Taysha Gene Therapies Presents New Preclinical In-vitro Data on TSHA-102 in Rett Syndrome Supporting miRARE Regulation of MECP2 Expression at the European Society of Gene & Cell Therapy (ESGCT) 30th Annual Congress

In vitro data demonstrated the miRARE control element downregulates MECP2 transgene and protein expression in response to cellular levels of MeCP2 in cell culture models

Data recapitulate in vivo findings in neonatal mice demonstrating TSHA-102 regulated MeCP2 expression in deficient CNS cells and avoided toxic overexpression in cells already expressing MeCP2

Available clinical data from the two adult patients dosed with TSHA-102 in the first cohort (low dose) to be reported in mid-November; dosing of first pediatric Rett syndrome patient expected in the first quarter of 2024

DALLAS, Oct. 24, 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 announced new preclinical *in vitro* data on TSHA-102 in Rett syndrome as part of a poster presentation at the European Society of Gene & Cell Therapy (ESGCT) 30th Annual Congress. TSHA-102 is a self-complementary intrathecally delivered AAV9 investigational gene transfer therapy that utilizes a novel miRNA-Responsive Auto-Regulatory Element (miRARE) technology designed to mediate levels of *MECP2* in the CNS on a cell-by-cell basis without risk of overexpression. These data demonstrate the function of the miRARE-RHD1pA regulatory element and its impact on *MECP2* transgene and protein expression in human and mouse cell lines, providing further support for the regulatory control of miRARE.

"Appropriate control of *MECP2* transgene expression based on cellular levels of MeCP2 is fundamental to the development of a safe and effective gene therapy for Rett syndrome, given the mosaic pattern of *MECP2* silencing in females with Rett syndrome," said Sukumar Nagendran, M.D., President, and Head of R&D of Taysha. "These new *in vitro* data recapitulating our *in vivo* findings in neonatal mice further our mechanistic understanding of how the miRARE technology controls post-transcriptional *MECP2* expression and reinforce the potential of TSHA-102 to address the root cause of Rett syndrome. We look forward to reporting available clinical data from the two adult patients dosed with TSHA-102 in the low-dose cohort of the REVEAL Phase 1/2 adult trial in mid-November and expect to dose the first pediatric patient with TSHA-102 in first quarter of 2024."

The preclinical study presented at ESGCT used human (2v6.11) and mouse (N2a) cell culture models to explore the function of miRARE and its impact on *MECP2* transgene and protein expression in the presence or absence of cellular MeCP2 using both viral AAV9 transduction and plasmid transfection containing either miRARE-regulated or SV40 (unregulated) elements.

***In vitro* data showed post-transcriptional gene silencing by miRARE in response to cellular MeCP2 levels can be recapitulated in human and mouse cell lines:**

- miRARE controlled dose-dependent transgene expression of MeCP2 protein via a similar mechanism in both human and mouse cell lines
- miRARE partially silenced transgene expression in neuronal and non-neuronal cell lines; the expression and subsequent downregulation were 4-5-fold higher in neuronal cell lines, supporting tissue-specific expression of MeCP2
- Transgene protein expression was highest in homozygous cells and slightly greater than wild-type in heterozygous cells, demonstrating transgene expression of MeCP2 protein is sensitive to cellular levels of MeCP2 and increases in human cells with both endogenous *MECP2* copies disrupted
- Transgene silencing occurred in part by inducing mRNA decay but more substantially by reducing miniMeCP2 protein accumulation, suggesting that the miRARE technology also acts in cis to prevent translation

About TSHA-102
TSHA-102 is a self-complementary intrathecally delivered AAV9 investigational gene transfer therapy in clinical evaluation for Rett syndrome. TSHA-102 utilizes a novel miRNA-Responsive Auto-Regulatory Element (miRARE) platform designed to mediate levels of MECP2 in the CNS on a cell-by-cell basis without risk of overexpression. TSHA-102 has received Fast Track designation and Orphan Drug and Rare Pediatric Disease designations from the FDA and has been granted Orphan Drug designation from the European Commission.

About Rett Syndrome
Rett syndrome is a rare neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene, which is a gene that's essential for neuronal and synaptic function in the brain. The disorder is characterized by intellectual disabilities, loss of communication, seizures, slowing and/or regression of development, motor and respiratory impairment, and shortened life expectancy. Rett syndrome primarily occurs in females and is one of the most common genetic causes of severe intellectual disability. Currently, there are no approved disease-modifying therapies that treat the genetic root cause of the disease. Rett syndrome caused by a pathogenic/likely pathogenic *MECP2* mutation is estimated to affect between 15,000 and 20,000 patients in the U.S., EU and UK.

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 TSHA-102 to positively impact quality of life and alter the course of disease in the patients we seek to treat and our research, development and regulatory plans for TSHA-102, including timing of expected clinical data and the dosing of additional patients. 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, and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2023, 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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