Stoke Therapeutics Announces Positive New Safety & Efficacy Data from Patients Treated with STK-001 in the Phase 1/2a Studies (MONARCH & ADMIRAL) and the SWALLOWTAIL Open-Label Extension (OLE) Study in Children and Adolescents with Dravet Syndrome

July 25, 2023

– Totality of data from these ongoing studies suggest clinical benefit for patients ages 2 to 18 years old, including reductions in seizures and improvements in cognition and behavior that support the potential for disease modification –

– Phase 1/2a ADMIRAL Study Data STK-001 (70mg): Patients treated with 2 or 3 initial doses experienced substantial and sustained reductions in convulsive seizure frequency; Median reductions at 3 months after last dose (n=6) of 80% and 89% (n=3) at 6 months after last dose, compared to baseline –

– OLE Study Data STK-001 (30mg, 45mg): Sustained reductions in convulsive seizure frequency and improvements in cognition and behavior –

– MONARCH & ADMIRAL Study Safety Data: STK-001 has been generally well-tolerated among 74 patients treated with single and multiple doses of 10mg to 70mg –

– Additional data anticipated in Q1 2024 following completion of Phase 1/2a studies –

– Management will host a webinar and conference call for analysts and investors at 8:00 a.m. Eastern Time today –

BEDFORD, Mass.--(BUSINESS WIRE)--Jul. 25, 2023-- 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 positive new safety and efficacy data from patients treated with STK-001 in the two ongoing Phase 1/2a studies (MONARCH and ADMIRAL) and the SWALLOWTAIL open-label extension (OLE) study in children and adolescents with Dravet syndrome. These new data suggest clinical benefit for patients 2 to 18 years of age treated with multiple doses of STK-001. The observed reductions in convulsive seizure frequency as well as substantial improvements in cognition and behavior support the potential for disease modification in a highly refractory patient population.

"Together these data support the potential for STK-001 to address the underlying cause of Dravet syndrome by treating both seizures and the cognitive and behavioral issues that make this disease so complex and devastating. Our ongoing studies are providing a better understanding of a dose and dosing regimen that may generate substantial and sustained benefits for patients, while continuing to be generally well tolerated," said Edward M. Kaye, M.D., Chief Executive Officer of Stoke Therapeutics. "We are on track to complete the Phase 1/2a studies by year-end and look forward to sharing these data, and data from the open-label extension studies, in the first quarter of 2024."

"The patients in these studies were already taking the best available anti-seizure medicines, making the additional observed reductions in seizures quite meaningful. One of the most exciting things we are seeing is the early sign that, for the first time, we may have a therapy that can address the syndrome, in addition to the seizures," said Joseph Sullivan, M.D., 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 into Dravet Syndrome. "What we know from the natural history data is that the profound deficits in cognitive functioning among patients with Dravet syndrome do not tend to improve on their own, which makes the improvements indicated in multiple assessments of cognition and behavior compelling."

About the Phase 1/2a Studies
MONARCH and ADMIRAL are multi-center, Phase 1/2a studies of children and adolescents who have an established diagnosis of Dravet syndrome. The primary objectives for MONARCH in the United States and ADMIRAL in the United Kingdom are 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 is to assess the efficacy of STK-001 as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency.

Key Efficacy Findings from a Combined Analysis of Phase 1/2a Studies MONARCH & ADMIRAL
The combined efficacy analysis reported today was based on clinically evaluable data from 45 patients who were treated with multiple doses (30mg, 45mg, 70mg) in either of these two ongoing studies. The greatest reduction in convulsive seizure frequency has been observed among the small number (n=11) of patients treated with two or three doses of 70mg in the ADMIRAL study. The analysis of the 70mg multiple dose cohort from ADMIRAL study consists primarily of patients treated with three doses of STK-001 (n=5). The Company anticipates that the remaining ADMIRAL study data will consist primarily of patients treated with two doses of 70mg (n=6). (See Key Safety Findings below.)

Based on these new data and an increasing understanding of the STK-001 mechanism of action and time necessary to produce a clinical effect, the Company performed multiple analyses, including a "through" analysis that incorporates data from a period of time during and after dosing and an "at" analysis that captured data at a specific timepoint after dosing was completed. The results of both analyses are reported below. The Company believes that the "at" analysis more accurately captured the effect of STK-001 and will be the most relevant for use in future studies, and the overall development program for STK-001.

Reductions in Convulsive Seizure Frequency Were Observed Across Dose Cohorts*

Median % Reduction from Baseline in Convulsive Seizure Frequency	30mg MAD (3 doses, n=18)	45mg MAD (3 doses, n=16)	70mg MAD** (3 doses, n=5)

			(2 doses, n=6)
At 3 Months After Last Dose	27% (n=16)	19% (n=14)	80% (n=6†)
At 6 Months After Last Dose	4% (n=13)	45% (n=8)	89% (n=3†)
Day 29 **Through 3** Months After Last Dose	28% (n=17)	18% (n=16)	42% (n=8†)
Day 29 **Through 6** Months After Last Dose	24% (n=16)	26% (n=14)	42% (n=6†)

* Patient numbers were primarily variable due to the fact that patients with ≥50% of the data points in each time period were included in the applicable "through" cohort (bottom two data rows), even if the patient had not yet reached the last timepoint in the time period.

** ADMIRAL patients only. The MONARCH study is evaluating single doses of 70mg and data from this cohort are not yet available.

†5/6 patients (at 3 months), 3/3 patients (at 6 months), 5/8 patients (day 29 through 3 months) and 5/6 patients (day 29 through 6 months) after last dose were treated with 3 doses of 70mg

Key Efficacy Findings From the SWALLOWTAIL Open-Label Extension Study
Following treatment in the Phase 1/2a MONARCH study, patients who meet study entry criteria are eligible to continue treatment with STK-001 in SWALLOWTAIL. An analysis of a subset of these patients was performed to assess the potential impact of ongoing treatment with STK-001. This analysis was based only on the group of patients who received a cumulative total dose of at least 30mg of STK-001 in MONARCH and then continued treatment in SWALLOWTAIL with 30mg or 45mg doses every four months. Twenty-six patients met these criteria when they began treatment in SWALLOWTAIL.

Data from this analysis provide evidence of the potential for disease modification with ongoing treatment with STK-001. Durable reductions in convulsive seizure frequency were observed throughout the course of treatment. Data from a mixed model repeated measures (MMRM) analysis indicated substantial improvements from baseline through 12 months in multiple assessments of cognition and behavior, including:

- Expressive and receptive communication as measured by the Vineland Adaptive Behavior Scale (VABS-III)
- Gross motor skills as measured by VABS-III
- Executive function as measured by the Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P)
- Global Impression of Change scores as reported by caregivers and by clinicians

Data from the Company's BUTTERFLY natural history study showed little to no change in these assessments among patients treated with currently available anti-seizure medicines.

Key Safety Findings from an Analysis of the Phase 1/2a MONARCH and ADMIRAL Studies:
The safety analysis for the Phase 1/2a studies reported today was based on data from 74 patients who were treated with single or multiple doses of STK-001 (10mg, 20mg, 30mg, 45mg, 70mg) and followed for up to six months after their last dose.

- STK-001 was generally well-tolerated among 74 patients treated with single and multiple doses of 10mg to 70mg in the Phase 1/2a studies and there were no discontinuations related to study drug.
- 32% (24/74) of patients experienced a treatment-emergent adverse event (TEAE) that was related to study drug. The most common TEAEs related to study drug were CSF protein elevations, vomiting, and irritability.
- 20% (15/74) of patients had a treatment-emergent serious adverse event (TESAE). The TESAEs experienced by 14 of the 15 were not considered related to study drug.
    - One patient who received multiple doses of 70mg STK-001 in the ADMIRAL study experienced Suspected Unexpected Serious Adverse Reactions (SUSARs) that were attributed by the investigator to STK-001. The patient went on to complete the study.
    - Subsequently, the study protocol for ADMIRAL was amended to allow investigators to decide whether to administer two or three doses of STK-001 (70mg) in the ADMIRAL study before patients would be eligible to enroll in the LONGWING OLE.

Safety findings from patients who continued treatment in SWALLOWTAIL OLE (n=44) were consistent with the findings from MONARCH and ADMIRAL with the exception of a greater incidence of CSF protein elevation. In SWALLOWTAIL, 64% (28/44) of patients had at least 1 CSF protein value >50 mg/dL. No clinical manifestations have been observed in these patients, although one patient discontinued treatment in SWALLOWTAIL due to elevated CSF protein.

Key PK and CSF Exposure Findings:

- A dose-dependent increase in study drug exposure was observed in plasma. The plasma PK profile was consistent across MONARCH and ADMIRAL patients who were treated at the same dose level.
- STK-001 drug levels increased in CSF following 3 doses of 30mg and 45mg, suggesting STK-001 accumulation in CNS tissues. CSF exposure was measurable up to six months following multiple intrathecal doses of STK-001, indicating sustained exposure of STK-001 in the brain. CSF exposure data from the 70mg cohort will be included in the end of study

analysis.

Clinical Progress Updates and Next Steps

- These data are planned for presentation at the 35th International Epilepsy Congress September 2-6, 2023 in Dublin, Ireland, and also at the American Epilepsy Society (AES) December 1-5, 2023 in Orlando, Fla.
- The Company anticipates additional data, including the end of study data from MONARCH (including patients treated with a single dose of 70mg) and ADMIRAL, as well as additional data from the SWALLOWTAIL and LONGWING OLEs, in the first quarter of 2024.
- The Company plans to share an update on Phase 3 planning in the first half of 2024, pending the results from the completed Phase 1/2a studies and ongoing OLEs.

Stoke Webinar and Conference Call for Analysts and Investors
Stoke will host a webinar and conference call for analysts and investors at 8:00 a.m. Eastern Time on Tuesday, July 25, 2023, to present positive new data from the two ongoing Phase 1/2a studies (MONARCH and ADMIRAL) and the SWALLOWTAIL open-label extension study in children and adolescents with Dravet syndrome. The webinar will be broadcast live on the Investors & News section of Stoke's website at https://investor.stoketherapeutics.com/. An archived replay of the webinar will be available for at least 90 days following the event. 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 webinar by clicking here.

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 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 Phase 1/2a MONARCH Study (United States)
The MONARCH study is 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 are 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 is to assess the efficacy as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency. Stoke also intends to measure non-seizure aspects of the disease, such as quality of life, as secondary endpoints. Additional information about the MONARCH study can be found at https://www.monarchstudy.com/.

Patients who participated in the MONARCH study and meet study entry criteria are 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. We expect that SWALLOWTAIL will also provide valuable information on the preliminary effects of STK-001 on seizures along with non-seizure aspects of the disease, such as quality of life and cognition.

Enrollment and dosing in SWALLOWTAIL are ongoing.

About the Phase 1/2a ADMIRAL Study (United Kingdom)
The ADMIRAL study is 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 are 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 is 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. Stoke also intends to measure non-seizure aspects of the disease, such as overall clinical status and quality of life, as secondary endpoints.

Patients who participated in the ADMIRAL study and meet study entry criteria are 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. We expect that LONGWING will also provide valuable information on the preliminary effects of STK-001 on seizures along with non-seizure aspects of the disease, such as quality of life and cognition.

Enrollment and dosing in LONGWING are ongoing.

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, resulting in disease. 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 functional (or wild-type) genes produce more protein. TANGO aims to restore missing proteins by increasing – or stoking – protein output from healthy genes, thus compensating for the mutant 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 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 ability of STK-001 to treat the underlying causes of Dravet syndrome and reduce seizures or show improvements in non-seizure comorbidities at the indicated dosing levels or at all, and the timing and expected progress of clinical trials, data readouts and presentations. Statements including words such as "plan," "will," "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 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; the timing and results of preclinical and clinical trials; the risk that 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 and preliminary interim data readouts of ongoing trials may show results that change when such trials are completed; the Company's ability to fund development activities and achieve development goals; the Company's ability to protect its intellectual property; 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, 2022, 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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