the coronavirus pandemic; risks associated with current and potential future healthcare reforms; Stoke's ability to protect its intellectual property; and other risks set forth in our filings with the Securities and Exchange Commission, including the risks set forth in our quarterly report on Form 10-Q for the quarter ended March 31, 2020. These forward-looking statements are based on our current beliefs and expectations and speak only as of the date hereof and Stoke specifically disclaims any obligation to update these forward-looking statements or reasons why actual results might differ, whether as a result of new information, future events or otherwise, except as required by law.

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