Taysha Gene Therapies Presents Preclinical Data on TSHA-102 for Rett Syndrome Demonstrating Cellular Regulation of MeCP2 Expression in Key Mouse Models at the American Society of Gene and Cell Therapy 26th Annual Meeting

New preclinical data after neonatal administration in wild-type mice showed no detectable impact on survival, neurobehavioral functions and overall health, suggesting TSHA-102, engineered with novel miRARE technology, avoided toxic overexpression of MeCP2 within cells already expressing MeCP2

Data reinforce previous findings in Mecp2$^{-/Y}$ knockout mice demonstrating TSHA-102 regulated cellular MeCP2 levels and significantly improved survival, overall neurobehavioral function and growth

Data in neonatal mouse models highlight the potential of the miRARE technology to enable safe expression levels of MeCP2, which may address the risks associated with both under and overexpression of MeCP2 resulting from the mosaic pattern of MECP2 silencing in females with Rett syndrome

Dosing of the first adult patient with TSHA-102 in the Phase 1/2 REVEAL trial in Rett syndrome is expected in Q2 2023

DALLAS, May 19, 2023 (GLOBE NEWSWIRE) -- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a clinical-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), today presents preclinical data from neonatal mouse models on TSHA-102 for Rett syndrome, including new data in wild-type mice, at the American Society of Gene and Cell Therapy (ASGCT) 26th Annual Meeting. TSHA-102 utilizes a mini*MECP2* gene and a novel miRNA-Responsive Auto-Regulatory Element (miRARE) technology designed to regulate cellular *MECP2* expression. In a Taysha-sponsored study, the safety and efficacy of TSHA-102 were explored in both neonatal wild-type and *Mecp2*$^{-/Y}$ knockout mice, respectively. Preclinical in-life data on early intervention of TSHA-102 in neonatal mice suggest miRARE enables the expression of the MeCP2 protein in deficient CNS cells while preventing toxic overexpression within cells expressing normal levels of MeCP2.

"These encouraging new preclinical data in wild-type mice indicate that TSHA-102, engineered with our miRARE technology, avoided overexpression of MeCP2 within cells already expressing MeCP2, while maintaining normal survival, neurobehavioral function and overall health," said Sukumar Nagendran, M.D., President, and Head of R&D. "These new data augment previous findings in the *Mecp2*$^{-/Y}$ knockout mouse model, suggesting that THSA-102 regulated expression of *MECP2* in both normal and *MECP2* deficient cells, which is critical given that Rett syndrome represents such a challenging case for human gene therapy because the therapeutic window for *MECP2* transgene expression is narrow. Either *MECP2* deficiency or duplication can lead to serious neurodevelopmental disease. We believe these new data from neonatal wild-type mice support the potential of miRARE to enable the optimal amount of MeCP2. This would be critical to modulating the cellular expression of MeCP2 in an appropriate, clinically relevant manner, given the mosaic pattern of *MECP2* silencing characteristic of female patients with Rett syndrome."

Sarah Sinnett, Ph.D., University of Texas Southwestern Medical Center, Co-Inventor of miRARE technology, added, "TSHA-102 pairs a therapeutic gene with miRARE, all within a single vector genome. The miRARE technology was designed to mitigate the risk of MeCP2 overexpression through a post-transcriptional feedback repression mechanism. We are pleased that miRARE permitted efficacy in *Mecp2*$^{-/Y}$ mice without compromising safety in wild-type mice. Importantly, these findings could translate into clinical benefits for treating patients with Rett syndrome."

Preclinical data in neonatal wild-type mice suggest miRARE suppressed toxic overexpression after early intervention with TSHA-102:

- In wild-type mice treated with TSHA-102, new data showed no deleterious impact on survival, neurobehavioral functions and overall health, suggesting miRARE regulated expression of MeCP2 with the below results from the study:
  - No toxicity relative to vehicle treatment
  - No reduction in survival over 36-weeks
  - No treatment effect on Bird Score (a measure of Rett syndrome-like behaviors and pathologies) analysis relative to vehicle treatment
  - No impact on overall growth over the course of the study

This builds on prior preclinical data in neonatal *Mecp2*$^{-/Y}$ knockout mice showing miRARE regulated *MECP2* expression levels in deficient CNS cells with early intervention of TSHA-102:

- In *Mecp2*$^{-/Y}$ knockout mice (mouse model recapitulating developmental, physiological, and behavioral features of human Rett syndrome) treated with TSHA-102 with the below results from the study:
  - 47% survived the 36-week study vs a median survival of 8.1 weeks with vehicle-treated knockout mice, representing a significant ($p<0.0001$) >4-fold extension of their lifespan
  - Restoration of normal and faster-than-normal growth
  - Aggregate Bird Score was significantly improved at several time points, with a significant delay in the onset of severe Rett syndrome-like phenotypes, including the delayed average age of onset for severe clasping from approximately 7 to 21 weeks and severely abnormal gait from approximately 8 to 20 weeks

TSHA-102 is a self-complementary intrathecally delivered AAV9 investigational gene transfer therapy in clinical evaluation for Rett syndrome, a rare

genetic neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene. TSHA-102 is currently being evaluated in the Phase 1/2 REVEAL trial in adult patients with Rett syndrome. The dosing of the first adult patient with TSHA-102 is expected in Q2 2023, with initial available clinical data, primarily on safety, anticipated thereafter in Q2 2023. TSHA-102 has received Orphan Drug and Rare Pediatric Disease designations from the U.S. Food and Drug Administration (FDA) and has been granted Orphan Drug designation from the European Commission for the treatment of Rett syndrome.

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. Together, we leverage our fully integrated platform with a goal 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," "plans," 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-102, 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, 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, 2022, 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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