Achieving Developmental Milestones and Broad Restoration of Function in Rett Syndrome: The Potential of TSHA-102 Gene Therapy

Elsa Rossignol[1], Elizabeth Berry-Kravis[2], Richard Haas[3], Robin Ryther[4], Jenny Downs[5], Inge Meijer[1], Tessa Clarkson[6], Rumana Haque-Ahmed[7], Minna Montgomery[8], Laura Pisani[7], Suku Nagendran[7]

[1]Departments de Neurosciences and Pediatric, Université de Montréal and Centre Universitaire Hospitalier Sainte-Justine, Montreal, Quebec, Canada; [2]Departments of Pediatrics, Neurological Sciences, Anatomy and Cell Biology, Rush University Medical Center, Chicago, IL, USA; [3]University of California San Diego, San Diego, CA, USA; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]The Kids Research Institute Australia, Centre for Child Health Research, University of Western Australia, Nedlands, Australia; [6]Tessa Clarkson Consulting, LLC, Littleton, CO, USA; [7]Taysha Gene Therapies, 3000 Pegasus Park Drive, Suite 1430, Dallas, TX, USA; [8]SSI Strategy, 9 Campus Drive, 1st floor, Parsippany, NJ, USA

Aim

To investigate the safety and preliminary efficacy of low- and high-dose TSHA-102 in adolescent/adult and pediatric females with Rett syndrome

Background

- Rett syndrome (RTT) is a rare neurodevelopmental disorder estimated to affect between 15,000 and 20,000 individuals in the U.S., EU, and U.K, with no approved therapies targeting its genetic root cause[1,2]
- Caused by a loss-of-function mutation in the *MECP2* gene[2], RTT results in lost or missed developmental milestones (DMs) across three core functional domains (communication, fine motor function, and gross motor function) among other disease characteristics impacting activities of daily living[3]
  - Taysha's analysis of the NIH-funded IRSF longitudinal RTT Natural History Study (NHS) data demonstrated individuals ≥6 YOA have reached a developmental plateau, with a 0% to <6.7% likelihood of gaining new or regaining DMs that were lost after a defined number of years (**Figure 1**)[3]
  - New skill gains or functional improvements would not be expected from individuals in the developmental plateau population
- TSHA-102 is a one-time gene therapy for RTT, designed to enable optimal and controlled transgene expression of *MECP2* across the CNS following intrathecal administration (**Figure 2**)[4,5]
- The REVEAL adolescent/adult (NCT05606614) and pediatric (NCT06152237) studies are first-in-human trials of TSHA-102 for individuals with RTT[6,7]
- Here, we present the safety and efficacy data (up to 18 months for the first dosed participant) from Part A of the REVEAL studies, including results from a new supplemental analysis reflecting the therapeutic impact of TSHA-102 on skill gains and improvements outside of the natural history defined DMs, which further highlights the broad therapeutic impact on activities of daily living

Figure 1: 28 DMs from the NHS included in the REVEAL pivotal trial primary endpoint that reflect meaningful functional gains to caregivers, with a ~0% likelihood of being achieved after ≥6 YOA if untreated

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) 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

Figure 2: TSHA-102 construct: An investigational one-time gene therapy designed to regulate *MECP2*

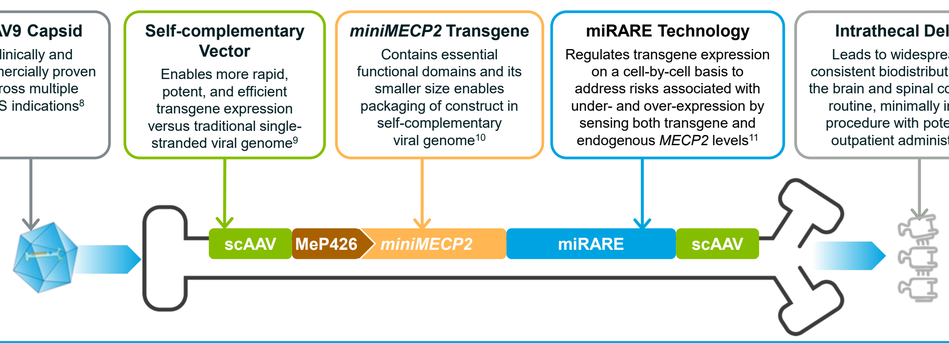
AAV9 Capsid
Clinically and commercially proven across multiple CNS indications[8]

Self-complementary Vector
Enables more rapid, potent, and efficient transgene expression versus traditional single-stranded viral genome[9]

***miniMECP2* Transgene**
Contains essential functional domains and its smaller size enables packaging of construct in self-complementary viral genome[10]

miRARE Technology
Regulates transgene expression on a cell-by-cell basis to address risks associated with under- and over-expression by sensing both transgene and endogenous *MECP2* levels[11]

Intrathecal Delivery
Leads to widespread and consistent biodistribution across the brain and spinal cord using a routine, minimally invasive procedure with potential for outpatient administration[4]



Methods

- The REVEAL studies are ongoing Phase 1/2, open-label, dose-escalation (Part A) and dose-expansion (Part B), registrational, multi-center trials. Part A was designed to establish POC to inform the Part B pivotal trial design; methods for Part A are outlined below (**Figure 3**)[6,7]
- Following immunosuppression initiation at Day −7, a single dose of TSHA-102 was delivered via intrathecal infusion through lumbar puncture on Day 0
- Safety evaluations (clinical and laboratory) are being assessed
- POC efficacy was assessed according to the following criteria (**Figure 4**):
  - **Primary evidence of efficacy (Part B REVEAL pivotal trial primary endpoint):** Applied rigorous evaluation criteria to available video-evidenced DM data that enabled a reliable, objective assessment of TSHA-102 efficacy
  - **Supportive evidence of functional gain:** New supplemental analysis of skills and improvements derived from structured assessments (MSEL-A, R-MBA, and ORCA) demonstrated additional functional skill gains and improvements across core disease characteristics outside of the natural history defined DMs, which further highlight the broad therapeutic impact of TSHA-102 on activities of daily living

Figure 3: Dose-escalation (Part A) study overview[3]

Objectives
- TSHA-102 safety and preliminary efficacy
- Evaluate two dose levels to, if possible, establish maximum administered dose (MAD) or maximum tolerated dose (MTD)

Low Dose:		High Dose:	
$5.7x10^{14}$ total vg	N=4	$1.0x10^{15}$ total vg	N=8

Key Inclusion Criteria
- Females with pathogenic confirmation of *MECP2* mutation
- Clinical Global Impression Scale-Severity (CGI-S) score ≥4 at screening

Pediatric (5–8 YOA) | Adolescent/Adult (≥12 YOA)

Key Assessments Across Both Part A Studies
- CGI-I
- R-MBA
- CGI-S
- Additional endpoints

Figure 4: Evaluation process for natural history defined DMs versus additional skills and improvements

Primary Evidence of Efficacy

Developmental Milestones

Functional gain of ≥1 of the **28 DMs defined in the NHS** assessed independently via rigorous video-evidenced evaluation

Evaluation Criteria:
- ✓ **Baseline:** Video data/medical history confirming milestone was either never gained or lost sufficiently long ago, such that the likelihood of spontaneous gain/regain is <6.7%[3]
- ✓ **Post-treatment evidence:** Video documentation of milestone demonstration
- ✓ **Evaluation method:** Determined by multiple independent central raters based on prespecified definitions of achievement for each milestone

Supportive Evidence of Functional Gain

Additional Skills and Improvements in Core Disease Characteristics

Functional gain or improvement in a core disease characteristic **outside of the 28 natural history defined DMs** and measured by validated, structured scales

Rett-validated Efficacy Scale:	Purpose:	Data Collection and Evaluation Method:
Adapted Mullen Scales of Early Learning (MSEL-A)	○ Assesses expressive and receptive language skills	✓ Video-recorded evaluation conducted in clinic ✓ Centrally rated by multiple independent raters ✓ N=5 participants with available data
Revised Motor Behavior Assessment (R-MBA)	○ Assesses frequency, severity or independence of RTT characteristics	✓ Video-recorded evaluation conducted in clinic ✓ Clinician-reported ✓ N=10 participants with available data
Observer-Reported Communication Ability (ORCA)	○ Assesses communication skills	✓ Structured evaluation conducted in home setting ✓ Caregiver-reported ✓ N=5 participants with available data

All reported skills/improvements required: **(a)** baseline data, **(b)** documented gain or improvement sustained through latest assessment.

Conclusions

- TSHA-102 was generally well tolerated at the low and high dose, with no treatment-related SAEs or DLTs
- 100% of pediatric, adolescent and adult participants gained/regained ≥1 defined DM across the core functional domains of communication, fine and gross motor post-TSHA-102, with ~0% likelihood of being achieved without treatment based on NHS data
  - A total of 22 DMs were achieved across the 10 participants, as assessed by multiple independent central raters based on video-evidenced evaluation according to prespecified definitions of achievement for each DM
  - DMs were achieved early post-TSHA-102, with new gains/regains demonstrated over time
- Improvements were consistently observed across multiple clinician-assessed outcome measures, including R-MBA and CGI-I, which corroborates the DM gains/regains demonstrated post-TSHA-102
- In addition to the 22 DMs, 100% of participants gained multiple additional functional skills and improvements across core disease characteristics, which further characterize the broad and consistent therapeutic impact of TSHA-102 on functional abilities and activities of daily living
  - A total of 165 additional skill gains/improvements were achieved across the 10 participants, as assessed by validated, structured scales
- The high-dose cohort consistently outperformed the low-dose cohort across multiple outcome measures at 6 months post-treatment, with dose-dependent effects deepening over time (≥9 months post-treatment), supporting the accelerated functional benefit observed with the high dose
- DMs and additional skills/improvements consistently demonstrated post-TSHA-102 reflect the broad, multi-domain functional gains and improvements post-TSHA-102 that impact activities of daily living

Results

Baseline characteristics

- As of May 20, 2025, data cut, 12 participants (low dose, N=4; high dose, N=8) have received TSHA-102. Participants are 6–21 YOA, have diverse clinical histories and varied *MECP2* mutations to reflect a real-world population
- Efficacy data based on May 19, 2025, data cut (N=10); Safety data based on May 20, 2025, data cut (N=12)

Safety

- TSHA-102 was generally well tolerated at the low and high dose, with no treatment-related SAEs or DLTs (**Table 1**)
- All TEAEs related to TSHA-102 were mild to moderate in severity, with the most common being elevated liver enzymes (N=4, 33%; includes hepatic enzyme increased, hypertransaminasemia, transaminases increased, and liver function test increased), 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 experienced mild elevations <2x ULN
  - Acute excursions (>5x ULN) less common, clinically asymptomatic, and steroid treatment-responsive
- Seizures have been generally well controlled following TSHA-102

Table 1: Number of TEAEs (Event [E])

	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

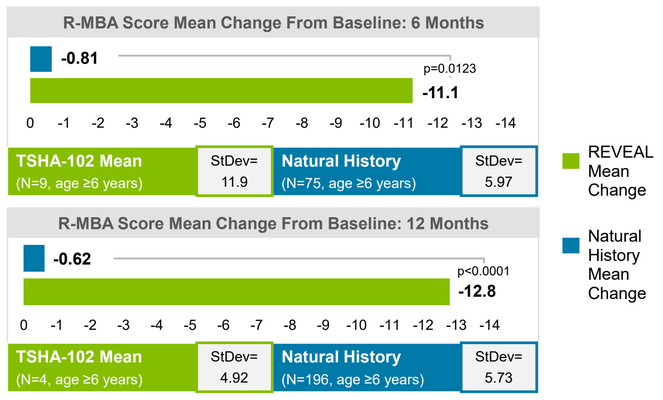
Efficacy

Table 2: 100% of participants (N=10) gained/regained ≥1 defined DM post-TSHA-102*, with an ~0% likelihood of being achieved without treatment based on NHS data[3]

	Age at Dosing (years)	Post-treatment follow-up (months)	DM Gain Post-TSHA-102
Low Dose $5.7x10^{14}$ vg	20	18	✓
	21	18	✓
	6	12	✓
	7	12	✓
High Dose $1x10^{15}$ vg	15	9	✓
	21	9	✓
	16	6	✓
	8	6	✓
	6	6	✓
	7	3	✓

*DM gains and regains were assessed by multiple independent central raters with strict eligibility criteria applied.

Figure 5: TSHA-102 demonstrated a statistically significant mean R-MBA score improvement compared to natural history at both 6 and 12 months* (R-MBA lower score = improvement)



*REVEAL 6 months: N=9 (low-dose cohort: N=4, high-dose cohort: N=5); REVEAL 12 months: N=4, low-dose cohort. MBA NHS data[9] converted to R-MBA; mean scores reported were calculated from baseline to 6 and 12 months.

Table 3: 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]	**Participants 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	**Participants 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	**Participants with CGI-S improvement (%) at latest visit**	**25%**	**33%**	✓

*REVEAL low-dose cohort: N=4, high-dose cohort: N=5 at 6 months and N=2 at ≥9 months.

Figure 6: 100% of participants (N=10) achieved multiple additional skills/improvements across core disease characteristics (communication, fine motor, gross motor, autonomic/other) outside of the natural history defined DMs*

Primary Evidence of Efficacy
A Total of 22 DMs Gained/Regained
- ✓ **Spoke in phrases 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 (five or more)**
- ✓ **Holds bottle unpropped**
- ✓ **Finger fed**
- ✓ **Reached for a toy**
- ✓ **Transferred an object from one hand to another**
- ✓ **Walked with support**
- ✓ **Stood while holding on**
- ✓ **Pulled to standing**
- ✓ **Sat without support**

Supportive Evidence of Functional Gain
A Total of 165 Additional Skills and Improvements Achieved

MSEL-A = 34 total gains	ORCA = 59 total gains	R-MBA = 72 total improvements
⊕ Played with sounds ⊕ Vocalized two-syllable sounds ⊕ Recognized body parts (one or more) ⊕ Identified objects ⊕ Understood action words ⊕ Identified the function of objects ⊕ Identified colors (one or more) ⊕ Understood size/length concepts ⊕ Understood comparative concepts ⊕ Followed directions ⊕ Followed two related commands ⊕ Followed three unrelated commands ⊕ Differentiated between objects with increasing levels of complexity	⊕ Used gesture to communicate (e.g. point, eye gaze) ⊕ Understood mood (based on facial expression/tone of voice) ⊕ Anticipated a game/activity in response to verbal cue ⊕ Responded when told "no" or "stop" ⊕ Expressed refusal by saying "no" ⊕ Used gesture to say "hello" and "goodbye" ⊕ Used gesture/word to identify a person by name ⊕ Responded to yes/no and open-ended questions ⊕ Took turns during game/activity ⊕ Used AAC device to communicate ⊕ Followed two-step directions part of daily routine ⊕ Expressed frustration when misunderstood ⊕ Communication understood by known individuals	**Improved:** ⊕ Motor skills ⊕ Purposeful hand use ⊕ Frequency of reach for objects/people ⊕ Chewing function ⊕ Speech and verbal communication ⊕ Response to spoken words ⊕ Ability to make choices ⊕ Sustained social interest and eye contact **Reduced or Absent:** ⊕ Hand stereotypies ⊕ Breath holding and hyperventilation ⊕ Seizure episodes ⊕ Choking/gagging episodes ⊕ Dystonia and hypertonia/rigidity ⊕ Bradykinesia ⊕ Truncal rocking ⊕ Bruxism ⊕ Aberrant behavior (e.g. self harming)

*Participants with available data: N=10 for developmental milestones and R-MBA, N=5 for MSEL-A and ORCA.

Figure 7: Examples of multi-domain functional gains and improvements demonstrated post-TSHA-102 impacting activities of daily living, based on DMs and additional skills/improvements achieved

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

PRE-TREATMENT	POST-TSHA-102
Non-verbal	Uses phrases / sentences with meaning
Understood simple words	Complex ideas and engaging in conversations
Made choices <10% of time using eye gaze	Makes choices 100% of time by pointing

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

PRE-TREATMENT	POST-TSHA-102
Stereotypies 76–100% of time	Stereotypies 1–25% of time
No purposeful hand use	Plays with toys and transfers intentionally
Required caregiver-assisted feeding	Finger feeds and holds a bottle unpropped

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

PRE-TREATMENT	POST-TSHA-102
Most severe dystonia (fixed positional deformity)	No dystonia
Non-ambulatory	Walks with support
Required caregiver support for positional transfers and to stand	Pulls self to standing position and stands while holding on

Autonomic/Other Improvements
Improve core features of RTT that have a **meaningful impact on quality of life**

PRE-TREATMENT	POST-TSHA-102
Hyperventilating/ breath holding 26–50% of time	Absent or reduced hyperventilating/ breath holding
Weekly-monthly seizure episodes	Seizure-free ≥6 months
Required a g-tube for feeding	Oral feeds

Key takeaway

REVEAL Part A demonstrates the potential of TSHA-102 to improve function and enable achievement of developmental milestones across core areas of disease in pediatric, adolescent, and adult patients with Rett syndrome. All participants gained or regained developmental milestones post-TSHA-102 that are not expected based on natural history and are meaningful to caregivers, families, and clinicians. In addition, all participants achieved additional skills and improvements outside of the natural history defined developmental milestones that further highlight the broad therapeutic impact of TSHA-102 on activities of daily living.

Taysha plans to initiate participant enrollment in the Part B REVEAL pivotal trial in the fourth quarter of 2025.

Presenting author: Dr. Elsa Rossignol (elsa.rossignol@umontreal.ca)
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Abbreviations: AAC, Augmentative and Alternative Communication; AAV9, adeno-associated virus serotype 9; CGI-I, Clinical Global Impression Scale-Improvement; CGI-S, Clinical Global Impression Scale-Severity; CNS, central nervous system; CSF, cerebrospinal fluid; DLT, dose-limiting toxicity; DM, developmental milestone; IRSF, International Rett Syndrome Foundation; MAD, maximum administered dose; *MECP2*, methyl-CpG-binding protein 2; miRARE, microRNA autoregulatory element; MSEL-A, Mullen Scale of Early Learning Assessment; MTD, maximum tolerated dose; NfL, neurofilament light; NHS, Natural History Study; NIH, National Institutes of Health; ORCA, Observer-Reported Communication Assessment; POC, proof-of-concept; R-MBA, Revised Motor Behavior Assessment Scale; RTT, Rett syndrome; SAE, serious adverse event; sc, self-complementary; StDev, standard deviation; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; vg, vector genome; YOA, years of age

References: 1. Gold WA, et al. *ACS Chem Neurosci*. 2018;9:167-76; 2. Amir RE, et al. *Ann Neurol*. 2000;47(5):670-9; 3. Rossignol E, et al. Presented at 2025 IRSF Rett Syndrome Scientific Meeting; June 9–11, 2025; Boston, MA; 4. Haque E, et al. Presented at 2025 IRSF Rett Syndrome Scientific Meeting; June 9–11, 2025; Boston, MA; 5. Sinnett SE, et al. *Brain*. 2021;144(10):3005-19; 6. Taysha Gene Therapies Inc. REVEAL Adult Study. https://clinicaltrials.gov/study/NCT05606614. Updated June 10, 2025, Accessed Aug 2025; 7. Taysha Gene Therapies Inc. REVEAL Pediatric Study. https://clinicaltrials.gov/study/NCT06152237. Updated May 11, 2025, Accessed June 2025; 8. Li X, et al. *Int J Mol Sci*. 2023;24(9):7736; 9. Gray SJ, et al. *Mol Ther*. 2011;19(6):1058-69; 10. Tillotson R, et al. *Nature*. 2017;550(7676):398-401; 11. Haque E, et al. Presented at ESGCT 30th Annual Congress, October 24-27, 2023; Brussels, Belgium.

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