Stoke Therapeutics Announces Landmark New Data That Support the Potential for STK-001 to be the First Disease-Modifying Medicine for the Treatment of Patients with Dravet Syndrome

March 25, 2024

– Phase 1/2a End of Study Data: 70mg doses demonstrated substantial and sustained reductions in convulsive seizure frequency on top of the best available anti-seizure medicines; Median reductions of 85% (n=10) at 3 months and 74% (n=9) at 6 months after last dose –

– Open Label Extension Studies: Durable reductions in seizures and clinically meaningful improvements in multiple measures of cognition and behavior were maintained over 12 months with continued dosing at 30mg and 45mg –

– STK-001 generally well-tolerated –

– Company to meet with regulatory agencies to discuss registrational study design with initial doses of 70mg followed by continued dosing at 45mg –

– Webcast and conference call for analysts and investors at 4:30 p.m. Eastern Time today –

BEDFORD, Mass.--(BUSINESS WIRE)--Mar. 25, 2024-- 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 landmark new data from two open-label Phase 1/2a studies and two open-label extension (OLE) studies of children and adolescents ages 2 to 18 with Dravet syndrome who were treated with STK-001. Data from these studies showed clinically meaningful effects, including substantial and durable reductions in convulsive seizure frequency and improvements in multiple measures of cognition and behavior that support the potential for disease modification. These improvements were observed among a highly refractory group of patients who were already taking the best available anti-seizure medicines. STK-001 has been generally well-tolerated in studies to date.

Today, the Company also announced clearance from the U.S. Food and Drug Administration (FDA) that allows patients to receive three doses of 70mg followed by continued dosing at 45mg. Based on this regulatory update and these data, the Company plans to meet with regulatory agencies to discuss a registrational study that includes initial doses of 70mg followed by continued dosing at 45mg.

“The totality of these data provide compelling evidence that support the potential for STK-001 to be a disease-modifying medicine for patients with Dravet syndrome by treating the underlying cause of the disease, rather than just the symptoms,” said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. “STK-001 is the first medicine in development to demonstrate substantial and durable reductions in seizure frequency and improvements in multiple measures of cognition and behavior. These effects were observed in patients who were already taking the best available anti-seizure medicines, which confirms our highly differentiated mechanism of action and approach to treating this disease. We look forward to meeting with regulatory agencies to discuss our plans for a randomized, controlled registrational study and to providing an update coming out of those discussions later in 2024.”

“For decades, the primary goal of treating Dravet syndrome has been to control the frequency and severity of seizures, but, as we can now see from natural history data, many patients still experience high rates of seizure frequency and fall further and further behind in their neurodevelopment,” said Joseph Sullivan, M.D., FAES, Professor of Neurology and Pediatrics and Director of the Pediatric Epilepsy Center of Excellence at the University of California San Francisco, and a prominent researcher in Dravet syndrome. “A 50% reduction in seizures is an important measure of clinical efficacy, so an 80% reduction on top of any benefit patients may already be getting from their baseline anti-seizure regimen is profound. The further evidence of improvements in skills like communication, behavior, socialization and movement distinguish this approach from anything we have seen to date and mark our entry into a new era in the treatment of Dravet syndrome.”

Phase 1/2a Study Results: Substantial and Sustained Reductions in Convulsive Seizure Frequency

The Phase 1/2a studies were multi-center and included children and adolescents who have an established diagnosis of Dravet syndrome. Patients enrolled in these studies were highly refractory to treatment and taking the best available anti-seizure medicines: 85% of patients were taking at least three and 54% were taking at least four medicines to control seizures. Half the patients in the studies were taking concomitant fenfluramine.

New data from a combined analysis of 19 clinically evaluable patients who were treated with one, two or three doses of 70mg demonstrated substantial reductions in convulsive seizure frequency compared to baseline at 3 months and at 6 months after the last dose, one of several secondary endpoints in each study.

Observed Reductions in Convulsive Seizure Frequency Among Patients Treated with 70mg Doses of STK-001 in the Phase 1/2a Studies

Median % Reduction from Baseline in Convulsive Seizure Frequency	70mg (1 dose, n=8)	70mg (2 or 3 doses, n=11)
At 3 Months After Last Dose	43% (n=8)	85% (n=10†)
At 6 Months After Last Dose	57% (n=7*)	74% (n=9†)

*Seizure data excluded from month 5-6 for 1 patient because >50% seizure diary was missing

†Seizure data excluded for 2 patients (1 patient prior to 3m after last dose, 1 prior to 6m after last dose) following a change in background anti-seizure medicines

Open Label Extension Studies: Durable reductions in seizures and clinically meaningful improvements in multiple measures of cognition and behavior over 12 months with continued dosing at 30mg and 45mg

Eligible patients who completed treatment in the Phase 1/2a studies continued treatment with STK-001 in one of two OLEs. At the time of the analysis, 92% (68/74) of eligible patients had enrolled in the OLEs and 84% (57/68) remained in the studies.

Durable reductions in convulsive seizure frequency were observed throughout the course of treatment. This analysis only included patients who received ≥30mg of STK-001 in the Phase 1/2a studies and then continued treatment with STK-001 (30mg or 45mg) every four months in the OLEs. Clinically meaningful improvements from baseline through 12 months were observed in multiple measures of cognition and behavior, including multiple sub-domains of the Vineland Adaptive Behavior Scale (VINELAND-3).

These improvements are in stark contrast to recent natural history study data that showed that, on average, patients with Dravet syndrome experienced no meaningful improvement in convulsive seizure frequency and exhibited widening gaps in cognition and behavior compared to neurotypical peers, despite treatment with the best available anti-seizure medicines.

Key Safety Findings

At the time of the analyses, 81 patients had been treated with STK-001. Safety findings are summarized below.

- STK-001 was generally well-tolerated across the Phase 1/2a and OLE studies.
- In the Phase 1/2a studies:
    - 30% (24/81) of patients experienced a treatment-emergent adverse event (TEAE) that was related to study drug. The most common were CSF protein elevations and procedural vomiting; and
    - 22% (18/81) of patients had a treatment-emergent serious adverse event. These events were assessed as unrelated to study drug except for the previously reported case of one patient who experienced Suspected Unexpected Serious Adverse Reactions (SUSARs).
- A greater incidence of CSF protein elevation was observed in the OLEs. 74% (50/68) of patients in the OLEs had at least 1 CSF protein value >50 mg/dL. No clinical manifestations have been observed in these patients.
- Across the studies, one patient discontinued treatment due to study drug. As previously reported, this patient discontinued treatment in the OLE due to elevated CSF protein.

Stoke Webcast and Conference Call for Analysts and Investors

Stoke will host a webcast and conference call for analysts and investors at 4:30 p.m. Eastern Time on March 25, 2024, to present landmark new data from two Phase 1/2a studies and two ongoing open-label extension (OLE) studies in children and adolescents ages 2 to 18 with Dravet syndrome. The webcast will be broadcast live on the Investors & News section of Stoke's website at https://investor.stoketherapeutics.com/. Participants who want to join the call and ask a question may register here to receive the dial-in numbers and unique PIN to seamlessly access the call. Otherwise please access the listen-only webcast by clicking here. An archived replay of the webcast will be available for at least 90 days following the event.

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 intellectual disability, developmental delays, movement and balance issues, language and speech disturbances, growth defects, sleep abnormalities, disruptions of the autonomic nervous system and mood disorders. The disease is classified as a developmental and epileptic encephalopathy due to the developmental delays and cognitive impairment associated with the disease. Compared with the general epilepsy population, people living with Dravet syndrome have a higher risk of sudden unexpected death in epilepsy, or SUDEP. There are no approved disease-modifying therapies for people living with Dravet syndrome. One out of 16,000 babies are born with Dravet syndrome, which is not concentrated in a particular geographic area or ethnic group.

About STK-001

STK-001 is an investigational new medicine for the treatment of Dravet syndrome currently being evaluated in ongoing clinical trials. 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 NaV1.1 protein expression by leveraging the non-mutant (wild-type) copy of the *SCN1A* gene to restore physiological NaV1.1 levels, thereby reducing both occurrence of seizures and significant non-seizure comorbidities. STK-001 has been granted orphan drug designation by the FDA and the EMA, and rare pediatric disease designation by the FDA as a potential new treatment for Dravet syndrome.

About the U.S. Studies: MONARCH (Phase 1/2a) and SWALLOWTAIL (OLE)

The MONARCH study was a Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study were to assess the safety and tolerability of STK-001, as well as to determine the pharmacokinetics in plasma and exposure in cerebrospinal fluid. A secondary objective was to assess the efficacy as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency.

Following completion of MONARCH, patients who met study entry criteria were eligible to continue treatment in SWALLOWTAIL, an open-label extension (OLE) study designed to evaluate the long-term safety and tolerability of repeat doses of STK-001. The study is also evaluating the long-term effects of STK-001 on convulsive seizure frequency and on behavior, cognition and overall quality of life. Dosing in SWALLOWTAIL is ongoing.

About the UK Studies: ADMIRAL (Phase 1/2a) and LONGWING (OLE)

The ADMIRAL study was a Phase 1/2a open-label study of children and adolescents ages 2 to <18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study were to assess the safety and tolerability of multiple doses of STK-001, as well as to determine the pharmacokinetics in plasma and exposure in cerebrospinal fluid. A secondary objective was to assess the effect of multiple doses of STK-001 as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency. Overall clinical status and quality of life were secondary endpoints of ADMIRAL.

Following completion of ADMIRAL, patients who met study entry criteria were eligible to continue treatment in LONGWING, an open-label extension (OLE) study designed to evaluate the long-term safety and tolerability of repeat doses of STK-001. The study is also evaluating the long-term effects of STK-001 on convulsive seizure frequency and on behavior, cognition and overall quality of life. Dosing in LONGWING is ongoing.

About the BUTTERFLY Observational Study

The BUTTERFLY study was a multicenter, longitudinal, prospective, observational study of children and adolescents ages 2 to 18 who have been diagnosed with Dravet syndrome as a result of an *SCN1A* gene mutation. This study was designed to evaluate neurodevelopmental status and change from baseline to 24 months. Secondary and exploratory endpoints in the study evaluated changes in other disease measures, including seizures and additional non-seizure comorbidities. No investigational medications or other treatments were provided. Participants continued to receive their usual care, including anti-seizure medications, and were observed for up to two years. The study was conducted at approximately 20 sites in the United States. Two-year results were presented at the American Epilepsy Society in December 2023 and showed that, on average, patients experienced no meaningful improvement in convulsive seizure frequency and exhibited widening gaps in cognition and behavior compared to neurotypical peers, despite treatment with the best available anti-seizure medicines.

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/.

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-001 to treat the underlying causes of Dravet syndrome and reduce seizures or show improvements in behavior and cognition at the indicated dosing levels or at all, and the timing and expected progress of clinical trials, data readouts, regulatory meetings, regulatory decisions and other presentations. Statements including words such as "expect," "plan," "will," "continue," 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, including STK-001; the timing of data readouts and interim and final results of preclinical and clinical trials; the receipt and timing of potential regulatory decisions; 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; the Company's ability to fund development activities and achieve development goals into 2025; the Company's ability to protect its intellectual property; the direct or indirect impact of global business, political and macroeconomic conditions, including inflation, interest rate volatility, cybersecurity events, uncertainty with respect to the federal budget, instability in the global banking system and volatile market conditions, and global events, including public health crises, and ongoing geopolitical conflicts, such as the conflicts in Ukraine and the Middle East; 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, 2023, its quarterly reports on Form 10-Q, and the other documents it 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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