Taysha Gene Therapies Announces Pivotal Part B Trial Design Details for TSHA-102 in Rett Syndrome Enabled by IRSF Natural History Data and Positive Clinical Data from Part A of the REVEAL Adult/Adolescent and Pediatric Trials Evaluating TSHA-102

Natural history data analysis established patients ≥ six years of age are in developmental plateau, with a ~0% likelihood of gaining/regaining developmental milestones across the core functional domains of Rett syndrome

Written alignment from FDA supports single-arm, open label pivotal trial with primary endpoint of developmental milestone gain/regain in the developmental plateau population (≥ 6 years, intend N=15) with each patient serving as their own control

100% of patients in REVEAL Part A (N=10, 6-21 years) gained/regained ≥ one developmental milestone post-TSHA-102 with concordant improvements across multiple outcome measures; high dose consistently outperformed low dose, with dose-dependent effects deepening over time

No treatment-related SAEs or DLTs following low dose and high dose of TSHA-102

FDA advised the Company to submit pivotal Part B trial protocol and SAP as an amendment to the IND application, which is expected to occur in the current quarter; pivotal trial initiation activities anticipated in Q3 2025

DALLAS, May 28, 2025 (GLOBE NEWSWIRE) -- Taysha Gene Therapies, Inc. (Nasdaq: TSHA) (Taysha or the Company), a clinical-stage biotechnology company focused on advancing adeno-associated virus (AAV)-based gene therapies for severe monogenic diseases of the central nervous system (CNS), today announced details of its planned pivotal Part B trial design for TSHA-102 following written alignment from the U.S. Food and Drug Administration (FDA). Additionally, the Company announced positive clinical data from Part A of the REVEAL Phase 1/2 adolescent/adult and pediatric trials evaluating TSHA-102 in Rett syndrome. The alignment reached with the FDA was supported by the Company's analysis of the International Rett Syndrome Foundation's (IRSF) longitudinal Rett syndrome natural history study data, as well as clinical data from the ongoing REVEAL Phase 1/2 trials.

"Our rigorous analysis of the robust natural history study dataset demonstrated that after six years of age, the likelihood of achieving defined developmental milestones across the core functional domains of Rett syndrome is highly improbable. Therefore, it is quite striking that we observed a 100% responder rate following treatment with TSHA-102, with all pediatric, adolescent and adult patients across varying disease severity gaining or regaining one or more developmental milestone that represents activities of daily living that are important to caregivers and clinicians. We believe this objective and clinically meaningful primary endpoint has the potential to redefine treatment expectations and expand the possibilities of gene therapy for patients with Rett syndrome," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "We believe aligning with the FDA on key elements of our proposed pivotal trial design validates these important findings that underpin our pivotal trial design and strengthen our conviction in the transformative potential of TSHA-102. Importantly, this progress sets us on an efficient and expeditious path to potentially deliver TSHA-102 to patients and families suffering from this devastating disease with high unmet need. We plan to submit the pivotal trial protocol and SAP as an amendment to the IND application this quarter and anticipate initiating this pivotal program in the third quarter of 2025."

Dr. Jeffrey Neul, M.D., Ph.D., Rett Specialist who served as Administrative Head of the Rett Syndrome Natural History Study added, "This innovative analysis and cumulative incidence models of the Rett syndrome natural history dataset help shape our understanding of the disease trajectory by establishing that the likelihood of gain and regain of developmental milestones is predictable after six years of age. Importantly, these data allow us to objectively measure how transformative therapies impact functional aspects of the disease that are essential to activities of daily living. I believe these insights uncovered via the collaboration of academic researchers and a patient advocacy group with industry partner, Taysha, will be instrumental in shaping the future of therapeutic development for Rett syndrome."

Laura Hameed, Chief Executive Officer of the International Rett Syndrome Foundation (IRSF), added, "On behalf of IRSF, I want to thank the families, clinicians, and researchers whose dedication made the Rett syndrome Natural History Study possible. Their participation provided a deeper understanding of how Rett progresses over time, insights that are now helping shape meaningful clinical outcome measures and could someday lead to new treatments. We're pleased to support Taysha's efforts to build on this foundation and are hopeful about the progress it represents for families living with Rett syndrome."

Analysis of IRSF's Longitudinal Rett Syndrome Natural History Study Data Supported Taysha's Pivotal Trial Design for TSHA-102

- N = ~1100 females with confirmed Rett syndrome diagnosis, with up to 14 years follow-up, representing the largest available Rett syndrome natural history study dataset
- Developed age- and time-based cumulative incidence models of longitudinal natural history data across 28 developmental milestones in the core functional domains of fine motor, gross motor and communication
- Findings demonstrated patients ≥ six years of age have reached a developmental plateau, with an exceedingly low (0% to <6.7%) likelihood of gaining new or regaining developmental milestones that were lost after a defined number of years

Obtained Written Alignment with the FDA on Key Elements of TSHA-102 Pivotal Part B Trial Design Following Discussions Under the Regenerative Medicine Advanced Therapy (RMAT) Pathway

- Single-arm, open-label trial with patients serving as their own control (intend N=15)
- Enrollment of females in the developmental plateau population of Rett syndrome (≥ 6 years)
- Primary endpoint will assess developmental milestone gain or regain

    - During advanced discussions with the FDA, reached alignment on the definition of a responder: “gain/regain of ≥ one defined developmental milestone.” The FDA provided guidance on an additional analysis to further support the responder definition, which the Company has completed and intends to submit, alongside the final protocol and statistical analysis plan (SAP), as part of the Investigational New Drug (IND) amendment.
    - Video-based determination of milestone gain/regain will be performed by independent, blinded central raters according to predefined definitions of achievement for each developmental milestone
- Safety of TSHA-102 will be evaluated in females in the pre-developmental plateau population of Rett syndrome (2-6 years), with efficacy data extrapolated from the developmental plateau population
- 12-month primary analysis, and intend to perform a 6-month interim analysis
- The FDA advised the Company to submit the pivotal Part B trial protocol and the associated SAP as an amendment to its IND application, eliminating the need for formal end-of-phase meeting

Clinical Data from Part A of Ongoing REVEAL Phase 1/2 Adolescent/Adult and Pediatric Trials

Efficacy data based on May 19, 2025, data cutoff, included 10 females with Rett syndrome aged 6-21 years (high dose, N=6; low dose, N=4) treated with the high dose ($1x10^{15}$ total vg) or low dose ($5.7x10^{14}$ total vg) of TSHA-102

- 100% of pediatric, adolescent and adult patients gained ≥ one defined developmental milestone across the core functional domains of fine motor, gross motor and communication post-TSHA-102, with a ~0%* likelihood of being achieved without treatment based on natural history data
    - A total of 22 developmental milestones were achieved across the 10 patients, as determined by multiple independent central raters based on video-evidenced evaluation according to predefined definitions of achievement for each developmental milestone
    - Developmental milestones were achieved early post-TSHA-102, with new gains/regains demonstrated over time (i.e., spoke in phrases with meaning, finger fed, walked with support)
    - High dose cohort achieved 100% responder rate 25% faster than the low dose cohort, supporting the accelerated functional benefit observed with the high dose
- Improvements observed across multiple clinician-assessed outcome measures, including Revised Motor Behavior Assessment (R-MBA) and Clinician Global Impression – Improvement (CGI-I), corroborated the developmental milestone gains/regains demonstrated post-TSHA-102
- High dose cohort outperformed low dose cohort across multiple outcome measures six months post-treatment, with dose-dependent effects deepening over time ≥ nine months post-treatment

Safety data based on May 20, 2025, data cutoff, included 12 females with Rett syndrome aged 6-21 years treated with TSHA-102 (high dose, N=8; low dose, N=4)

- High dose and low dose of TSHA-102 have been generally well tolerated with no treatment-related serious adverse events (SAEs) or dose limiting toxicities (DLTs)
- All treatment-emergent AEs related to TSHA-102 were mild to moderate in severity

Presentation with additional details and accompanying figures are available on a Current Report on Form 8-K being filed concurrently with this press release and available on the SEC’s website at www.sec.gov.

Anticipated Milestones

- Expect to submit pivotal Part B trial protocol and associated SAP as an amendment to the IND application in the current quarter
- Taysha will host three oral presentations related to TSHA-102 at the upcoming 2025 IRSF Rett Syndrome Scientific Meeting taking place in Boston from June 9-11, 2025
- Pivotal Part B trial site activation and trial initiation activities anticipated in the third quarter of 2025

About TSHA-102
TSHA-102 is a self-complementary intrathecally delivered AAV9 investigational gene transfer therapy in clinical evaluation for Rett syndrome. Designed as a one-time treatment, TSHA-102 aims to address the genetic root cause of the disease by delivering a functional form of *MECP2* to cells in the CNS. TSHA-102 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. TSHA-102 has received Regenerative Medicine Advanced Therapy, Fast Track and Orphan Drug and Rare Pediatric Disease designations from the FDA, Orphan Drug designation from the European Commission and Innovative Licensing and Access Pathway designation from the Medicines and Healthcare products Regulatory Agency.

About Rett Syndrome
Rett syndrome is a rare neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene encoding methyl CpG-binding protein 2 (MeCP2), which is essential for regulating neuronal and synaptic function in the brain. The disorder is characterized by loss of communication and hand function, slowing and/or regression of development, motor and respiratory impairment, seizures, intellectual disabilities and shortened life expectancy. Rett syndrome progression is divided into four key stages, beginning with early onset stagnation at 6 to 18 months of age followed by rapid regression, plateau and late motor deterioration. 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 U.K.

About Taysha Gene Therapies
Taysha Gene Therapies (Nasdaq: TSHA) is a clinical-stage biotechnology company focused on advancing adeno-associated virus (AAV)-based gene therapies for severe monogenic diseases of the central nervous system. Its lead clinical program TSHA-102 is in development for Rett syndrome, a rare neurodevelopmental disorder with no approved disease-modifying therapies that address the genetic root cause of the disease. With a singular focus on developing transformative medicines, Taysha aims to address severe unmet medical needs and dramatically improve the lives of patients and their caregivers. The Company's management team has proven experience in gene therapy development and commercialization. Taysha leverages this experience, its manufacturing process and a clinically and commercially proven AAV9 capsid in an effort to rapidly translate treatments from bench to bedside. For more information, please visit 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, including the reproducibility and durability of any favorable results initially seen in patients dosed to date in clinical trials, including with respect to functional milestones, and our other product candidates 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, including the timing of initiating additional trials, reporting data from our clinical trials and making regulatory submissions, communications from the FDA on the regulatory pathway for TSHA-102, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and our current cash resources supporting our planned operating expenses and capital requirements into the fourth quarter of 2026. 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, 2024, and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, 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. 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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**Cumulative incidence models of natural history data demonstrate the likelihood of developmental milestone gain/regain ranged from 0% to <6.7% in this population*

Source: Taysha Gene Therapies, Inc.