Taysha Gene Therapies Announces Publication of Positive Preclinical Data for TSHA-104 Demonstrating Therapeutic Potential in SURF1-associated Leigh Syndrome in Journal Molecular Therapy: Methods & Clinical Development

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TSHA-104 restored to normal levels elevation of blood lactate on exhaustive exercise in dose-dependent manner in SURF1 knockout mice

TSHA-104 increased COX1 activity in brain and muscle in dose-dependent manner in SURF1 knockout mice

Combination of intrathecal and intravenous delivery did not prove benefit over intrathecal alone

No associated toxicity risks or severe tissue damage were seen

There are no approved treatments for the underlying cause of the disease and the burden of disease and risk of mortality are high

DALLAS--(BUSINESS WIRE)--Sep. 15, 2021-- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a patient-centric, pivotal-stage gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS) in both rare and large patient populations, today announced publication of new preclinical data for TSHA-104 in SURF1-associated Leigh syndrome in *Molecular Therapy: Methods & Clinical Development*.

SURF1 deficiency is a monogenic mitochondrial disorder that is the most common cause of cytochrome c oxidase deficient Leigh syndrome, a rapidly progressive neurological disorder that leads to degeneration of the CNS. Leigh syndrome typically presents in the first year of life and is characterized by progressive loss of mental and movement abilities that can result in death in early childhood. Approximately 10-15% of people with Leigh syndrome have a *SURF1* mutation, and the estimated prevalence of SURF1 deficiency is 300 to 400 patients in the United States and European Union. There are currently no approved therapies to treat SURF1-associated Leigh syndrome.

“SURF1 is part of cytochrome c oxidase, a mitochondrial enzyme known as COX involved in the metabolic production of ATP. Children with SURF1 deficiency have severely impaired COX activity and cannot generate ATP by aerobic respiration appropriately. This disruption in overall energy metabolism increases anaerobic respiration, leading to elevated levels of lactate and the clinical phenotype of Leigh syndrome,” said Suyash Prasad, MBBS, M.Sc., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. “We are pleased that the published preclinical data for TSHA-104 demonstrate that the gene replacement therapy can address the hallmark characteristics of mitochondrial dysfunction by delivering a functional *SURF1* gene, ultimately restoring COX activity and mitochondrial function and correcting elevated lactate levels in the body.”

RA Session II, President, Founder and CEO of Taysha, added, “In the mouse model, we are seeing expression of SURF1 in the brain and spinal cord at levels sufficient to effectively restore COX activity in the brain, liver and muscle with one intrathecal administration of TSHA-104. We are encouraged by the ability of TSHA-104 to diminish exhaustive exercise-induced lactic acidosis, supporting intact mitochondrial function under states of stress in these preclinical models. This proof-of-concept study indicates TSHA-104 is safe and effective in rescuing metabolic dysfunction in preclinical models of SURF1 deficiency.”

A one-time intrathecal injection of TSHA-104 resulted in codon-optimized human SURF1 expression in multiple relevant brain and spinal cord regions in SURF1 knockout mice. A combination of intrathecal and intravenous delivery did not provide any benefit over intrathecal delivery alone, supporting continued use of intrathecal administration. TSHA-104 increased mitochondrially encoded cytochrome c oxidase 1 (MT-CO1) abundance four weeks post-injection in the CNS and peripheral tissues and increased COX1 activity in brain and muscle in a dose-dependent manner. Biochemical COX activity correlated with histological COX content level, supporting regional COX activity. Following exhaustive exercise-induced lactic acidosis TSHA-104 was able to rescue elevated lactate levels in SURF1 knockout mice dose-dependently. The safety profile assessed by non-GLP (Good Laboratory Practice) evaluation in wild-type mice using a similar dosing regimen determined no associated toxicity risks or severe tissue damage detected up to one year post-injection. Collectively this proof-of-concept study demonstrates TSHA-104 can safely and sufficiently rescue mitochondrial dysfunction in SURF1 knockout mice, supporting further translational development for the treatment of SURF1-associated Leigh syndrome.

TSHA-104 is an AAV9-based gene replacement therapy encoding the human SURF1 protein that is administered intrathecally for the treatment of SURF1-associated Leigh syndrome. TSHA-104 has been granted Orphan Drug and Rare Pediatric Disease designations by the FDA.

About Taysha Gene Therapies

Taysha Gene Therapies (Nasdaq: TSHA) is on a mission to eradicate monogenic CNS disease. With a singular focus on developing curative medicines, we aim to rapidly translate our treatments from bench to bedside. We have combined our team’s proven experience in gene therapy drug development and commercialization with the world-class UT Southwestern Gene Therapy Program to build an extensive, AAV gene therapy pipeline focused on both rare and large-market indications. Together, we leverage our fully integrated platform—an engine for potential new cures—with a goa of dramatically improving patients’ lives. More information is available at www.tayshagtx.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipates," "believes," "expects," "intends," "projects," and "future" or similar expressions are intended to identify forward-looking statements. Forward-looking statements include statements concerning the potential of our product candidates, including TSHA-104, to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, TSHA-104's eligibility for accelerated approval in the United States and Europe, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed, and the potential market opportunity for these product candidates. Forward-looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding our business are described in detail in our Securities and Exchange Commission ("SEC") filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2020, which is available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. Such risks may be amplified by the impacts of the COVID-19 pandemic. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

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