Taysha Gene Therapies Announces Positive Clinical Data Across Adult and Pediatric Patients from Low Dose Cohort in Ongoing REVEAL Phase 1/2 Trials Evaluating TSHA-102 in Rett Syndrome

Durable improvements across consistent clinical domains in both adult and pediatric patients, including motor skills, communication/socialization, autonomic function, seizures, and an encouraging safety profile seen across adult (up to 52 weeks) and pediatric (up to 22 weeks) patients with different genetic mutation severity

Longer-term data from both adult patients showed sustained and new improvements across multiple efficacy measures and clinical domains following the completion of steroid taper (patient one: sat unassisted for first time in over a decade, normalized sleep, stabilized seizures; patient two: improved hand stereotypies and breathing, seizure-free for 8.5 months at 25% lower anti-seizure medication)

Initial data from first two pediatric patients showed improvements across multiple efficacy measures and clinical domains, with early evidence of developmental gains (patient one: improved hand function, grasp and gross motor coordination, gained visual reception and receptive language skills; patient two: gained ability to stand up from chair and walk up a stair, increase in seizure-free days)

IDMC approved Company's request for early advancement to cohort two (high dose) in the REVEAL pediatric trial ; dosing expected in Q3 2024 following IDMC review of initial safety data from the first high dose patient in the adolescent and adult trial

Company will host webcast today at 8:00 AM Eastern Time

DALLAS, June 18, 2024 (GLOBE NEWSWIRE) -- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), 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 positive longer-term clinical data from the ongoing REVEAL Phase 1/2 adolescent and adult trial and initial clinical data from the REVEAL Phase 1/2 pediatric trial evaluating TSHA-102 in Rett syndrome.

"We are highly encouraged by the safety profile and broad clinical response observed across multiple domains in both the adult and pediatric patients with different genetic mutation severity treated with the low dose of TSHA-102," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "The longer-term follow up data indicate a durable response with sustained and new improvements across multiple clinical domains in both adult patients, and importantly, both pediatric patients showed initial improvements across consistent clinical domains, with early evidence of developmental gains following treatment with TSHA-102. We believe these improvements in adult and pediatric patients further reinforce the potential of TSHA-102 to be transformative for a broad range of patients with Rett syndrome."

Elsa Rossignol, M.D., FRCP, FAAP, Associate Professor in Neuroscience and Pediatrics at the Université de Montréal and Principal Investigator of the REVEAL adolescent and adult trial at the CHU Sainte-Justine added, "TSHA-102 was well-tolerated in both adult patients treated, with no serious adverse events or dose-limiting toxicities as of week 52 and week 36 post-treatment for the first and second patient, respectively. It's encouraging that we continue to see improvements across multiple clinical domains in the longer-term assessments with no diminution of effect. The first adult patient sustained improvements at week 52 post-treatment after the completion of her steroid and sirolimus taper, including regaining movement in her legs, the gained ability to sit unassisted for the first time in over a decade and gained function in her non-dominant hand. She continues to show vastly increased interest in social communication and activities, as well as improvements in breathing dysrhythmia and normalized sleep behaviors for the first time in 20 years. The second adult patient showed sustained improvements following the completion of her steroid taper at week 25 post-treatment, including reduced hand stereotypies for the first time since regression at age three, sustained improvements in breathing dysrhythmia and a significant reduction in seizures, as she has been seizure-free for 8.5 months relative to experiencing 2-4 seizures per week pre-treatment. Additionally, the patient showed improvement in posture and stability at week 25 post-treatment. We believe these longer-term clinical data support the durability and broad clinical benefits of TSHA-102 in adult patients with the most advanced stage of Rett syndrome."

REVEAL Phase 1/2 Adolescent and Adult Trial (Canada and U.S.): a first-in-human, open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in adolescent and adult females aged 12 years and older with Rett syndrome due to *MECP2* loss-of-function mutation. TSHA-102 is administered as a single lumbar intrathecal injection. Dose escalation will evaluate two dose levels of TSHA-102 sequentially. The maximum tolerated dose (MTD) or maximum administered dose (MAD) established in Part A will then be administered during dose expansion in Part B of the study.

- Completed dosing in cohort one (low dose, n=2) of $5.7x10^{14}$ total vg
- Dosed first patient in cohort two (high dose, n=3) of $1x10^{15}$ total vg in the second quarter of 2024
- Initial available safety and efficacy data from cohort two expected in the second half of 2024

Longer-term data from the first adult patient (20 years old; large *MECP2* deletion; associated with severe phenotype) and second adult patient (21 years old; missense *MECP2* mutation; associated with milder phenotype) with late motor deterioration, stage four Rett syndrome dosed with TSHA-102 in the low dose cohort:

- Generally well-tolerated with no serious adverse events (SAEs) related to TSHA-102 or dose-limiting toxicities (DLTs) as of 52-week assessment post-treatment for patient one and 36-week assessment post-treatment for patient two
- Sustained and new improvements observed across multiple clinical domains relative to baseline, as of 52-weeks post-treatment for patient one, based on clinical observations reported by the Principal Investigator (PI), including:
    - **Motor skills**: improved hand function and gained ability to sit unassisted for first time in over a decade and move

legs (patient one), and improved hand stereotypies for the first time since regression at age three and improved posture and stability (patient two)

- **Communication/Socialization**: improved social interest, vocalization and ability to use eye-gaze driven communication device (patient one), and improved social interest with increased response to spoken words and eye contact (patient two)
- **Autonomic function**: improved breathing patterns, normalized sleep quality/duration for first time in 20 years and improved circulation (patient one), and improved breathing patterns and circulation (patient two)
- **Seizures**: stable seizure events (patient one), and significantly reduced seizure events (patient two)

- Seizure Diary and caregiver reports:
  - **Patient one at week 52 post-treatment**: stable seizure events at lower levels of anti-seizure medication relative to baseline
  - **Patient two at week 36 post-treatment**: significantly reduced seizure events at 25% lower levels of anti-seizure medication relative to baseline (2-4 seizures per week), with 8.5 months reported seizure-free
- Clinical improvements seen across multiple efficacy measurements relative to baseline include:
  - **Patient one at week 52 post-treatment**: Sustained improvement in Clinical Global Impression–Improvement (CGI-I), Clinical Global Impression–Severity (CGI-S) and Seizure Diaries, with new improvement in Revised Motor Behavior Assessment (R-MBA), Parental Global Impressions–Improvement (PGI-I) and Rett Syndrome Behavior Questionnaire (RSBQ) following completion of steroid and sirolimus taper
  - **Patient two at week 25 post-treatment**: Sustained improvement in CGI-I and PGI-I, with new improvement in R-MBA and Seizure Diaries following completion of steroid taper

Colleen Buhrfiend, M.D., Assistant Professor of Pediatrics at RUSH University Medical Center said, “Following treatment with TSHA-102, both pediatric patients with different genotypes and disease severity had challenging side effects related to immunosuppressant treatment but showed a well-tolerated safety profile with no SAEs or DLTs related to TSHA-102 as of week 22 and week 11 post-treatment for the first and second pediatric patient, respectively, as well as some initial improvements across multiple clinical domains and early evidence of new developmental gains. Specifically, at week 12 post-treatment, the first patient’s truncal stability and balance improved, which enabled her to sit unassisted for a longer duration and move her leg on her own to better take a step with assistance. Her hand function improved, and she was able to hold an object for three minutes following treatment compared to up to 12 seconds pre-treatment. Additionally, she communicated new words using an eye-gaze driven communication device and gained the ability to identify object functions for the first time. At week eight post-treatment, the second pediatric patient’s gait, speed and stability improved, resulting in the ability to walk longer distances. Her hand function showed initial improvement, and she gained some new skills that were previously lost, including the ability to stand up from a chair and walk up a stair. The initial improvements observed across multiple areas of disease in both pediatric patients are encouraging early signs of possible benefit.”

REVEAL Phase 1/2 Pediatric Trial (U.S. and U.K.): an open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in pediatric females with Rett syndrome due to *MECP2* loss-of-function mutation. TSHA-102 is administered as a single lumbar intrathecal injection. Part A of the study will focus on determining MAD and MTD in patients aged 5 to 8 years old. Part B is the dose expansion phase and will evaluate TSHA-102 at the MAD or MTD in two age cohorts (5 to 8 years and 3 to 5 years).

- Completed dosing in cohort one (low dose, n=2) of $5.7x10^{14}$ total vg
- Received IDMC approval of Company’s request to advance early to cohort two (high dose, n=3) evaluating $1x10^{15}$ total vg, with dosing to occur following IDMC review of the 42-day safety data from the first high dose patient in the adolescent and adult trial
- Dosing of first pediatric patient in cohort two expected in the third quarter of 2024
- Initial available safety and efficacy data from cohort two expected in the second half of 2024

Initial results from the first pediatric patient (6 years old; *MECP2* deletion; associated with moderate phenotype) and second pediatric patient (7 years old; missense *MECP2* mutation; associated with milder phenotype) with pseudo stationary symptoms, stage three Rett syndrome dosed with TSHA-102 in the low dose cohort:

- Generally well-tolerated with no SAEs related to TSHA-102 or DLTs as of 22-week assessment post-treatment for patient one and 11-week assessment post-treatment for patient two; there were two SAEs reported in the second pediatric patient that were not deemed treatment-related (both were related to underlying disease and one was also attributed to immunosuppression) and have resolved
  - Significant challenges with AEs dues to immunosuppressive regimen
- Initial improvements observed across multiple clinical domains relative to baseline as of 12-weeks post-treatment for patient one and 8-weeks post-treatment for patient two, based on clinical observations reported by the PI:

- **Motor skills**: improved hand function with the ability to hold an object for three minutes vs up to 12 seconds at baseline, improved truncal stability and balance with the gained ability to move her leg on her own to better take a step with assistance and sit unassisted for a longer duration, and improved swallowing and oral intake relative to gastrostomy tube feeding (patient one), and improved hand function and gait, speed and stability when walking with some new skills gained, including standing up from a chair and walking up a stair (patient two)
- **Communication/Socialization**: improved communication and ability to use eye-gaze driven communication device and gained visual reception and receptive language skills (patient one), and improved social interest and eye contact (patient two)
- **Autonomic function**: reduced breath holding (patient one), and improved breathing patterns (patient two)
- **Seizures**: stable seizure events (patient one), and increase in days reported seizure-free since dosing (patient two)

- Seizure Diary and caregiver reports:
  - **Patient one at 22-weeks post-treatment**: stable seizure events relative to baseline
  - **Patient two at 11-weeks post-treatment**: increase in days reported seizure-free since dosing relative to baseline (2-4 seizures daily), although a new anti-seizure medication was added to patient two's regimen at week four, which she has maintained through week 11 post-treatment
- Clinical improvements seen across multiple efficacy measurements relative to baseline include:
  - **Patient one at 12-weeks post-treatment**: CGI-I, PGI-I, R-MBA, Adapted Mullen Scales of Early Learning (MSEL-A) and Seizure Diaries
  - **Patient two at 8-weeks post-treatment**: CGI-I, PGI-I, RSBQ, R-MBA and Seizure Diaries

Presentation with additional details and accompanying figures are available through Taysha's website here.

Conference Call and Webcast Information
Taysha management will hold a conference call and webcast today at 8:00 a.m. ET to discuss these clinical data for TSHA-102 in Rett syndrome. Participants can register for the live webcast here. The live webcast and replay will be available through Taysha's website here.

2024 IRSF Rett Syndrome Scientific Meeting Presentation Details
These data will also be presented by Elsa Rossignol, M.D., FRCP, FAAP, Principal Investigator of the REVEAL adolescent and adult trial at CHU Sainte-Justine and Colleen Buhrfiend, M.D., of RUSH University Medical Center at the 2024 International Rett Syndrome Foundation (IRSF) Rett Syndrome Scientific Meeting during a poster presentation on Tuesday, June 18 at 5:15 p.m. MT and during an oral presentation on Wednesday, June 19 at 11:00 a.m. MT.

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 lumbar intrathecal 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, 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, including the anticipated timelines for reporting data for the TSHA-102 REVEAL trials and the trial design of the TSHA-102 REVEAL trials, 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 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, 2023, which is 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.

Company Contact:
Hayleigh Collins
Director, Head of Corporate Communications, and Investor Relations
Taysha Gene Therapies, Inc.
hcollins@tayshagtx.com

Media Contact:
Carolyn Hawley
Inizio Evoke
Carolyn.hawley@inizioevoke.com

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