Stoke Therapeutics Presents New In-Vivo Data That Demonstrated Dose-Related Target Engagement and OPA1 Protein Upregulation in Retinal Tissue Following Administration of STK-002

May 2, 2022

– Data presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting support the Company's work to advance STK-002 as the first potential disease modifying treatment for Autosomal Dominant Optic Atrophy (ADOA) –

– ADOA is the most common inherited optic nerve disorder –

BEDFORD, Mass.--(BUSINESS WIRE)--May 2, 2022-- 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 new preclinical data that demonstrated dose-related target engagement and increases in OPA1 protein levels in retinal tissue of non-human primates (NHPs) following intravitreal (IVT) administration of STK-002. Target engagement and OPA1 protein increases were sustained for at least eight weeks post-injection. A dose-related increase in OPA1 protein was also detected in retinal ganglion cells (RGCs) of NHPs treated with STK-002. STK-002 is a proprietary antisense oligonucleotide (ASO) in preclinical development for the treatment of Autosomal Dominant Optic Atrophy (ADOA), the most common inherited optic nerve disorder. The data were presented at the Association for Research in Vision and Ophthalmology (ARVO) 2022 Annual Meeting.

ADOA affects approximately one in 30,000 people globally with a higher incidence (one in 10,000) in Denmark 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.

"The progressive vision loss experienced by people living with ADOA is typically the result of a mutation in their *OPA1* gene, which leads to insufficient protein production and a loss of retinal ganglion cells," said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. "Stoke's approach is to selectively boost protein production from the healthy copy of the *OPA1* gene to prevent damage to the RGCs and, ultimately, slow or even stop vision loss. These data are encouraging because they show, for the first time, that we can increase protein levels in retinal tissue and in the retinal ganglion cells, giving us additional confidence that STK-002 could address the underlying cause of ADOA."

In this study, NHPs were given bilateral IVT injections of either placebo or STK-002 at low, mid or high doses. Assessments were made at four weeks for all dose groups and at eight weeks for the mid- and high-dose groups.

Highlights from the presentation include:

- IVT administration of STK-002 was well-tolerated in NHPs;
- Target engagement was demonstrated by the dose-related reductions in nonsense-mediated decay (NMD) transcripts in retinal tissue observed at four weeks and eight weeks;
- Significant increases in OPA1 protein in retinal tissue at four weeks that persisted at eight weeks in the mid- and high-dose groups;
- Dose-related increase in OPA1 protein in RGCs treated with STK-002 was detected using immunofluorescence;
- Concentrations of STK-002 in retinal tissue persisted at substantial levels at four weeks and at eight weeks in the mid- and high-dose groups; and
- Dose-related increases in STK-002 in RGCs were observed.

Details of Stoke's presentations at the ARVO Annual Meeting:

Presentation Title: STK-002, an Antisense Oligonucleotide (ASO) for the Treatment of Autosomal Dominant Optic Atrophy (ADOA), is Taken Up by Retinal Ganglion Cells (RGC) and Upregulates OPA-1 Protein Expression After Intravitreal Administration to Non-human Primates (NHP)

Presenter: Karen Anderson, D.V.M., Ph.D., Ophthalmology Program Lead, Stoke Therapeutics

Session: Gene therapy and other novel therapeutics in ophthalmic diseases 1

Date: May 2, 2022

Presentation Number: 1111

In addition, a presentation of data from an *in vitro* ADOA model of *OPA1* haploinsufficient RGCs was presented in a poster session today. In this study, haploinsufficient induced pluripotent stem cells (iPSCs) carrying *OPA1* mutations were treated with STK-002 and showed a dose-responsive reduction of non-productive OPA1 mRNA and an increase in total OPA1 mRNA in total neurospheres. The results support the hypothesis that TANGO ASOs can potentially be used to treat ADOA caused by *OPA1* haploinsufficiency and provide a useful *in vitro* model to evaluate TANGO ASOs.

Poster Title: Models of Autosomal Dominant Optic Atrophy (ADOA) using iPSCs and response to Targeted Augmentation of Nuclear Gene Output (TANGO) Antisense Oligonucleotides (ASOs) Treatment

Presenter: Raymond Oh, Ph.D., Associate Principal Scientist, Stoke Therapeutics

Session: Animal models of human ocular disease

Date: May 2, 2022

Poster Number: 1895 – A0041

The presentations at ARVO are now available online on the Investors & News section of Stoke's website at https://investor.stoketherapeutics.com/events-and-presentations.

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 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 STK-002

STK-002 is a proprietary antisense oligonucleotide (ASO) in preclinical development for the treatment of Autosomal Dominant Optic Atrophy (ADOA). Stoke believes that STK-002 has the potential to be the first disease-modifying therapy for people living with ADOA. 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.

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 Company's preclinical data and study results regarding STK-002; the ability of STK-002 to treat the underlying causes of ADOA; the timing and expected progress of clinical trials, data readouts and presentations for STK-002 and the Company's other product candidates; the timing or receipt of regulatory approvals; and the ability of TANGO to design medicines to increase protein production and the expected benefits thereof. Statements including words such as "could," "plan," "will," "continue," "expect," "potential," 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: the ability of STK-002 to safely and effectively treat the underlying causes of ADOA; the Company's ability to timely and successfully advance its preclinical studies, regulatory filings, clinical trials, data readouts and presentations related to STK-002 and its other product candidates; the Company's ability to obtain regulatory approval for and to commercialize STK-002; the results of preclinical studies and early clinical trials not being necessarily predictive of future results; the Company's ability to protect its intellectual property; the ability of TANGO to successfully design medicines to increase protein production and the expected benefits thereof; 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, 2021, 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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