October 2, 2025

Dear Rett Syndrome Community,

We are writing to share an update on TSHA-102, Taysha's investigational gene therapy for Rett syndrome. Below is a summary of the latest news.

Key Updates

- **The U.S. Food & Drug Administration (FDA) granted Breakthrough Therapy Designation** to TSHA-102 based on FDA's review of available clinical evidence of safety and efficacy from all 12 participants treated in Part A of REVEAL Phase 1/2 trials.
- **Taysha has finalized alignment on the REVEAL Pivotal Study** protocol and statistical analysis plan with the FDA, and we are on track to begin enrolling participants in the fourth quarter of 2025.
- **The REVEAL Pivotal Study will include a 6-month interim analysis** of the primary endpoint which could help accelerate discussions with the FDA about next steps, including potential approval. This was based on the developmental milestone evaluation in Part A that showed a 100% response rate for all participants with at least 6 months follow-up after administration of TSHA-102.

Frequently Asked Questions

What is Breakthrough Therapy Designation (BTD)?

- Breakthrough Therapy Designation is a special status granted by the FDA to therapies that show **early evidence of substantial improvement over available treatments** in one or more clinically significant endpoints.
- This designation allows for more frequent FDA guidance and the potential for faster review of a future Biologics License Application (BLA) for TSHA-102.

What is TSHA-102 and the REVEAL Pivotal Study?

- TSHA-102 is a **gene therapy delivered once directly into the fluid around the spinal cord** (called intrathecal delivery).
- The REVEAL Pivotal Study will test the efficacy and safety of TSHA-102 in **15 girls and young women** between the ages of **6 and under 22 years old** with typical Rett syndrome who are in a developmental plateau – a stage where gains in certain milestones are very rare.
- Each participant will receive TSHA-102, and a participant's abilities following administration of TSHA-102 will be compared to their abilities before they received TSHA-102.
- The **primary endpoint** in the study will measure whether participants gain or regain at least one of 28 important developmental milestones in areas like hand use (fine motor), mobility (gross motor) and communication, after receiving the study treatment.
- The 28 milestones are based on Taysha's analysis of the NIH-funded International Rett Syndrome Foundation (IRSF) natural history study data from approximately 1,100 females with up to 14 years of follow-up showing that there is **very low chance (0% to <6.7%) of gaining or regaining certain lost developmental milestones**.

Will there be a trial for younger girls?

- Females aged 6 and older with Rett syndrome are typically in a **developmental plateau -** a stage where there is a **very low chance (0% to <6.7%) of gaining or regaining certain lost developmental milestones**. This is based on Taysha's analysis of the NIH-funded International Rett Syndrome Foundation (IRSF) natural history study data from approximately 1,100 females with up to 14 years of follow-up.
- Because gaining or regaining a milestone at this stage is rare, this age group is ideal for showing whether a treatment like TSHA-102 is having a real impact.
- Taysha is also planning a **separate study** for girls between the ages of **2 and under 6 years**, who are in earlier stages of development. The data collected from this study will be an important part of our overall submission to regulators.

Can I sign up my loved one for a trial?

- We will share more information about how to sign up for the REVEAL Pivotal Study, including who may be eligible and where the study will take place as they become available.

What are your plans for a clinical trial outside of the U.S. and Canada?

- We are continuing to have discussions with regulatory agencies outside the U.S. and Canada to determine the best path forward for TSHA-102 into other countries.

If you have any questions, please email us at **patientaffairs@tayshagtx.com**.

We truly appreciate your continued partnership and look forward to sharing more news with you soon.

Sincerely,
The Taysha Patient Affairs Team
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