November 13, 2024

Dear Rett Patient Advocacy Leaders,

We are writing to share a series of updates about Taysha's investigational gene therapy for Rett syndrome (TSHA-102) which were provided in a press release today. Please find a summary of these updates below.

- **High Dose of TSHA-102 was Generally Well Tolerated.** TSHA-102 was generally well tolerated with no serious adverse events (SAEs) or dose-limiting toxicities (DLTs) in the first two adolescent/adult patients up to 20 weeks and in the first pediatric patient up to six-weeks. The third high dose adult/adolescent patient was dosed, and the second high dose pediatric patient was enrolled.
- **Continued Enrollment in High Dose Cohorts.** The Independent Data Monitoring Committee (IDMC) reviewed available clinical data from the two high dose adult/adolescent participants and the first high dose pediatric participant and approved proceeding with enrollment in both adolescent/adult and pediatric studies at the high dose level.
- **Completed Positive Regenerative Medicine Advanced Therapy (RMAT) Type B Meeting.** Aligned with the Food & Drug Administration (FDA) on the continued development approach for TSHA-102 and advanced discussion on Part B trial design, endpoints, and potential use of established natural history dataset, following the agency's review of available data.
- **Presented Biodistribution Data Further Supporting the Clinical Potential of Intrathecal Delivery.** Data from an analysis of five non-human primate (NHP) studies evaluating AAV9 gene therapy delivery were presented during a poster presentation at the 31st Annual Congress of the European Society of Gene & Cell Therapy in October 2024.

Please find below a list of answers to some frequently asked questions.

What are the goals of the REVEAL Adolescent & Adult (age 12+) and the REVEAL Pediatric Phase 1/2 (ages 5-8) Studies?

- The goals of the REVEAL studies are to evaluate whether TSHA-102 is safe and tolerable, to determine whether it may have beneficial effects and to assess two dose levels to find the highest tolerable dose.

How many participants have received TSHA-102 across the two REVEAL studies to date?

- A total of eight (8) participants have received a one-time administration of TSHA-102 to date.
- In the REVEAL Adolescent & Adult Study, five (5) participants have been dosed.
    - Two (2) participants have been dosed in cohort one (low dose).
    - Three (3) participants have been dosed in cohort two (high dose).
- In the REVEAL Pediatric Study, three (3) participants have been dosed.
    - Two (2) participants have been dosed in cohort one (low dose).
    - One (1) participant has been dosed in cohort two (high dose). A second participant has been enrolled in cohort two and dosing is scheduled in Q4 2024.
- Cohort one (low dose) across both REVEAL studies is now considered complete. Going forward, participants in both REVEAL Phase 1/2 studies will receive high dose TSHA-102.

Where are the REVEAL Phase 1/2 studies being conducted?

- The **REVEAL Adolescent and Adult Study (age 12+)** is being conducted in the U.S. and Canada. For additional information, a list of clinical trial sites and contact information please visit https://clinicaltrials.gov/study/NCT05606614.
    - In the U.S. and Canada, study site locations include San Diego, CA, Chicago, IL, Boston, MA, Saint Paul, MN, Dallas, TX and Montreal, QC.
- The **REVEAL Pediatric Study (ages 5-8)** is being conducted in the U.S., Canada, and the U.K. For additional information, a list of clinical trial sites and contact information please visit https://clinicaltrials.gov/study/NCT06152237.
    - In the U.S. and Canada, study site locations include San Diego, CA, Chicago, IL, Boston, MA, Saint Paul, MN, Saint Louis, MO, Philadelphia, PA, Nashville, TN, Dallas, TX and Montreal, QC. The U.K. site in London is scheduled to be activated in 2025.

What is Taysha's investigational gene therapy (TSHA-102)?

- Taysha's investigational gene therapy approach for Rett syndrome is made up of a transgene, regulator, and vector:
    - The healthy MECP2 gene (**transgene**) is designed to provide instructions needed to make MeCP2 protein. TSHA-102 uses a miniature, fully functional form of the MECP2 gene (miniMECP2).
    - The **regulator** is used to "turn on" or "turn off" the transgene, so that MeCP2 protein is only made in the cells that need it. TSHA-102 uses miRNA-Responsive Auto-Regulatory Element (miRARE) technology to fine-tune the production of MeCP2 protein—not too much and not too little.
    - The **vector,** an adeno-associated virus (AAV), acts as a delivery vehicle to bring miniMECP2 and miRARE to the cells of the brain and central nervous system.
- **Taysha's approach uses intrathecal (IT) administration**—often called a "spinal tap"— to directly deliver the investigational gene therapy to the cerebrospinal fluid (CSF) in the lower back. From there, it mixes with the CSF, which continuously circulates throughout the central nervous system, including the spinal cord and the brain.

When will the next release of interim findings from the REVEAL Studies take place?

- Taysha plans to share clinical data from the high dose cohorts and an update on clinical data from the low dose cohorts in both REVEAL trials in the first half of 2025.

We would like to thank the entire Rett community and the Rett patient advocacy groups for your continued partnership. We would also like to acknowledge the individuals and families who choose to participate in research to help better understand the potential of gene therapy for Rett syndrome.

We look forward to sharing more information as it is publicly available.

Sincerely,
The Taysha Patient Affairs Team
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