Stoke Therapeutics Presents Preclinical Data From Studies of STK-001 That Showed Improvements in Survival and Reductions in Seizure Frequency in a Mouse Model of Dravet Syndrome

December 7, 2019

New data from electroencephalography (EEG) recordings showed 76% of Dravet syndrome (DS) mice treated with STK-001 were seizure free compared to 48% of placebo-treated mice

An 80% reduction in the average number of spontaneous seizures was also observed among treated DS mice

Data support the clinical development of STK-001 as a potential new medicine for Dravet syndrome, a severe and progressive genetic epilepsy

BEDFORD, Mass.--(BUSINESS WIRE)--Dec. 7, 2019-- Stoke Therapeutics, Inc. (Nasdaq:STOK), a biotechnology company pioneering a new way to treat the underlying cause of severe genetic diseases by precisely upregulating protein expression, today announced preclinical data from studies of STK-001 that showed significant improvements in survival and reductions in seizure frequency in a mouse model of Dravet syndrome (DS). New data from electroencephalography (EEG) recordings showed 76% (16/21) of DS mice treated with STK-001 were seizure free compared to 48% (10/21) that were treated with a placebo. An 80% reduction in the average number of spontaneous seizures (3 seizures vs 16 seizures) was also observed among treated DS mice compared to placebo. EEG is a highly sensitive measure of seizure activity, which enables the detection of seizures that may not be otherwise visible. These data were presented in a poster session at the American Epilepsy Society (AES) Annual Meeting in Baltimore.

“The data on STK-001 from this mouse model give us confidence in our approach to treating the underlying cause of Dravet syndrome by restoring $Na_V1.1$ protein expression to near normal levels,” said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. “The reductions in mortality previously observed with STK-001 were compelling and the new EEG data provide further evidence of the potential for STK-001 to impact Dravet syndrome by reducing seizure frequency and possibly preventing seizures entirely. What is particularly remarkable is that these data were generated from a spontaneous seizure model, which we believe accurately reflects the clinical situation in people with Dravet syndrome.”

Dravet syndrome is a severe and progressive genetic epilepsy that begins within the first year of life. The effects of the disease go beyond seizures and often include cognitive regression or developmental stagnation, ataxia, speech impairment and sleep disturbances. Approximately 85% of Dravet syndrome cases are caused by spontaneous, heterozygous variants in the *SCN1A* gene. This gene encodes the voltage-gated sodium channel α subunit, $Na_V1.1$. STK-001 is a proprietary antisense oligonucleotide (ASO) designed to increase – or upregulate – protein production by manipulating the cell’s RNA splicing process.

In the studies presented in today’s poster, the efficacy of STK-001 was evaluated in a *Scn1a*-linked mouse model of Dravet syndrome that results in Nav1.1 haploinsufficiency. Seizures and Sudden Unexpected Death in Epilepsy (SUDEP) in these mice occurred spontaneously and were not provoked by temperature changes or other manipulation. Mice were administered a single intracerebroventricular (ICV) injection of STK-001 or placebo at postnatal day 2 or postnatal day 14 and monitored to postnatal day 90. The data showed improvements among mice treated with STK-001 compared to placebo, including:

- Significant increases in *Scn1a* mRNA and $Na_V1.1$ protein expression in the brain at day 90;
- Significant improvements in survival among DS mice treated at postnatal day 2 or postnatal day 14 compared to placebo;
    - 97% (33/34) mice survived to day 90 after treatment on postnatal day 2, compared to 23% (14/62) mice in the placebo-treated group ($p<0.0001$).
    - 85% (45/53) mice survived to day 90 after treatment at postnatal day 14, compared to 64% (47/74) mice in the placebo-treated group ($p<0.005$).
- An increase in the number of DS mice that experienced no seizures following administration of STK-001 at postnatal day 2, as measured by EEG. Between postnatal day 22 and postnatal day 46, 76% (16/21) of DS mice treated with STK-001 were seizure free compared to 48% (10/21) in the placebo-treated group;
- An 80% reduction in the average number of spontaneous seizures (3 seizures vs 16 seizures) detected between postnatal day 22 and postnatal day 46 in DS mice after treatment with STK-001 compared to placebo ($p<0.05$).

“Although we cannot make a direct correlation, these data are encouraging because they suggest a potential for STK-001 to reduce seizure frequency in Dravet syndrome patients. Showing a 50% improvement in the number of DS mice that had no detectable seizures is a significant finding, particularly considering the high seizure burden associated with Dravet syndrome,” said Lori Isom, Ph.D., Maurice H. Seevers Professor and Chair of Pharmacology, University of Michigan Medical School. “Across all measures, the data showed a consistent benefit for DS mice treated with STK-001 compared to placebo, making the totality of these data compelling.”

Details of the presentation are as follows:

Presentation Title: Targeted Augmentation of Nuclear Gene Output (TANGO) of *Scn1a* Prevents SUDEP in a Mouse Model of Dravet Syndrome
Session Date & Time: Saturday, December 7, 2019, 12:00 p.m. – 6:00 p.m. ET
Session Title: Poster Session 1
Presenter: Lori Isom, Ph.D., Maurice H. Seevers Professor and Chair of Pharmacology, University of Michigan Medical School

Location: The Baltimore Convention Center, Hall E

Additional preclinical data will be presented on Sunday, December 8, 2019 showing biodistribution, target engagement, pharmacodynamics, safety and tolerability in non-human primates treated with STK-001:

Presentation Title: TANGO Oligonucleotides for the Treatment of Dravet Syndrome: Safety, Biodistribution and Pharmacology in the Non-Human Primate
Session Date & Time: Sunday, December 8, 2019, 10:00 a.m. – 4:00 p.m. ET
Session Title: Poster Session 2
Presenter: Anne Christiansen, Ph.D., Associate Director, Neuroscience, Stoke Therapeutics
Poster Number: 2.195
Location: The Baltimore Convention Center, Hall E

The posters for these studies will be made available online upon presentation at the meeting on the Events and Presentations section of Stoke's website at https://www.stoketherapeutics.com/.

About STK-001

STK-001 is an investigational new medicine for the treatment of Dravet syndrome. 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 upregulate $Na_V1.1$ 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 U.S. Food and Drug Administration as a potential new treatment for Dravet syndrome. Stoke plans to submit an investigational new drug application (IND) to the U.S. Food and Drug Administration in early 2020.

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 cognitive regression or developmental stagnation, ataxia, speech impairment and sleep disturbances. Compared with the general epilepsy population, people living with Dravet syndrome have a higher risk of sudden unexpected death in epilepsy, or SUDEP. 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, Inc. (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 in which the patient has one healthy copy of a gene and one mutated copy that fails to produce a protein essential to health. These diseases, in which loss of approximately 50% of normal protein expression causes disease, are called autosomal dominant haploinsufficiencies. The company's lead investigational new medicine is STK-001, a proprietary antisense oligonucleotide (ASO) that has the potential to be the first disease-modifying therapy to address the genetic cause of Dravet syndrome, a severe and progressive genetic epilepsy. 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.

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-001 to improve survival and reduce seizure frequency in mice, as well as its biodistribution, target engagement and ability to increase protein expression in non-human primates; our ability to use study data to advance the development of STK-001; the ability of STK-001 to treat the underlying causes of Dravet syndrome; and the ability of TANGO to design medicines to increase protein production. Statements including words such as "plan," "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 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 our actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to the company's ability to develop, obtain regulatory approval for and commercialize STK-001 and its future product candidates, the timing and results of preclinical studies and clinical trials, the company's ability to protect 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 three months ended September 30, 2019. These forward-looking statements speak only as of the date hereof and we specifically disclaim 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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