Taysha Gene Therapies Announces FDA Breakthrough Therapy Designation and Provides Positive Regulatory Update on TSHA-102 in Rett Syndrome

Breakthrough Therapy designation granted based on FDA's review of available clinical evidence of safety and efficacy from all 12 patients treated in Part A of the REVEAL Phase 1/2 trials

Finalized FDA alignment on REVEAL pivotal trial protocol and SAP following resolution of remaining clinical and statistical queries to IND application amendment; on track to begin patient enrollment in Q4 2025

Key pivotal trial design elements remain unchanged, including 6-month interim analysis to potentially expedite BLA submission based on the rigorous developmental milestone evaluation in Part A showing an unprecedented response rate at 6 months post-TSHA-102 that deepened over time

DALLAS, Oct. 02, 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 the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to TSHA-102, an intrathecally delivered AAV9 gene therapy with disease modifying potential, for the treatment of Rett syndrome. Additionally, the Company announced that it has finalized alignment with the FDA on the REVEAL pivotal trial protocol and statistical analysis plan (SAP) that are intended to support the planned Biologics License Application (BLA) submission for TSHA-102, following the resolution of remaining clinical and statistical queries.

Breakthrough Therapy designation and finalized FDA alignment on the pivotal trial protocol and SAP were based on the FDA's review of positive clinical evidence from Part A of the REVEAL Phase 1/2 adolescent/adult and pediatric trials.

Breakthrough Therapy Designation Granted by FDA for TSHA-102 in Rett Syndrome

The FDA grants Breakthrough Therapy designation to expedite the development and regulatory review of an investigational therapy intended to treat a serious condition. A drug is eligible for this designation if it demonstrates preliminary clinical evidence of substantial improvement over available treatments in one or more clinically significant endpoints.

Clinical evidence supporting Breakthrough Therapy designation for TSHA-102 included previously disclosed Part A REVEAL clinical data demonstrating a generally well-tolerated safety profile and a 100% response rate post-TSHA-102 (May 2025 data cutoff) for the pivotal trial primary endpoint of the gain/regain of ≥ one defined developmental milestone, with <6.7% likelihood of being achieved without treatment based on natural history data. These findings were corroborated by dose-dependent improvements in multiple outcome measures, including Revised Motor Behavior Assessment (R-MBA) and Clinician Global Impression – Improvement (CGI-I).

"Breakthrough Therapy designation highlights the FDA's recognition of both the significant unmet medical need across the estimated 10,000 patients suffering from Rett syndrome in the U.S. and the potential of TSHA-102 to redefine the treatment paradigm for this devastating disease. This designation was granted following the FDA's review of available clinical data from the 12 patients treated in Part A of our REVEAL trials, which support the potential of TSHA-102 to improve function and enable achievement of developmental milestones across core areas of disease that may significantly impact patient and caregiver lives," said Rumana Haque-Ahmed, Chief Regulatory Officer of Taysha. "The disease burden in Rett syndrome continues to be significant, and we are encouraged by the potential of TSHA-102 to address its underlying cause. We look forward to continued collaboration with the FDA as we advance toward potential registration."

Finalized FDA Alignment on the REVEAL Pivotal Trial Protocol and SAP Following Resolution of Clinical and Statistical Queries to the Investigational New Drug (IND) Application Amendment for TSHA-102

Previously aligned upon key design elements for the REVEAL pivotal trial protocol and SAP in support of the planned BLA submission remain unchanged, including:

- **Inclusion of a 6-month interim analysis that may serve as the basis for BLA submission**: enabled by the rigorous, objective evaluation criteria used to evaluate developmental milestone achievement in Part A of the REVEAL Phase 1/2 trials and the unprecedented 83% response rate seen at six months following high dose TSHA-102 (5 out of 6 patients; May 2025 data cutoff) in Part A that deepened over time
- **Response rate of 33% (5 out of 15 patients) is the minimum threshold for success sufficient to reject the null hypothesis**: based on Taysha's natural history data analysis, the null hypothesis is that one out of 15 patients aged ≥6 years may gain/regain one of the 28 natural history defined developmental milestone without treatment, corresponding to a response rate of 6.7%

Sukumar Nagendran, M.D., President and Head of R&D of Taysha added, "We are pleased to have finalized alignment with the FDA on our pivotal trial protocol and SAP, including the 6-month interim analysis that has potential to expedite our BLA submission for TSHA-102 by at least two full quarters. Importantly, the inclusion of an interim analysis was enabled by the rigorous criteria we developed in Part A to evaluate the therapeutic impact of TSHA-102 and the unprecedented early responses observed across patients that continue to deepen over time. This regulatory progress reinforces our BLA readiness and allows us to focus on execution. We remain on track to initiate patient enrollment for our REVEAL pivotal trial in the fourth quarter of 2025."

The REVEAL pivotal trial is a single-arm, open-label trial with each patient serving as their own control. A single intrathecal administration of high dose TSHA-102 ($1x10^{15}$ total vector genomes (vg)) will be evaluated in 15 females between the ages of 6 and less than 22 years in the developmental

plateau population of Rett syndrome. The primary endpoint will assess response rate, defined as the percentage of patients who gain or regain one or more defined developmental milestone from a list of 28 across the core functional domains of communication, fine motor and gross motor, following dosing with TSHA-102. Selected milestones have a 0% to <6.7% likelihood of spontaneous gain/regain in the untreated Rett syndrome population aged ≥ 6 years based on natural history data. Standardized milestone assessments will be administered and captured on video at pre- and post-treatment timepoints, with determination of milestone gain/regain by video-evidence review by independent, blinded central raters based on prespecified definitions of achievement for each milestone.

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 Breakthrough Therapy, 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, but are not limited to, statements concerning the potential of TSHA-102 and Taysha's other product candidates to positively impact quality of life and alter the course of disease in the patients Taysha seeks to treat, its research, development and regulatory plans for its 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, Taysha's ability to realize the benefits of Breakthrough Therapy Designation and the potential market opportunity for Taysha's 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 Taysha's business are described in detail in its SEC filings, including in Taysha's Annual Report on Form 10-K for the full-year ended December 31, 2024 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2025, which are available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that Taysha makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Taysha disclaims any obligation to update these statements except as may be required by law.

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