June 19, 2025

**Dear Rett Patient Advocacy Leaders,**

We are grateful for your continued engagement and the thoughtful questions you've shared following our recent press release and presentations at the International Rett Syndrome Foundation (IRSF) Scientific Meeting in Boston (June 9–11, 2025). We hope to address some of your questions here.

**What is the status of Taysha's gene therapy clinical trials for Rett syndrome?**

- Taysha is studying TSHA-102, an investigational gene therapy for Rett syndrome, in two parts – Part A and Part B.
- **Part A** is designed to test the safety, tolerability, and potential benefits of TSHA-102. It also assesses two different dose levels ($5.7x10^{14}$ vg and $1x10^{15}$ vg) to determine the highest tolerable dose. Part A includes the **REVEAL Pediatric Study** for girls ages 5–8 and the **REVEAL Adolescent & Adult Study** for girls and women ages 12 and older.
    - Enrollment is complete in Part A, with a total of 12 participants, aged 6-21 years at the time of dosing. Four received the lower dose ($5.7x10^{14}$ vg) and eight received the higher dose (and $1x10^{15}$ vg). These participants will continue to be monitored throughout the study.
- **Part B** will be the **pivotal study**, which means it is intended to collect information about safety and potential benefits from additional participants to support potential regulatory approval.

**What are the latest interim results from Part A of the REVEAL Studies?***

- Safety data from Part A included 12 females with Rett syndrome aged 6-21 years at time of dosing (four in the low dose cohort and eight in the high dose cohort), as of May 20, 2025.
    - There were **no treatment-related serious adverse events or dose-limiting toxicities at the low or high dose**.
    - Side effects were **mild or moderate.** The most common included fever and tiredness, as well as temporary changes in liver enzyme and spinal fluid proteins, which are known to occur because of viral gene therapies.
- Data from Part A to determine potential benefits of TSHA-102 were available for 10 participants aged 6-21 years at time of dosing (four in the low dose cohort and six high dose cohort) as of May 19, 2025.
    - All participants gained or regained one or more developmental milestones across fine motor/hand function, gross motor function and communication following administration of TSHA-102. Milestone gains were determined by multiple independent researchers based on video evidence.
    - Across these 10 participants, a total of 22 milestones were achieved, including:
        - **Communication:** spoke in phrases (2 words or more) with meaning, used word(s) with meaning, followed a command without a gesture, followed a command with a gesture, pointed for something they wanted, identified body parts
        - **Fine motor/hand function:** held bottle unpropped, finger fed, reached for a toy, transferred an object from one hand to another
        - **Gross motor:** walked with support, stood while holding on, pulled to standing, sat without support
    - Participants also showed improvements across multiple standardized Rett syndrome assessments including the CGI-I and R-MBA.

**It is important to note that we cannot make any conclusions on interim findings of a clinical trial until all enrolled subjects are dosed and evaluated for the duration of the study, and once all the data have been collected and analyzed. Making conclusions about interim data may not accurately predict the full risk/benefit profile of an investigational product.*

**What's next – what are the plans for Part B of the study?**

- Part B, or the pivotal study, will be a **single-arm trial** (no placebo group), with each participant serving as their own control. This means that each participant's abilities following administration of TSHA-102 will be compared to their abilities before they received treatment.
- The study intends to enroll **approximately 15 females**, aged **6 years and older**, with classic Rett syndrome. The maximum age limit has not yet been determined.
- The study will evaluate whether participants gain or regain important developmental milestones across fine motor, gross motor and communication, as well as continue to evaluate safety.
- Taysha plans to submit the study protocol to the FDA in Q2 2025.

**Why are you assessing developmental milestones?**

- Taysha analyzed the International Rett Syndrome Foundation (IRSF) Natural History Study (NHS) data from 1,000+ participants with up to 14 years of follow-up. The analysis found that without treatment or intervention, gaining or regaining certain developmental milestones is rarely seen after age six.
- Therefore, evaluating whether participants aged six and older gain or regain developmental milestones can serve as an important measure of how well TSHA-102 is working.
- Feedback from caregiver research helped us understand which developmental milestones would be meaningful and improve activities of daily living. There are 28 developmental milestones that met these criteria and will be evaluated in the pivotal study.

**Will Taysha study TSHA-102 in girls younger than 6 years old?**

- A main goal of Part B, the pivotal REVEAL study, is to see whether participants gain or regain important developmental milestones after treatment. So, the researchers need to enroll girls aged 6 years and older who are in the "developmental plateau" stage and highly unlikely to gain/regain developmental milestones without treatment based on the IRSF NHS data.
- Additionally, Taysha will be conducting a **separate safety-focused study** to assess the tolerability of TSHA-102 in **younger girls aged 2-<6 years**. Details about this study will be shared with the community in the future.

**Can I sign up my loved one for a trial?**

- Part A is no longer enrolling new participants. We expect to share information about **eligibility criteria and site locations** for the pivotal study in Q3 2025.
- We encourage you to discuss with your physician whether a clinical trial may be a good fit for your family.

**Still have questions?** Please reach out to us at **patientaffairs@tayshagtx.com**.

**Thank You**

We are deeply inspired by the resilience of individuals and families affected by Rett syndrome. Whether you're participating in a clinical trial, natural history study or registry, sharing your experiences, or staying informed—you are helping shape the future of treatment.

Thank you for being part of this journey. We look forward to sharing more with you soon.

**Sincerely,**
**The Taysha Patient Affairs Team**
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