

Second Quarter 2025 Financial Results and Corporate Update

August 12, 2025



Taysha
GENE THERAPIES



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, communications with and feedback from the FDA and Health Canada on the regulatory pathway for TSHA-102, future financial position and cash runway, 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.

Agenda

Opening Remarks and TSHA-102 Regulatory Progress

Sean P. Nolan

Chairman and Chief Executive Officer

Rett Syndrome Natural History Data Supporting Pivotal Trial Design

Suku Nagendran, M.D.

President and Head of R&D

Previously Disclosed Part A Data from REVEAL Phase 1/2 Trials

Elsa Rossignol, M.D., FRCP, FAAP

Associate Professor at Université de Montréal, Director of the Rett Multidisciplinary Clinic of the CHU Sainte-Justine, and a Principal Investigator of REVEAL trials

Q2 2025 Financial Results

Kamran Alam

Chief Financial Officer

Recent Highlights

TSHA-102: designed to address root cause of Rett syndrome, with a clear path to registration

High Unmet Need and Significant Market Opportunity

- No approved therapies address genetic root cause of Rett syndrome
- 15,000-20,000 patients (U.S., EU+U.K.); 1 of 10,000 female births worldwide¹

Differentiated Approach Designed to Support Commercial Uptake

- One-time treatment with disease-modifying potential across broad Rett syndrome patient population
- Clinically and commercially proven AAV9 capsid with well-established safety profile, based on third-party gene therapy studies
- Delivered intrathecally (IT) as a routine, minimally invasive procedure with outpatient potential; facilitates widespread CNS biodistribution with minimal systemic exposure, potentially reducing risk of immune responses and systemic toxicities²

Pivotal Trial Design Enabled by Natural History Data

- Rett syndrome natural history data analysis established patients ≥ 6 years of age are in developmental plateau, with a 0% to $<6.7\%$ likelihood of gaining or regaining a developmental milestone,³ informing pivotal trial design and primary endpoint
- Single-arm, open label trial, enrolling 15 patients with patient serving as own control, assessing the % of patients aged 6 to <22 years (developmental plateau population) who gain/regain ≥ 1 developmental milestone as the primary endpoint

Advancing with Clear Path Toward Registration

- Commenced site activation for REVEAL pivotal trial following receipt of No Objection Letter (NOL) from Health Canada and FDA feedback; patient enrollment anticipated to begin in Q4 2025
- Potential registrational pathway for TSHA-102 for the treatment of females aged 2 years and older with Rett syndrome

Transformative Potential Supported by Part A Data⁴

- 100% response rate for pivotal trial primary endpoint of gain/regain of ≥ 1 developmental milestone as assessed by multiple independent central raters through video-evidenced evaluation
- No treatment-related SAEs or DLTs following low and high dose of TSHA-102

¹Amir, 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). ²Haque, Emdadul et al. " rAAV9 Vector Biodistribution in Brain and Spinal Cord via Lumbar Intrathecal Infusion in Nonhuman Primates (NHP): Assessing the Administration Route Leveraged in TSHA-102 Rett Syndrome Clinical Trials". 2025 International Rett Syndrome Foundation (IRSF) Rett Syndrome Scientific Meeting, 9-11 June 2025, Boston. ³Accessed from International Rett Syndrome Foundation. 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 $<6.7\%$). ⁴Efficacy data based on May 19, 2025, data cutoff (N=10); Safety data based on August 4, 2025, data cutoff (N=12). Study is ongoing and data is subject to change.

IND=investigational new drug application; SAE=serious adverse event; DLT=dose-limiting toxicity

Potential registrational pathway for TSHA-102 for the treatment of females aged 2 years and older with Rett syndrome

PART A: REVEAL Phase 1/2 Trials

Dosing complete (N=12 patients, 6-21 years)

- **Adolescent and Adult** (12+ years)

Cohort 1
 5.7×10^{14} total vg
N=2

Cohort 2
 1×10^{15} total vg
N=4

- **Pediatric** (5-8 years)

Cohort 1
 5.7×10^{14} total vg
N=2

Cohort 2
 1×10^{15} total vg
N=4

PART B: REVEAL Pivotal Trial

- **Developmental Plateau Population** (6 to <22 years)
- Evaluate efficacy and safety of TSHA-102

Cohort 3
 1×10^{15} total vg
N=15

Safety-Focused Study

- **Pre-developmental Plateau Population** (2 to <6 years)
- Evaluate safety and preliminary efficacy of TSHA-102, with efficacy data extrapolated from developmental plateau population

Potential Registrational Path

Females with
Rett syndrome
Age 2+

REVEAL Pivotal Trial for TSHA-102

Commenced site activation following FDA and Health Canada feedback

Study Overview

- **Study Design:** Single-arm, open-label trial, using patient as own control
- **Dose:** 1×10^{15} total vg (high dose), administered intrathecally
- **Sample Size:** Enrolling 15 females with Rett syndrome aged 6 to <22 years (developmental plateau population)¹
- **Primary Endpoint:** Response rate, defined as the percentage of patients who gain or regain \geq one developmental milestone from a list of 28
 - Video-based determination of milestone gain/regain will be performed by independent, blinded central raters
 - Plan to perform 12-month primary analysis & 6-month interim analysis
- **Key Secondary Endpoints:** Average number of total developmental milestones gained/regained per patient and clinician-assessed outcome measures, including R-MBA and CGI-I

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



Response rate = 100% (N = 10) across all patients treated with TSHA-102 post-treatment²

Next Steps

- Patient enrollment anticipated to begin in Q4 2025

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 population¹

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 \geq one of 28 defined developmental milestones post-TSHA-102

- ✓ Represent meaningful functional improvement based on caregiver research²
- ✓ Directly reflects activities of daily living
- ✓ Inherently individualized to show improvements in a heterogeneous disease
- ✓ FDA-endorsed primary endpoint

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

Natural History Study (NHS) Dataset¹

- 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 Data¹

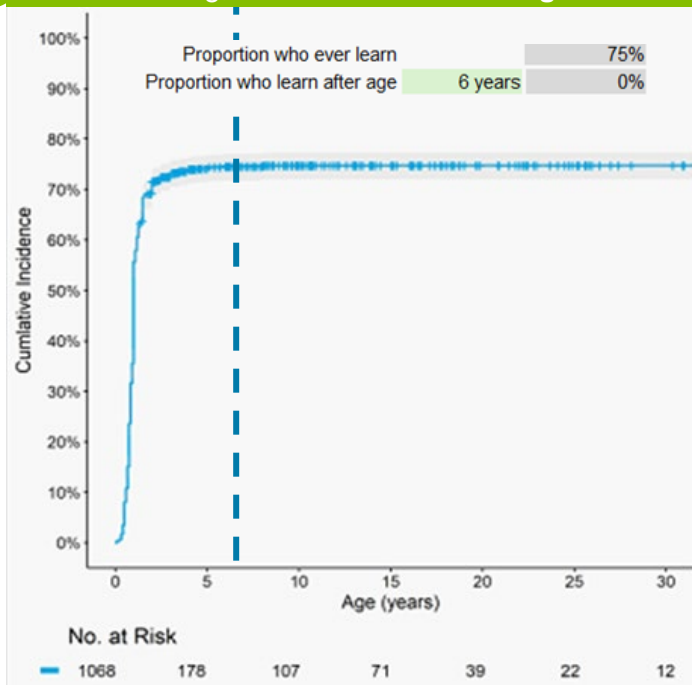
- Cumulative incidence models demonstrated **distinct age- and time-based trends in developmental milestone acquisition** that:
 - ✓ Strengthened understanding of longitudinal disease progression in Rett syndrome
 - ✓ Contextualized and substantiated disease-modifying potential of TSHA-102
 - ✓ Informed our discussions with the U.S. FDA on proposed pivotal trial design for TSHA-102

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



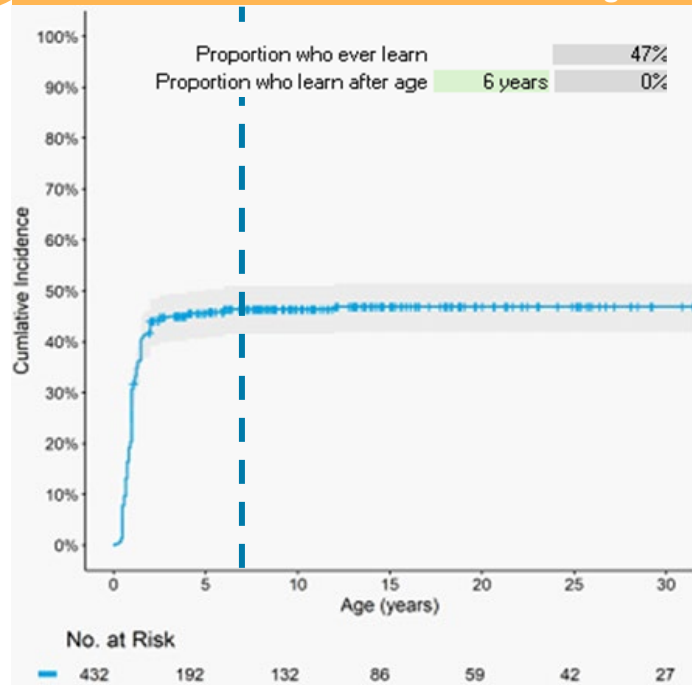
Communication Milestones

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



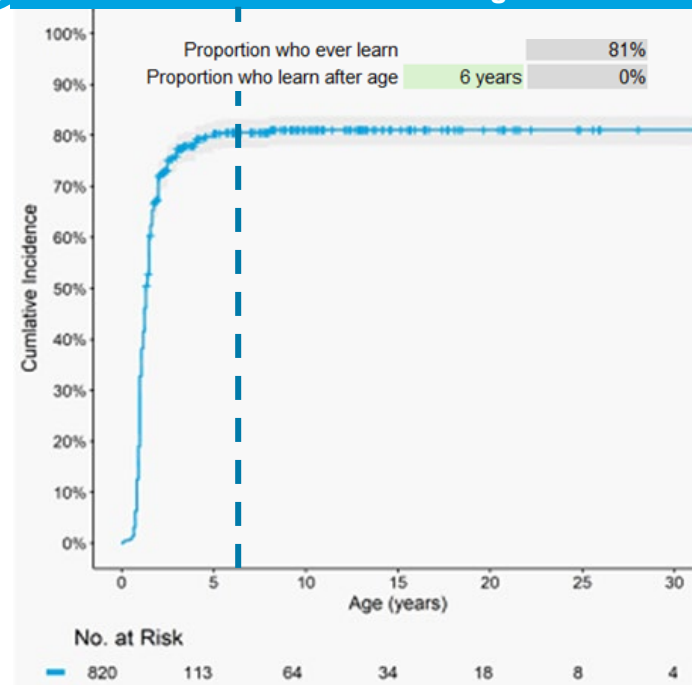
Fine Motor Milestones

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



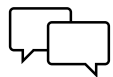
Gross Motor Milestones

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**”

Identified 28 developmental milestones from the NHS dataset¹ for inclusion in the primary endpoint that met predefined criteria



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

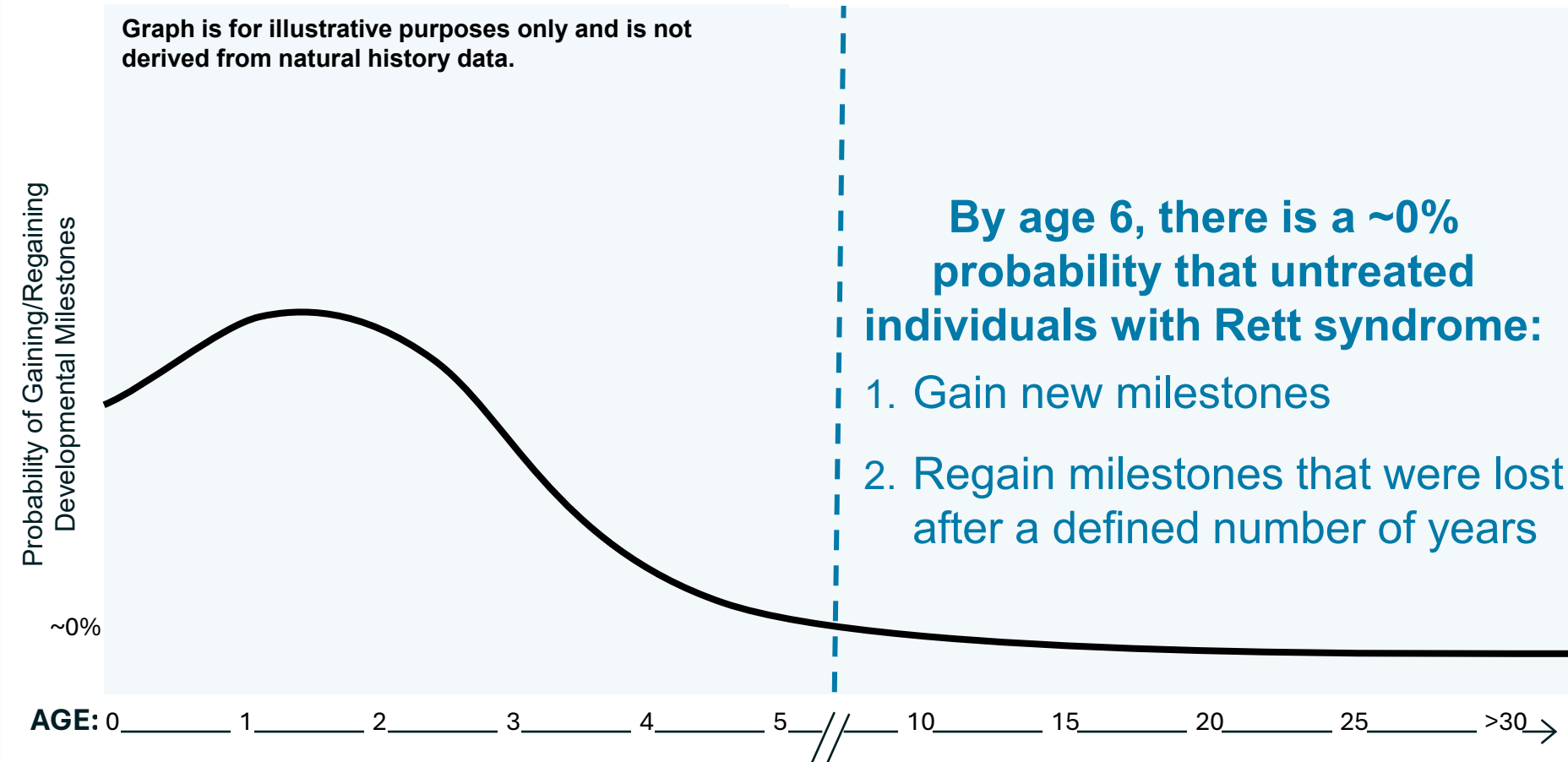
- Come to sitting
- Sat without support
- Stood while holding on
- Pulled to standing
- Stood independently
- Walked with support
- Walked independently
- Climbed up stairs with help
- Climbed down stairs with help
- Climbed up stairs without help
- Climbed down stairs without help
- Ran 10 feet without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

Selection criteria:

- ✓ Meaningful functional gains based on caregiver research
- ✓ Represent activities of daily living
- ✓ 0 to <6.7% likelihood gained/regained in patients age ≥6 years with untreated Rett syndrome¹

Rett syndrome NHS data analysis demonstrated that after 6 years of age, there is ~0% likelihood of gaining or regaining developmental milestones¹

Graph is for illustrative purposes only and is not derived from natural history data.



By age 6, there is a ~0% probability that untreated individuals with Rett syndrome:

1. Gain new milestones
2. Regain milestones that were lost after a defined number of years

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

Pre-Developmental Plateau Population (age 0-6 years):
demonstrate ongoing development

Developmental Plateau Population (age ≥6 years):
gain or regain of developmental milestones is unexpected

Rigorous developmental milestone evaluation criteria applied to Part A data enabled reliable, objective assessment of TSHA-102 efficacy

Relevant developmental milestones data was captured via videos, COAs, caregiver assessments and clinician notes in Part A

Developmental milestone evaluation criteria:

- ✓ **Baseline:** Milestone either never gained or lost sufficiently long ago, such that the likelihood of spontaneous gain/regain is <6.7%, based on review of patient medical history and available baseline video data
- ✓ **Post-treatment evidence:** Video documentation of milestone demonstration
- ✓ **Evaluation method:** Milestone gain/regain determined by multiple independent central raters based on prespecified definitions of achievement for each milestone outlined in the pivotal trial protocol

Reliable Part A data supporting TSHA-102's impact on developmental milestone achievement indicate the pivotal trial is well powered to establish efficacy of TSHA-102



Elsa Rossignol, M.D., FRCP, FAAP





















Associate Professor in Neuroscience and Pediatrics at the Université de Montréal, Director of the Rett Multidisciplinary Clinic of the CHU Sainte-Justine

Principal Investigator of REVEAL Phase 1/2 Trials



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 data¹

	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.

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

A total of 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**

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.’”

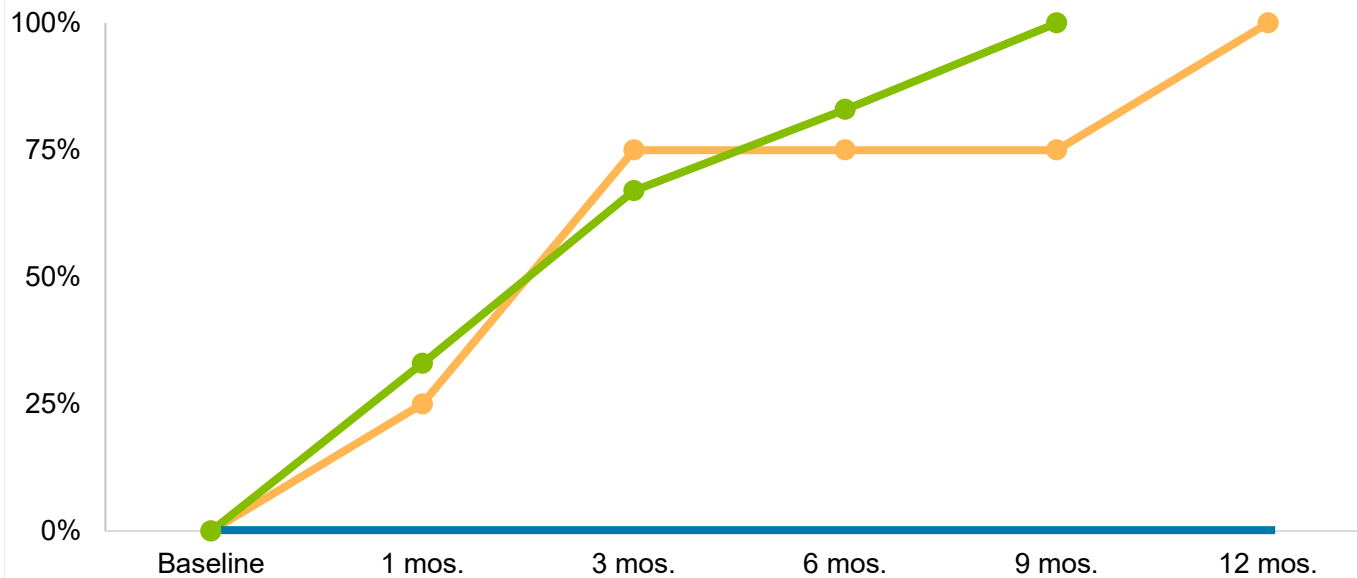
“She’s a lot easier to care for. She can **point a lot more deliberately to make choices and show us what she wants**, and she will keep gesturing until we get it for her. And she pushes away what she doesn’t want.”

“**[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 stereotypes] 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.”

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

Responder Rate: Time to Response



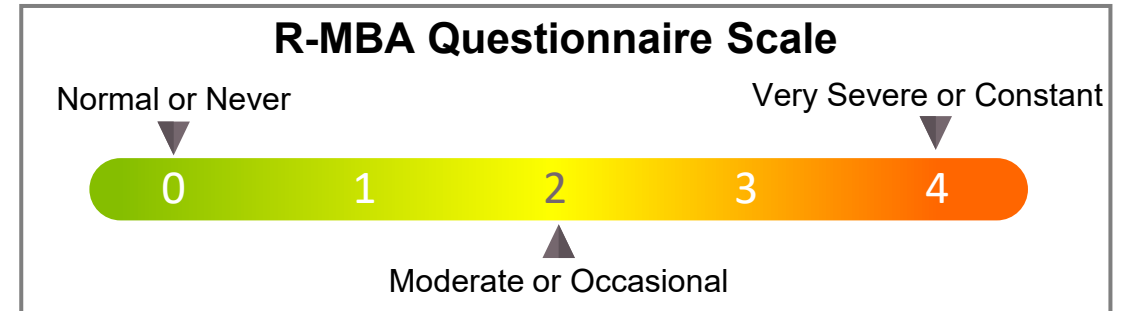
Low Dose TSHA-102	25%	75%	75%	75%	100%
High Dose TSHA-102	33%	67%	83%	100%	

- **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

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

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 syndrome¹
- **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 study²



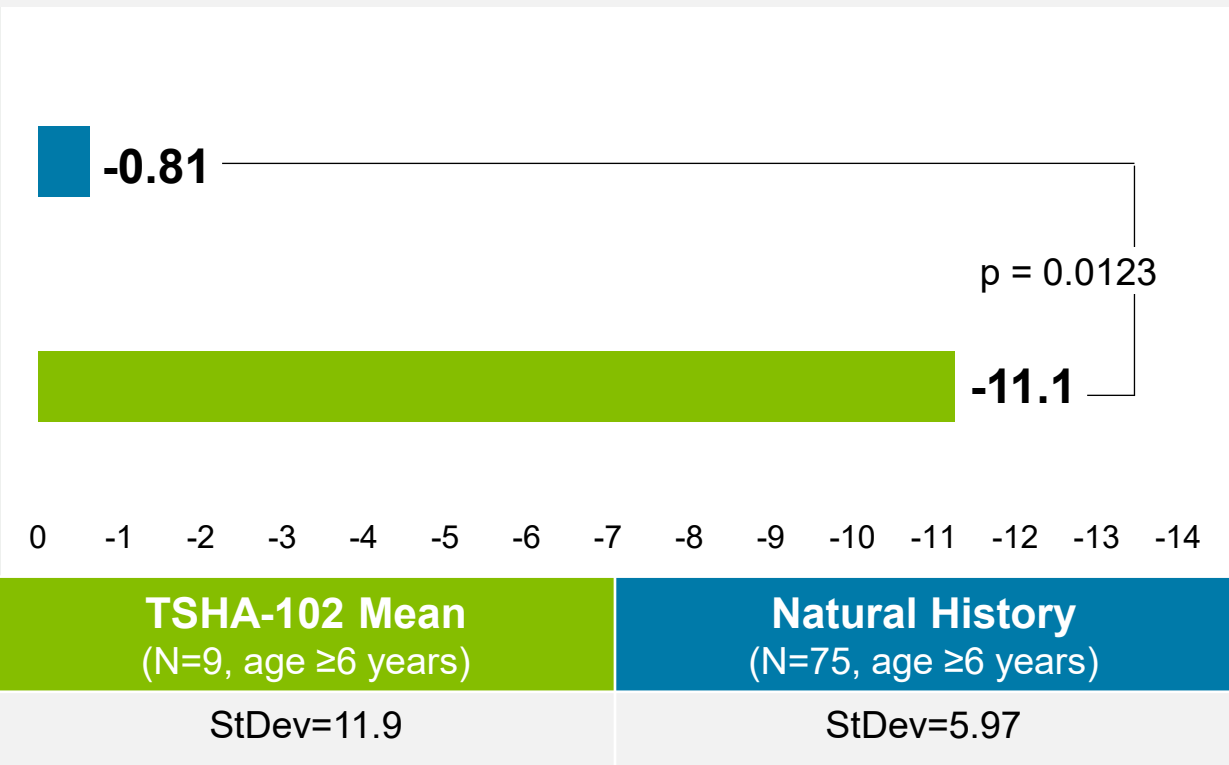
24-item questionnaire across five domains:

1. Motor Dysfunction
2. Functional Skills
3. Social Skills
4. Aberrant Behavior
5. Rett-specific Behavior (i.e. Respiratory)

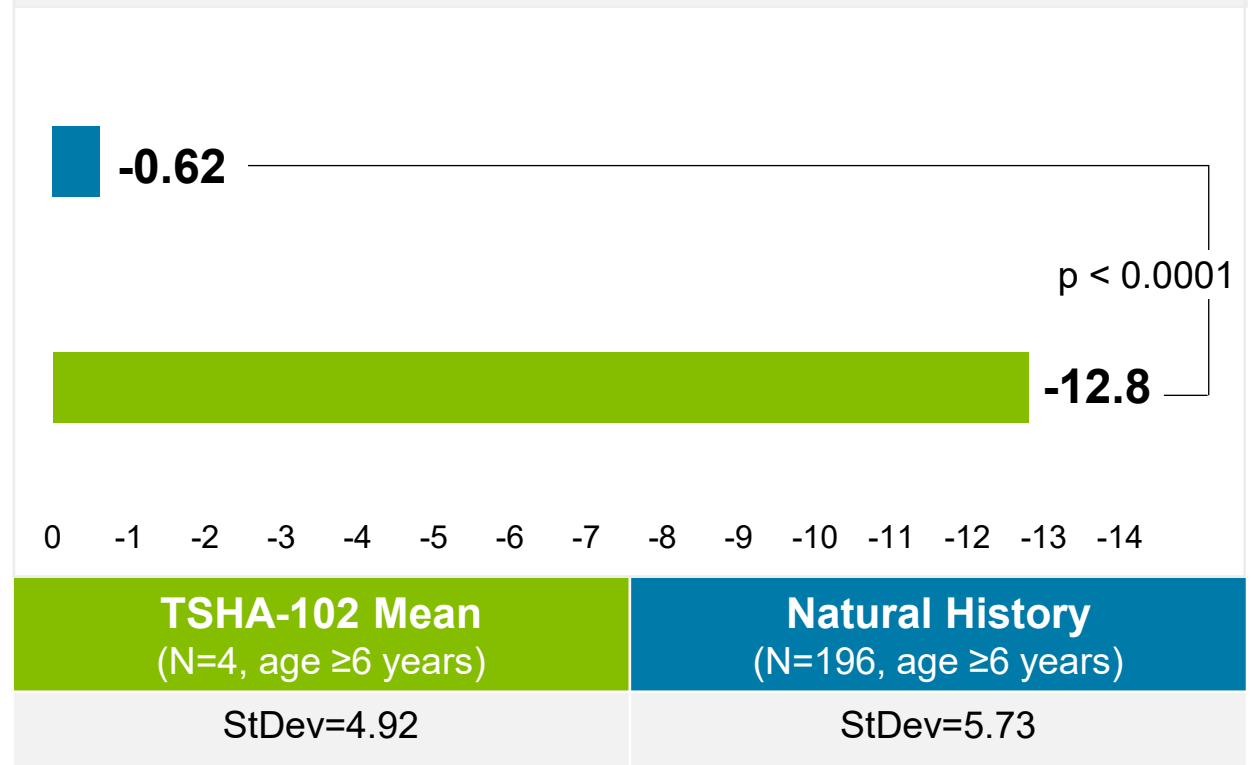
TSHA-102 demonstrated a statistically significant mean R-MBA score improvement compared to natural history at both 6 and 12 months

Lower score = improvement; R-MBA assessed in Rett syndrome NHS at ~6 months and ~12 months¹

R-MBA Score Mean Change From Baseline: 6 Months



R-MBA Score Mean Change From Baseline: 12 Months



Overview of Clinical Global Impression-Improvement (CGI-I) rating with Rett syndrome-specific anchors¹

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

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

Low Dose: Average CGI-I Score	3.0 (N=4)	2.3 (N=4)	3.0 (N=2)	3.3 (N=4)	2.0 (N=2)
High Dose: Average CGI-I Score	2.7 (N=6)	2.0 (N=5)	1.0 (N=2)		
Time Post TSHA-102:	3 months	6 months	9 months	12 months	18 months

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%	✓

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

Anticipated TSHA-102 program milestones supported by a strengthened financial position

Fourth Quarter 2025	Begin patient enrollment for REVEAL pivotal trial
Fourth Quarter 2025	Report new supplemental clinical data from Part A of REVEAL Phase 1/2 trials supporting broad therapeutic impact of TSHA-102

Well-capitalized through key milestones:

- Cash runway expected to fund operating expenses and capital requirements into 2028



Question and Answer Session

