Taysha Gene Therapies Announces Publication of Positive Proof-of-Concept Preclinical Data for an AAV-mediated UBE3A Gene Replacement Approach Demonstrating Therapeutic Potential for The Treatment of Angelman Syndrome in the Journal JCI Insight

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AAV-mediated UBE3A gene replacement recapitulates endogenous isoform ratios by replacing both the short and long isoforms of UBE3A in key regions of the brain, leading to improvements in motor learning, behavior outcomes, and seizure phenotypes in Angelman mouse models

Novel construct, originally developed in the laboratories of Dr. Ben Philpot and Dr. Steven Gray, packages both short and long isoforms of UBE3A into a single viral vector, which is expected to confer significant advantages over approaches that express only one of the isoforms

Proof-of-concept preclinical data support further study of UBE3A gene replacement therapy as a potentially safe and effective treatment for Angelman syndrome

Adding to an existing vectorized shRNA knockdown approach to unsilence the paternal UBE3A allele, UBE3A gene replacement bolsters Taysha's pipeline in Angelman syndrome and strengthens its position as a world-leader in developing gene therapies for monogenic CNS disease

Angelman syndrome investor day on Tuesday, October 26, 2021, 10:00 am-1:00 pm ET

DALLAS--(BUSINESS WIRE)--Oct. 25, 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 the publication of new preclinical data for an AAV-mediated UBE3A gene replacement approach for the treatment of Angelman syndrome in the *Journal of Clinical Investigation Insight* (*JCI Insight*).

Angelman syndrome (AS) is a monogenic neurodevelopmental disorder caused by deletions or mutations in the maternal ubiquitin protein ligase E3A (*UBE3A*) gene. *UBE3A* encodes both short and long protein isoforms. Whereas the short isoform is most abundant, clinical data indicate that long UBE3A isoforms also contribute to healthy brain development and function. Common signs and symptoms of Angelman syndrome typically appear early in childhood and include intellectual and developmental disabilities, walking and balance disorders, gastrointestinal issues, seizures, and little to no speech. There are currently no approved treatments for Angelman syndrome and current interventions are focused on managing medical and developmental issues. Angelman syndrome impacts approximately 55,000 patients in the United States and in Europe.

Ben Philpot, Ph.D., Associate Director of the UNC Neuroscience Center, said, "The highly evolutionarily conserved expression of both the short and long isoforms of UBE3A suggests their importance, and we have identified an approach capable of packaging both isoforms into a single viral vector. To recapitulate natural human UBE3A isoform levels, we ensured expression of short and long isoforms at the endogenous 3 to 1 ratio, as well as the selective expression in neurons where UBE3A is lost, thus limiting peripheral toxicity. We are highly encouraged by our preclinical data demonstrating recovery in motor performance, epilepsy, and anatomical markers, supporting the potential of *UBE3A* gene replacement for the treatment of Angelman syndrome. We look forward to continued advancement of this approach."

"The UBE3A gene replacement approach is unique from our first Angelman syndrome candidate, which uses vectorized RNA-mediated knockdown to unsilence the paternal copy of the *UBE3A* gene by targeting the antisense transcript responsible for silencing the gene," said Suyash Prasad, MBBS, M.Sc., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. "We are encouraged by the improvements in motor learning, behavior outcomes, and seizure phenotypes achieved with *UBE3A* gene replacement in mouse models of Angelman syndrome. We believe both the gene replacement and RNA-mediated knockdown strategies position Taysha as a world-leader in the discovery of treatments for Angelman syndrome, a significant neurodevelopmental disorder with no currently approved treatments."

Taysha's *UBE3A* gene replacement therapy is a cerebrospinal fluid-delivered AAV vector enabling dual isoform UBE3A expression for the treatment of Angelman syndrome. It was originally developed in the laboratories of Dr. Ben Philpot and Taysha's Chief Scientific Advisor, Dr. Steven Gray. In preclinical mouse models of Angelman syndrome, AAV-mediated *UBE3A* gene replacement recapitulated endogenous UBE3A isoform expression and UBE3A subcellular expression in neurons. Anatomical and behavioral phenotypes, including nest building, motor performance and seizure phenotypes, were recovered following treatment, providing proof-of-concept preclinical data supporting further study of UBE3A gene replacement therapy as a potentially safe and effective treatment for Angelman syndrome.

Dr. Philpot will present these and additional preclinical data for Taysha's AAV-mediated UBE3A gene replacement approach at the Company's upcoming Angelman investor day on Tuesday, October 26th. Please register for the event here. The virtual event will feature presentations from Key Opinion Leaders who will provide an overview of Angelman syndrome, discuss natural history data, both Taysha approaches for gene therapy treatment mechanisms, and Taysha's clinical development strategy.

*Disclosures - UT Southwestern and Dr. Gray hold financial interest in Taysha. Dr. Gray serves as Chief Scientific Advisor for Taysha. UT Southwestern maintains a financial interest in Taysha unrelated to this research.

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-106, 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-106'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, and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, both of which are 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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