UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 28, 2025

Taysha Gene Therapies, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-39536**	**84-3199512**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

3000 Pegasus Park Drive, Suite 1430 **Dallas, Texas**	**75247**
(Address of Principal Executive Offices)	**(Zip Code)**

(214) 612-0000
(Registrant's telephone number, including area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.00001 par value	TSHA	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On May 28, 2025, Taysha Gene Therapies, Inc. (the "***Company***") issued a press release entitled "Taysha Gene Therapies Announces Pivotal Part B Trial Design Details for TSHA-102 in Rett Syndrome Enabled by IRSF Natural History Data and Positive Clinical Data from Part A of the REVEAL Adult/Adolescent and Pediatric Trials Evaluating TSHA-102". The press release provides certain clinical and regulatory updates on TSHA-102. The full text of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and incorporated herein by reference.

The information in this Item 7.01 of this Current Report on Form 8-K (including Exhibit 99.1) is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***"), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 8.01 Other Events.

Clinical and Regulatory Update Presentation

On May 28, 2025, the Company also made available a presentation to be used to discuss the clinical and regulatory updates on TSHA-102. A copy of the presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K.

ATM Prospectus

On May 28, 2025, the Company notified the Agents (as defined below) that it was suspending and terminating the prospectus (the "***ATM Prospectus***") related to up to $100,000,000 of the Company's common stock, $0.00001 par value per share, issuable pursuant to the terms of the Sales Agreement (the "***Sales Agreement***"), dated October 5, 2021, as amended by that certain Amendment No. 1, dated March 30, 2022, with Goldman Sachs & Co. LLC, Wells Fargo Securities, LLC and Leerink Partners LLC, as sales agents (collectively, the "***Agents***"). The Company will not make any sales of its securities pursuant to the Sales Agreement unless and until a new prospectus, prospectus supplement or a new registration statement is filed. Other than the termination of the ATM Prospectus, the Sales Agreement remains in full force and effect.

A copy of the Sales Agreement was filed as Exhibit 1.2 to the Company's Registration Statement on Form S-3 (File No. 333-260069), filed with the Securities and Exchange Commission on October 5, 2021).

The disclosures on this Current Report on Form 8-K shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any state or jurisdiction in which such an offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Exhibit Description
99.1	Press Release, dated May 28, 2025.
99.2	Corporate presentation, dated May 28, 2025.
104	Cover Page Interactive Data File (the cover page XBRL tags are embedded within the inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Taysha Gene Therapies, Inc.

By: /s/ Kamran Alam
Kamran Alam
Chief Financial Officer

Date: May 28, 2025

Exhibit 99.1

Taysha Gene Therapies Announces Pivotal Part B Trial Design Details for TSHA-102 in Rett Syndrome Enabled by IRSF Natural History Data and Positive Clinical Data from Part A of the REVEAL Adult/Adolescent and Pediatric Trials Evaluating TSHA-102

Natural history data analysis established patients ≥ six years of age are in developmental plateau, with a ~0% likelihood of gaining/regaining developmental milestones across the core functional domains of Rett syndrome

Written alignment from FDA supports single-arm, open label pivotal trial with primary endpoint of developmental milestone gain/regain in the developmental plateau population (≥ 6 years, intend N=15) with each patient serving as their own control

100% of patients in REVEAL Part A (N=10, 6-21 years) gained/regained ≥ one developmental milestone post-TSHA-102 with concordant improvements across multiple outcome measures; high dose consistently outperformed low dose, with dose-dependent effects deepening over time

No treatment-related SAEs or DLTs following low dose and high dose of TSHA-102

FDA advised the Company to submit pivotal Part B trial protocol and SAP as an amendment to the IND application, which is expected to occur in the current quarter; pivotal trial initiation activities anticipated in Q3 2025

Dallas – May 28, 2025 – 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 details of its planned pivotal Part B trial design for TSHA-102 following written alignment from the U.S. Food and Drug Administration (FDA). Additionally, the Company announced positive clinical data from Part A of the REVEAL Phase 1/2 adolescent/adult and pediatric trials evaluating TSHA-102 in Rett syndrome. The alignment reached with the FDA was supported by the Company's analysis of the International Rett Syndrome Foundation's (IRSF) longitudinal Rett syndrome natural history study data, as well as clinical data from the ongoing REVEAL Phase 1/2 trials.

"Our rigorous analysis of the robust natural history study dataset demonstrated that after six years of age, the likelihood of achieving defined developmental milestones across the core functional domains of Rett syndrome is highly improbable. Therefore, it is quite striking that we observed a 100% responder rate following treatment with TSHA-102, with all pediatric, adolescent and adult patients across varying disease severity gaining or regaining one or more developmental milestone that represents activities of daily living that are important to caregivers and clinicians. We believe this objective and clinically meaningful primary endpoint has the potential to redefine treatment expectations and expand the possibilities of gene therapy for patients with Rett syndrome," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "We believe aligning with the FDA on key elements of our proposed pivotal trial design validates these important findings that underpin our pivotal trial design and strengthen our conviction in the transformative potential of TSHA-102. Importantly, this progress sets us on an efficient and expeditious path to potentially deliver TSHA-102 to patients and families suffering from this devastating disease with high unmet need. We plan to submit the pivotal trial protocol and SAP as an amendment to the IND application this quarter and anticipate initiating this pivotal program in the third quarter of 2025."

Dr. Jeffrey Neul, M.D., Ph.D., Rett Specialist who served as Administrative Head of the Rett Syndrome Natural History Study added, “This innovative analysis and cumulative incidence models of the Rett syndrome natural history dataset help shape our understanding of the disease trajectory by establishing that the likelihood of gain and regain of developmental milestones is predictable after six years of age. Importantly, these data allow us to objectively measure how transformative therapies impact functional aspects of the disease that are essential to activities of daily living. I believe these insights uncovered via the collaboration of academic researchers and a patient advocacy group with industry partner, Taysha, will be instrumental in shaping the future of therapeutic development for Rett syndrome.”

Laura Hameed, Chief Executive Officer of the International Rett Syndrome Foundation (IRSF), added, “On behalf of IRSF, I want to thank the families, clinicians, and researchers whose dedication made the Rett syndrome Natural History Study possible. Their participation provided a deeper understanding of how Rett progresses over time, insights that are now helping shape meaningful clinical outcome measures and could someday lead to new treatments. We’re pleased to support Taysha’s efforts to build on this foundation and are hopeful about the progress it represents for families living with Rett syndrome.”

Analysis of IRSF’s Longitudinal Rett Syndrome Natural History Study Data Supported Taysha’s Pivotal Trial Design for TSHA-102

- N = ~1100 females with confirmed Rett syndrome diagnosis, with up to 14 years follow-up, representing the largest available Rett syndrome natural history study dataset
- Developed age- and time-based cumulative incidence models of longitudinal natural history data across 28 developmental milestones in the core functional domains of fine motor, gross motor and communication
- Findings demonstrated patients ≥ six years of age have reached a developmental plateau, with an exceedingly low (0% to <6.7%) likelihood of gaining new or regaining developmental milestones that were lost after a defined number of years

Obtained Written Alignment with the FDA on Key Elements of TSHA-102 Pivotal Part B Trial Design Following Discussions Under the Regenerative Medicine Advanced Therapy (RMAT) Pathway

- Single-arm, open-label trial with patients serving as their own control (intend N=15)
- Enrollment of females in the developmental plateau population of Rett syndrome (≥ 6 years)
- Primary endpoint will assess developmental milestone gain or regain
    - During advanced discussions with the FDA, reached alignment on the definition of a responder: “gain/regain of ≥ one defined developmental milestone.” The FDA provided guidance on an additional analysis to further support the responder definition, which the Company has completed and intends to submit, alongside the final protocol and statistical analysis plan (SAP), as part of the Investigational New Drug (IND) amendment.

- Video-based determination of milestone gain/regain will be performed by independent, blinded central raters according to predefined definitions of achievement for each developmental milestone

- Safety of TSHA-102 will be evaluated in females in the pre-developmental plateau population of Rett syndrome (2-6 years), with efficacy data extrapolated from the developmental plateau population
- 12-month primary analysis, and intend to perform a 6-month interim analysis
- The FDA advised the Company to submit the pivotal Part B trial protocol and the associated SAP as an amendment to its IND application, eliminating the need for formal end-of-phase meeting

Clinical Data from Part A of Ongoing REVEAL Phase 1/2 Adolescent/Adult and Pediatric Trials

Efficacy data based on May 19, 2025, data cutoff, included 10 females with Rett syndrome aged 6-21 years (high dose, N=6; low dose, N=4) treated with the high dose ($1x10^{15}$ total vg) or low dose ($5.7x10^{14}$ total vg) of TSHA-102

- 100% of pediatric, adolescent and adult patients gained ≥ one defined developmental milestone across the core functional domains of fine motor, gross motor and communication post-TSHA-102, with a ~0%* likelihood of being achieved without treatment based on natural history data
  - A total of 22 developmental milestones were achieved across the 10 patients, as determined by multiple independent central raters based on video-evidenced evaluation according to predefined definitions of achievement for each developmental milestone
  - Developmental milestones were achieved early post-TSHA-102, with new gains/regains demonstrated over time (i.e., spoke in phrases with meaning, finger fed, walked with support)
  - High dose cohort achieved 100% responder rate 25% faster than the low dose cohort, supporting the accelerated functional benefit observed with the high dose
- Improvements observed across multiple clinician-assessed outcome measures, including Revised Motor Behavior Assessment (R-MBA) and Clinician Global Impression – Improvement (CGI-I), corroborated the developmental milestone gains/regains demonstrated post-TSHA-102
- High dose cohort outperformed low dose cohort across multiple outcome measures six months post-treatment, with dose-dependent effects deepening over time ≥ nine months post-treatment

Safety data based on May 20, 2025, data cutoff, included 12 females with Rett syndrome aged 6-21 years treated with TSHA-102 (high dose, N=8; low dose, N=4)

- High dose and low dose of TSHA-102 have been generally well tolerated with no treatment-related serious adverse events (SAEs) or dose limiting toxicities (DLTs)
- All treatment-emergent AEs related to TSHA-102 were mild to moderate in severity

Presentation with additional details and accompanying figures are available on a Current Report on Form 8-K being filed concurrently with this press release and available on the SEC's website at www.sec.gov.

Anticipated Milestones

- Expect to submit pivotal Part B trial protocol and associated SAP as an amendment to the IND application in the current quarter
- Taysha will host three oral presentations related to TSHA-102 at the upcoming 2025 IRSF Rett Syndrome Scientific Meeting taking place in Boston from June 9-11, 2025
- Pivotal Part B trial site activation and trial initiation activities anticipated in the third quarter of 2025

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 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 statements concerning the potential of TSHA-102, including the

reproducibility and durability of any favorable results initially seen in patients dosed to date in clinical trials, including with respect to functional milestones, and our other product candidates to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, including the timing of initiating additional trials, reporting data from our clinical trials and making regulatory submissions, communications from the FDA on the regulatory pathway for TSHA-102, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and our current cash resources supporting our planned operating expenses and capital requirements into the fourth quarter of 2026. 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 our business are described in detail in our Securities and Exchange Commission (SEC) filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2024, and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, which are available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

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* *Cumulative incidence models of natural history data demonstrate the likelihood of developmental milestone gain/regain ranged from 0% to <6.7% in this population*

Exhibit 99.2

TSHA-102 Rett Syndrome Program Update

May 2025

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Legal disclosure

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding the potential of TSHA-102, the durability and reproducibility of the clinical data from the REVEAL trials, the anticipated Part B trial design, our research, development and regulatory plans, and our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2024, our Quarterly Report on Form 10-Q for the quarter ended March 31, 2025, and our other filings with the SEC, which are available on the SEC’s website at www.sec.gov. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

This presentation shall not constitute an offer to sell or the solicitation of an offer to buy these securities, nor shall there be any sale of these securities in any state or jurisdiction in which such offer, solicitation, or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

Agenda

Rett Syndrome Overview and Natural History Data Analysis

FDA Alignment on Key Elements of Pivotal Part B Trial

TSHA-102 Clinical Data from Part A of REVEAL Phase 1/2 Trials

- Developmental Milestones
- R-MBA
- CGI-I
- Safety Data

Key investment highlights

TSHA-102: potential one-time treatment designed to address the root cause of Rett syndrome

Next Steps:

Expect to submit pivotal trial protocol and SAP as an amendment to the IND application in Q2 2025

Pivotal trial initiation activities expected in Q3 2025

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[1]Amir, R E et al. "Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2." *Nature genetics* vol. 23,2 (1999): 185-8. doi:partners. 10.1038/13810. (estimated prevalence of *15,000-20,000 patients with typical Rett syndrome caused by a MECP2 mutation*). [2]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners (likelihood of gain/regain ranged from 0% to <6.7%). [3]Finalization of SAP, including sample size, responder rate and interim analysis, expected to occur following Company's submission of IND amendment and SAP in Q2 2025. [4]Efficacy data based on May 19, 2025, data cutoff (N=10); Safety data based on May 20, 2025, data cutoff (N=12); Patient 11 is 12 weeks post-treatment and Patient 12 is 6 weeks post-treatment. Study is ongoing and data is subject to change. IND=investigational new drug application; SAE=serious adverse event; DLT=dose-limiting toxicity

Rett Syndrome Overview and Natural History Data Analysis

International Rett Syndrome Foundation
www.rettsyndrome.org

Natural History Data accessed from the International Rett Syndrome Foundation (IRSF). We thank IRSF and the governance committee for their partnership.

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There are no approved disease-modifying treatments that address the genetic root cause of Rett syndrome

High Unmet Medical Need

- Current standard of care focused on symptom management[1]
- Patients typically require 24/7 care and lifelong assistance[2]
- High caregiver burden with significant impact on quality of life and activities of daily living[2]

Significant Market Opportunity

- Estimated **15,000 and 20,000 patients in major global markets** (U.S., EU+U.K.)[3]
- **1 of every 10,000 female births worldwide**[3]
- Commercial launch and uptake of DAYBUE highlights market demand[4]

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[1]Fu, Cary et al. "Consensus guidelines on managing Rett syndrome across the lifespan." *BMJ paediatrics* open vol. 4,1 e000717. 13 Sep. 2020, doi:10.1136/bmjpo-2020-000717. [2]Coenraads, Monica et al. "Voice of the Patient Report: *Rett Syndrome Externally-Led Patient-Focused Drug Development Meeting*." 9 Aug. 2022, https://rettpfdd.org/site/assets/files/1/2022-rett-syndrome-voice-of-the-patient-report.pdf. [3]Amir, R E et al. "Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2." *Nature genetics* vol. 23,2 (1999): 185-8. doi:10.1038/13810. (estimated prevalence of *15,000-20,000 patients with typical Rett syndrome caused by a MECP2 mutation*).[4]Based on net product sales for the three months ended March 31, 2025 (source: Acadia Pharmaceuticals Reports First Quarter 2025 Financial Results and Operating Overview).

Rett syndrome caregiver research indicates improved function or achievement of developmental milestones would significantly improve quality of life

Communication

Gained or improved communication of basic needs—through eye gaze, gestures, or words—would enable self-advocacy and strengthen social connections

- Ex: follow a command without a gesture, pointed for something they wanted, use word(s) with meaning, identify body parts (pointed with eyes or fingers)

"If she can actually tell me what she wants, or make a choice between two things, even if it's just looking at something purposefully…because now I don't know what's going on."
– Caregiver of 20-year-old

Fine Motor Function

Gained or improved hand function would restore a sense of control and purpose, and enable play and social engagement

- Ex: finger feed, use fork or spoon to eat without assistance, reached for a toy, drank from a cup held without assistance

"Feeding herself, entertaining herself…being able to flip pages or purposefully hold a book, change the channel on a remote...would be a game changer for us."
– Caregiver of 8-year-old

Gross Motor Function

Gained or improved gross motor function would foster independence and reduce the physical burden of caregiving

- Ex: walked independently or with support, stood while holding on, sat without support, climbed up stairs without help

"If we got a safe and secure sitting position from her, that would be a win. We would be able to have her sitting and not have to be right next to her. We could have her at the dining table with us."
– Caregiver of 5-year-old

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Results from caregiver research conducted in October 2024 by independent third-party research firm with 22-U.S.-based caregivers of females with RTT (aged 5-39). These findings have identified key developmental milestones that may provide an important foundation for selection of endpoints in future Rett syndrome gene therapy trials.

Longitudinal natural history data informed key elements of TSHA-102 pivotal trial design

Natural History Study (NHS) Dataset[1]

- N = ~1100 females with confirmed Rett syndrome diagnosis; up to 14 years follow-up
- Captures longitudinal data on the functional gain, loss and regain of **developmental milestones** across core domains of Rett syndrome:

Communication
Ex: Pointed for something they wanted | Used word(s) with meaning

Fine Motor Function
Ex: Finger feed | Drank from a cup held without assistance

Gross Motor Function
Ex: Sat without support | Walked with support

- These functional skills and activities of daily living are highly important to caregivers

Developed Age- and Time-Based Models of Developmental Milestone NHS Data[1]

- Cumulative incidence models demonstrated **distinct age- and time-based trends in developmental milestone acquisition** that:

✓ Strengthened understanding of longitudinal disease progression in Rett syndrome

✓ Contextualized and substantiated disease-modifying potential of TSHA-102

✓ Informed our discussions with the U.S. FDA on proposed pivotal trial design for TSHA-102

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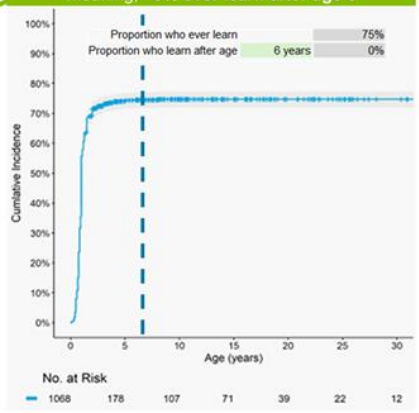
[1]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners.

NHS cumulative incidence models showed that the likelihood of gaining/regaining 28 defined developmental milestones is **predictable in the age ≥ 6 population**[1]

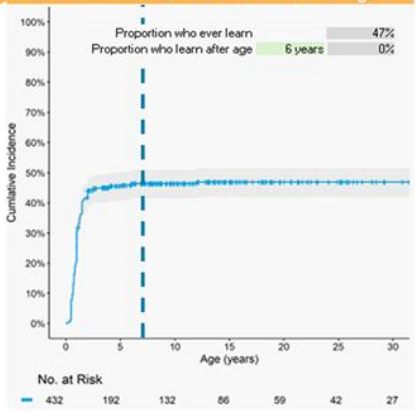
Communication Milestones

Ex: of patients who learn to use word(s) with meaning, **~0% ever learn after age 6**



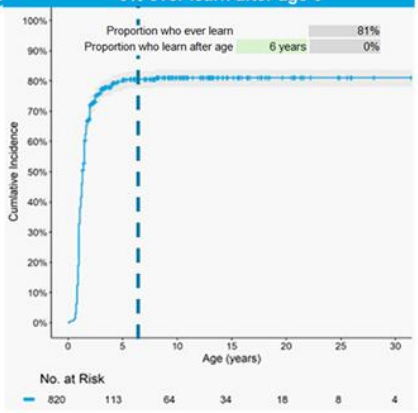
Fine Motor Milestones

Ex: of patients who learn to drink from a cup held without assistance, **~0% ever learn after age 6**



Gross Motor Milestones

Ex: of patients who learn to walk with support, **~0% ever learn after age 6**



We leveraged these findings to establish the **"Developmental Plateau Population"**

[1]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Incidence models of NHS data conducted by third-party statistical partners.

Identified 28 developmental milestones from the NHS dataset that would reflect:

meaningful functional gains to caregivers, with **a ~0% likelihood** of being achieved after ≥6 years if untreated[1]

Communication

- Pointed for something they wanted
- Waved “Bye-Bye”
- Followed a command with a gesture
- Identified body parts (pointed with eyes or fingers)
- Followed a command without a gesture
- Used word(s) with meaning
- Spoke in phrases (2 words or more) with meaning

Fine Motor

- Reached for toy
- Holds bottle unpropped
- Used raking grasp to retrieve an object
- Used pincer grasp (refined or modified)
- Transferred an object from one hand to another
- Finger fed
- Drank from a cup held without assistance
- Used a fork or spoon to eat with assistance
- Used a fork or spoon to eat without assistance

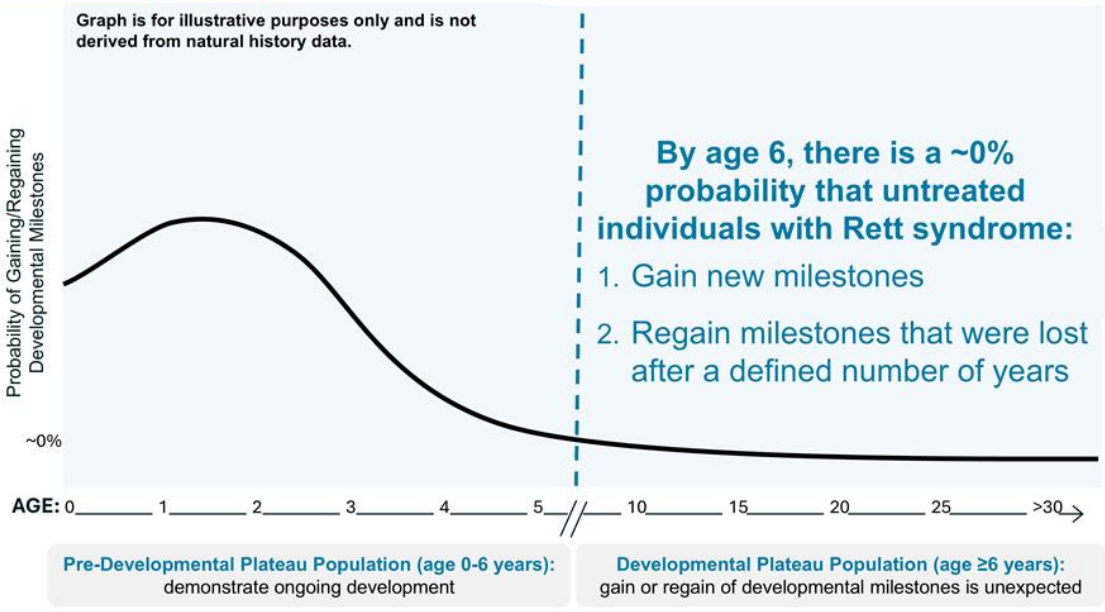
Gross Motor

- Come to sitting
- Sat without support
- Stood while holding on
- Pulled to standing
- Stood independently
- Walked with support
- Walked independently
- Climbed up stairs with help
- Climbed down stairs with help
- Climbed up stairs without help
- Climbed down stairs without help
- Ran 10 feet without falling

Taysha GENE THERAPIES

[1]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners. Likelihood in this population ranged from 0-3%. NHS=natural history study

Rett syndrome NHS data analysis demonstrated that **after 6 years of age, there is ~0% likelihood of gaining or regaining developmental milestones**[1]



The **gain of new skills or restoration of previously lost skills** presents an ***objective, data-driven* way** to assess the efficacy of TSHA-102 **in a broad Rett syndrome population**

[1]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners. NHS=natural history study

Pivotal Part B Trial Design for TSHA-102: data-driven assessment of functional gains in a broad Rett syndrome population

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Obtained written alignment from the FDA on key elements of pivotal Part B REVEAL trial design

NHS models provide **data-driven, objective approach** to assessing functional gains in a single arm trial

Study Overview

- **Study Design:** Single-arm, open-label trial, using patient as own control
- **Dose:** Intend 1x10^{15} total vg (high dose)
- **Sample Size**: Intend 15 females with Rett syndrome age ≥6 years (developmental plateau population)[1]
- **Primary Endpoint:** Developmental milestone gain or regain
  - During advanced discussions with FDA, aligned on the definition of a responder: gain/regain of ≥ one defined developmental milestone[1]
  - Video-based determination of milestone gain/regain will be performed by independent, blinded central raters
- 12-month primary analysis; intend 6-month interim analysis[1]
- Safety of TSHA-102 will be evaluated in females with Rett syndrome 2-6 years of age with efficacy extrapolated from developmental plateau population

Company Believes REVEAL Part A Data Continues to Support Advancement to Pivotal Trial

Responder rate = 100% (N = 10) across all patients treated with TSHA-102 post-treatment[2]

Next Steps

- In written correspondence, the FDA advised Company to submit pivotal trial protocol and SAP as an amendment to the IND application; expected in Q2 2025

[1]Finalization of SAP, including sample size, responder rate and interim analysis, expected to occur following Company's submission of IND amendment and SAP.
[2]Based on May 19, 2025, data cutoff. Study is ongoing, and data is subject to change.
NHS=natural history study; SAP=statistical analysis plan; IND=investigational new drug

Primary endpoint: milestone gain is an objective, clinically meaningful and inherently individualized assessment of function in the developmental plateau population

~0% probability of milestone gain/regain after age 6 in the untreated population[1]

Supported by cumulative incidence models from longitudinal NHS developmental milestone data

Fine motor, gross motor, and communication developmental milestones captured as binary (yes/no) measures

Gain or regain of ≥ one of 28 defined developmental milestones post-TSHA-102

- ✓ Represent meaningful functional improvement based on caregiver research[2]
- ✓ Directly reflects activities of daily living
- ✓ Inherently individualized to show improvements in a heterogeneous disease
- ✓ FDA-endorsed primary endpoint

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[1]Incidence models derived from NHS data; accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281; a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners. [2]Results from caregiver research conducted in October 2024 by independent third-party research firm with 22-US-based caregivers of females with RTT (aged 5 to 39). NHS=natural history study

TSHA-102 Clinical Data from Part A of REVEAL Phase 1/2 Trials

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100% of patients (n=10) gained/regained ≥ one defined developmental milestone post-TSHA-102

with a **~0% likelihood** of being achieved without treatment based on NHS data[1]

	Cohort 1: Low Dose 5.7x10^{14} total vg				Cohort 2: High Dose 1x10^{15} total vg					
	LD:P1	LD:P2	LD:P3	LD:P4	HD:P1	HD:P2	HD:P3	HD:P4	HD:P5	HD:P6
AGE AT DOSING (years):	20	21	6	7	15	21	16	8	6	7
POST-TREATMENT FOLLOW UP:	18 mos.	18 mos.	12 mos.	12 mos.	9 mos.	9 mos.	6 mos.	6 mos.	6 mos.	3 mos.
	Developmental Milestone Gained Post-TSHA-102				Developmental Milestone Gained Post-TSHA-102					
	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Developmental milestone gains and regains were assessed by multiple independent central raters, who evaluated functional skills through video evidence at baseline and post-treatment, applying predefined binary criteria.

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Based on May 19, 2025, data cutoff (N=10). Data presented reflects current data in the Electronic Data Capture System, subject to change. [1]Incidence models derived from NHS data; accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT. Cumulative incidence models of NHS data conducted by third-party statistical partners.

Patients gained/regained developmental milestones **across the core functional domains** of Rett syndrome post-TSHA-102

22 developmental milestones were achieved across 10 patients treated with TSHA-102

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

Enable **expression of needs**, preferences, emotions, and foster **social connections**

Fine Motor

- Holds bottle unpropped
- Finger fed
- Reached for a toy
- Transferred an object from one hand to another

Reflect self-care skills and purposeful hand use that **enable independence**

Gross Motor

- Walked with support
- Stood while holding on
- Pulled to standing
- Sat without support

Enhance mobility and independence, and **reduce the physical burden of caregiving**

Based on May 19, 2025, data cutoff (N=10). Developmental milestone gains and regains were assessed by multiple independent central raters through video evidence.

REVEAL caregiver testimonials post-TSHA-102 highlight the impact of functional **developmental milestone gains** on quality of life

"All of our days are better. Her improvements are much beyond anything we had expected or hoped for."

"She's **gained multiple words** – 'no,' 'yeah,' 'mom,' 'dad' – makes consistent sounds with meaning – and even **says some phrases** – 'ok, bye' and 'no more.'"

"She's a lot easier to care for. She can **point a lot more deliberately to make choices and show us what she wants**, and she will keep gesturing until we get it for her. And she pushes away what she doesn't want."

"[**Standing while holding on**] has been a godsend when it comes to toileting while out in the community because now, I can have her stand and hang on to my arm to toilet or wipe her… and the consistency of keeping her hand down [without constant stereotypies] allows us to practice more with a walker, which has been huge."

"Her hands are more relaxed, and she tries to grab everything with a **raking grasp**. She can **follow directions** in a snap, like if we say, 'let's go,' she gets up, heads to the door. She's babbling now, which she didn't do before, and is definitely trying to tell us something."

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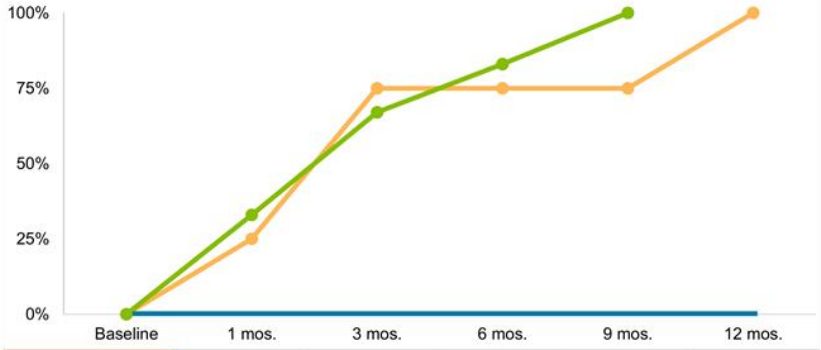
Based on documented testimonials from caregivers of participants treated with TSHA-102 in REVEAL Phase 1/2 trials, as of May 19, 2025, data cutoff.

High dose TSHA-102 achieved 100% responder result at a **25% faster rate** compared to low dose TSHA-102

Responder Rate: Time to Response



	Baseline	1 mos.	3 mos.	6 mos.	9 mos.	12 mos.
Low Dose TSHA-102	25%	75%	75%	75%	100%	
High Dose TSHA-102	33%	67%	83%	100%		

Natural History (Developmental Plateau Population)[1] = ~0%

- **Accelerated functional benefit seen with high dose TSHA-102**
- Early clinical response may increase the likelihood of reversing the disease trajectory and may be predictive of long-term clinical outcomes in Rett syndrome
- Consistent pattern of early gains that are sustained, with new achievements continuing to emerge over time following TSHA-102

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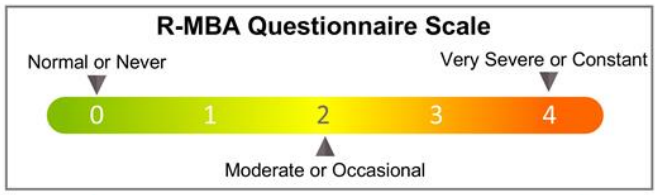
Based on May 19, 2025, data cutoff (N=10). Data presented reflects current data in the Electronic Data Capture System, subject to change. Low Dose N=4 across all time points; High Dose N=6 at 1-3 months., N=5 at 6 months, N=2 at 9 months, based on available follow up. [1]Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT.Cumulative incidence models of NHS data conducted by third-party statistical partners.

Overview of Revised Motor Behavior Assessment (R-MBA)

- Clinician-reported assessment that measures the onset of disease regression, growth, motor and communication skills, and disease behaviors for individuals with Rett syndrome[1]
- **Associated with developmental milestone acquisition and function impacting quality of life**
- Measures the severity or frequency of a diverse set of symptoms to capture phenotypic variability
- Assessed in Rett syndrome natural history study[2]



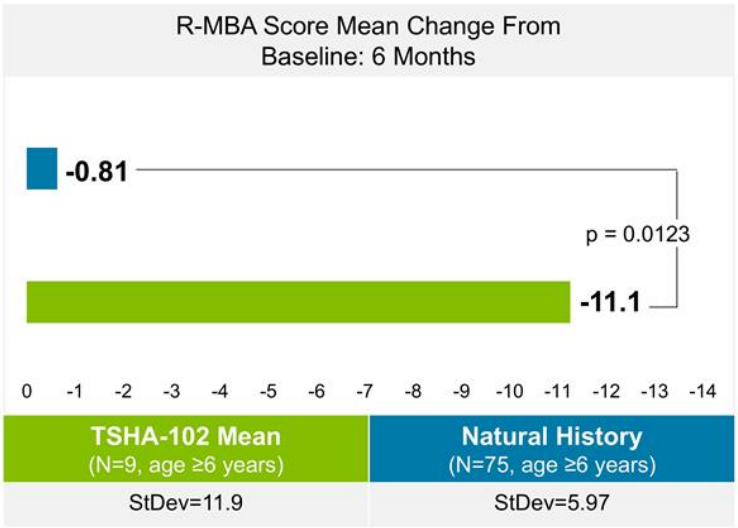
24-item questionnaire across five domains:

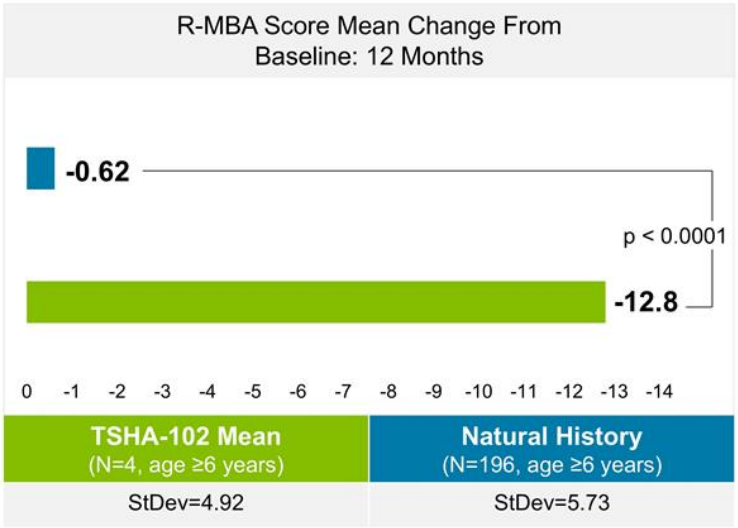
1. Motor Dysfunction
2. Functional Skills
3. Social Skills
4. Aberrant Behavior
5. Respiratory Behavior

[1]Raspa, M. et al. A Psychometric Evaluation of the Motor-Behavioral Assessment Scale for Use as an Outcome Measure in Rett Syndrome. Nov 2020. [2]MBA natural history data converted to R-MBA; Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281; a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT.

TSHA-102 demonstrated a **statistically significant** mean R-MBA score improvement compared to natural history at both 6 and 12 months

Lower score = improvement; R-MBA assessed in Rett syndrome NHS at ~6 months and ~12 months[1]





Statistical analyses are based on May 19, 2025, data cutoff: TSHA-102 R-MBA mean 6 months: N=9 (Low dose cohort: N=4, High dose cohort: N=5). TSHA-102 R-MBA mean 12 months: N=4, Low dose cohort.
[1]MBA natural history data converted to R-MBA; mean scores reported were calculated from baseline to 6 and 12 months: Accessed from International Rett Syndrome Foundation (IRSF). ClinicalTrials.gov: NCT02738281: a prospective cohort of individuals with a pathologic mutation in the MECP2 gene, commonly associated with RTT.

Overview of Clinical Global Impression-Improvement (CGI-I) rating with Rett syndrome-specific anchors[1]

CGI-I: Clinician-rated scale
assessing improvement from baseline

- Designed as a global clinical assessment
- Factors considered to determine change included duration, onset, durability of change and the context of sign/symptom change across the Rett syndrome specific domains of the CGI

Score	CGI-I
1	**Very much improved**
2	**Much improved**
3	**Minimally improved**
4	No change
5	Minimally worse
6	Much worse
7	Very much worse

[1]Neul, Jeffrey L et al. "Improving Treatment Trial Outcomes for Rett Syndrome: The Development of Rett-specific Anchors for the Clinical Global Impression Scale." Journal of child neurology vol. 30,13 (2015): 1743-8. doi:10.1177/0883073815579707

TSHA-102 demonstrated early global improvement, with dose-dependent effects deepening over time in CGI-I

Average CGI-I score of 1.0 (*very much improved*) in high dose cohort vs. average CGI-I score of 2.8 in low dose cohort at ≥9 months post-TSHA-102

Based on May 19, 2025, data cutoff. Data presented reflects current data in the Electronic Data Capture System, subject to change. CGI-I average scores based on latest assessment for each patient. No data available at 12 and 18 months in high dose cohort.

Consistent dose response observed across key measures at 6 months post-TSHA-102, with the separation between dose cohorts increasing over time

Endpoint		Low Dose Cohort	High Dose Cohort	Dose-Dependent Response?
Developmental Milestones	Responder Rate (%)	100% by 12 months	100% by 9 months	✓
	Responder Rate at 6 Months (%)	75%	83%	
R-MBA[1]	Patients with R-MBA Improvement (%) at latest visit	100%	100%	✓
	Mean Score Improvement at 6 Months	-9.8	-12.2	
	Mean Score Improvement at ≥9 Months	-11.5	-18.0	
CGI-I	Patients with CGI-I Improvement (%) at latest visit	75%	100%	✓
	Mean CGI-I Score at 6 Months	2.3	2.0	
	Mean CGI-I Score at ≥9 Months	2.8	1.0	
CGI-S	Patients with CGI-S Improvement (%) at latest visit	25%	33%	✓

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Data cut through May 19, 2025. Study is ongoing and data is subject to change.
Low dose data: N=4. High dose data: N=5 at 6 months; N=2 at ≥9 months.
[1]R-MBA mean score change post-TSHA-102 is relative to baseline; lower score=improvement from baseline.

TSHA-102 was generally well tolerated at the low and high dose with no treatment-related SAEs or DLTs

Number of Events Across 12 Pediatric, Adolescent and Adult Patients Dosed in Part A of REVEAL Phase 1/2 Trials	Low Dose $5.7x10^{14}$ vg (N=4)		High Dose $1x10^{15}$ vg (N=8)		Total (N=12)	
	N	E	N	E	N	E
TEAE Related to TSHA-102:	4	[10]	5	[14]	9	[24]
Serious TEAE Unrelated to TSHA-102:	2	[7]	4	[6]	6	[13]
Serious TEAE Related to TSHA-102:	0	0	0	0	0	0

- All TEAEs related to TSHA-102 were mild-moderate in severity, with the most common being elevated liver enzymes* (N=4, 33%), pyrexia (N=3, 25%), lethargy (N=2, 17%), and elevated levels of NfL in CSF (clinically insignificant) (N=2, 17%)
- Expected transaminase elevations observed
  - Majority experience mild elevations <2x ULN
  - Acute excursions (>5x ULN) less common, clinically asymptomatic and steroid treatment-responsive
- Seizures have generally been well controlled following TSHA-102

*Includes the following: hepatic enzyme increased, hypertransaminasemia, transaminases increased and liver function test increased

[1]Data cut through May 20, 2025 (N=12); Patient 11 is 12 weeks post-treatment and Patient 12 is 6 weeks post-treatment. Study is ongoing and data are subject to change.
SAE=Serious adverse event; TEAE=Treatment-emergent AE; DLT=Dose-limiting toxicity; N=Number of participants; E=Number of event; CSF=Cerebrospinal fluid; ULN=Upper limit normal; NFL=Neurofilament light chain

Thank you

May 2025

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Appendix

May 2025

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Option Agreement with Astellas

- In October 2022, we granted Astellas an exclusive option to an exclusive license of certain rights related to TSHA-102 (the "Rett Option"). Subject to certain limited extensions, Astellas may exercise the Rett Option, at its sole discretion, through a specified period of time (the "Rett Option Period"), following Astellas' receipt of certain clinical data from the female pediatric trial (the "Rett Data Package"). We expect to deliver the Rett Data Package to Astellas in mid-2025. The Rett Option Period expires 90 days after Astellas receives the Rett Data Package.

- Under the Option Agreement, we also granted to Astellas certain rights with respect to a change of control of our company during the Rett Option Period, including a right of first offer in the event that we receive an offer or proposal from a third party that would result in a change of control, and we have agreed to (A) not solicit or encourage any inquiries, offers or proposals for, or that could reasonably be expected to lead to, a change of control, or (B) otherwise initiate a process for a potential change of control, in each case, without first notifying Astellas and offering Astellas the opportunity to submit an offer or proposal to us for a transaction that would result in a change of control. If Astellas fails or declines to submit any such offer within a specified period after the receipt of such notice, we will have the ability to solicit third party bids for a change of control transaction. If during the Rett Option Period, Astellas submits an offer for a transaction that would result in a change of control of our company, we will negotiate with Astellas in good faith the potential terms and conditions of such a transaction for 45 days. If we are unable to mutually agree on such terms, such right of first offer will expire. We have granted Astellas certain additional rights related to a change of control, which are discussed in our SEC filings.

- Because we are substantially dependent on TSHA-102, which is our sole product candidate in clinical development, we believe that if Astellas exercises the Rett Option, it would constitute an offer for the sale of substantially all of the assets of our company, which would result in a change of control requiring stockholder approval. If it were determined this exercise of the Rett Option is not an offer that would result in a change of control, the parties shall negotiate the terms of the license agreement in good faith. If the parties are unable to mutually agree on such terms within 120 days, the terms of such license agreement may, at Astellas' discretion, be determined by "baseball arbitration," wherein each party is required to submit a proposed final license agreement to arbitrators, and the arbitrators are required to select one of the proposed license agreements without modification.

- It is possible that, if Astellas exercises the Rett Option, Astellas will not agree that the exercise of the Rett Option for the exclusive license of TSHA-102 would result in a change of control, and we cannot predict whether or how the parties would resolve such dispute. While it is inherently difficult to assess the potential outcome of any such dispute, we may be exposed to additional risks as a result, including, but not limited to, reputational harm and litigation, and we can provide no assurances that we will prevail in such litigation.