

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

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Aim

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

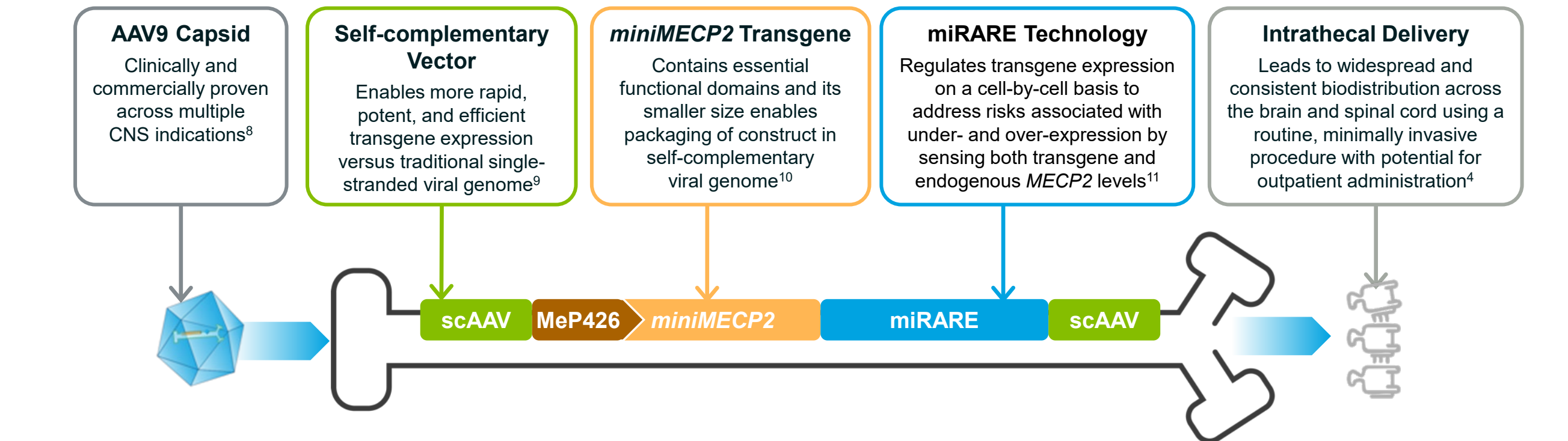
Background

- 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* gene², 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 living³
 - 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



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



Methods

- The REVEAL studies are ongoing Phase 1/2, open-label, dose-escalation (Part A) and dose-expansion (Part B), registration, 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 overview³

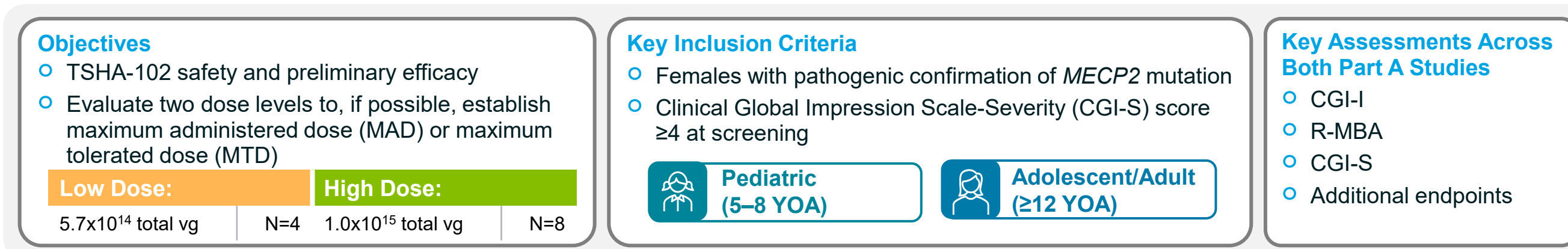


Figure 4: Evaluation process for natural history defined DMs versus additional skills and improvements

Primary Evidence of Efficacy	Supportive Evidence of Functional Gain
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 milestones were either never gained or lost sufficiently long ago, such that the likelihood of spontaneous gain/regain is <6.7% ✓ 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	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: Adapted Mullen Scales of Early Learning (MSEL-A) - Assesses expressive and receptive language skills Revised Motor Behavior Assessment (R-MBA) - Assesses frequency, severity or independence of RTT characteristics Observer-Reported Communication Ability (ORCA) - Assesses communication skills
	Data Collection and Evaluation Method: ✓ Video-recorded evaluation conducted in clinic ✓ Centrally rated by multiple independent raters ✓ N=5 participants with available data ✓ Video-recorded evaluation conducted in clinic ✓ Clinician-reported ✓ N=10 participants with available data ✓ 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 data³

	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)

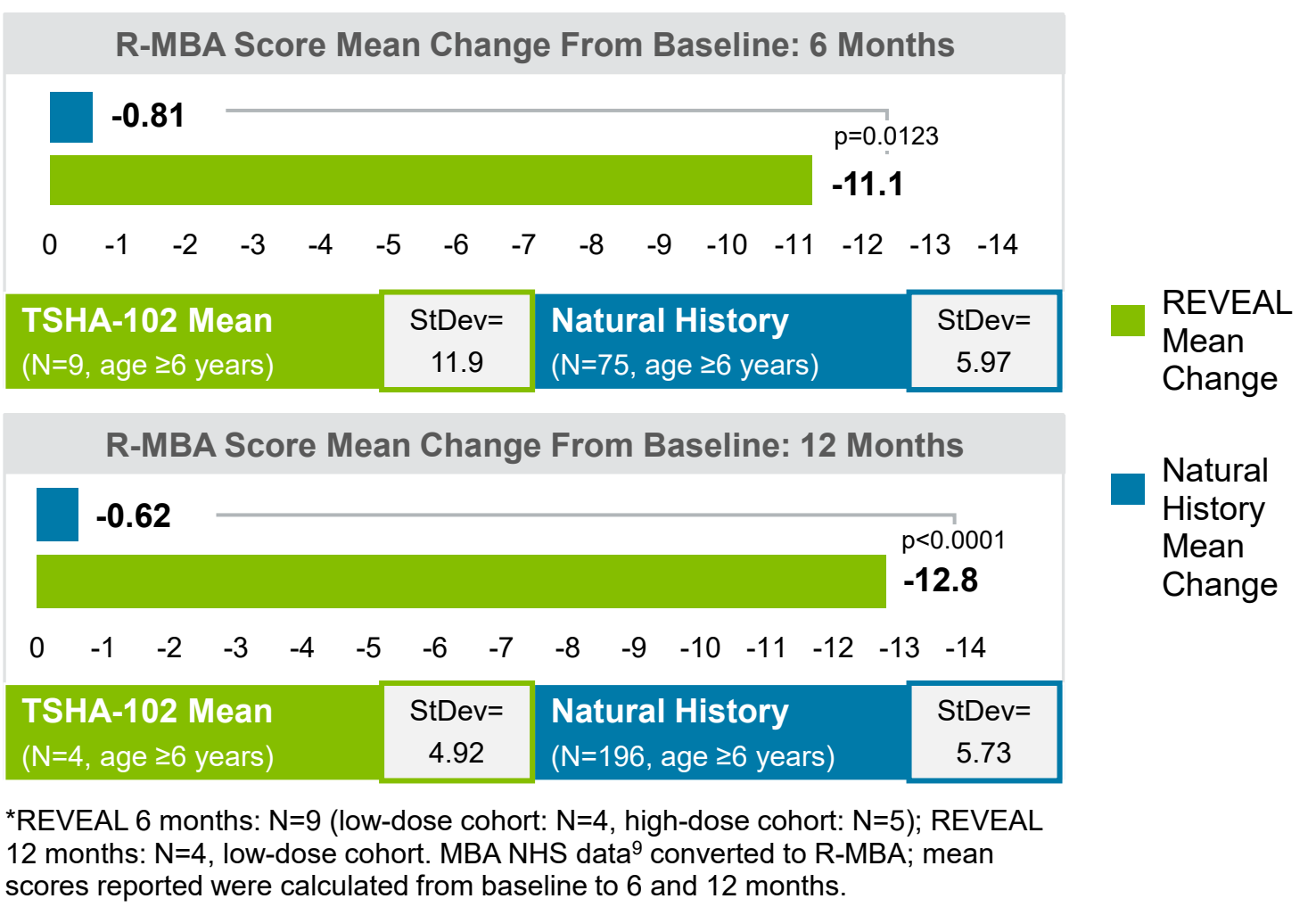


Table 3: Consistent dose response observed across key measures at 6 months post-TSHA-102, with the separation between dose cohorts increasing over time*

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%	
	Participants with R-MBA improvement (%) at latest visit	100%	100%	
	Mean score improvement at 6 months	-9.8	-12.2	✓
R-MBA ¹	Mean score improvement at ≥9 months	-11.5	-18.0	
	Participants with CGI-I improvement (%) at latest visit	75%	100%	
CGI-I	Mean CGI-I score at 6 months	2.3	2.0	✓
	Mean CGI-I score at ≥9 months	2.8	1.0	
	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	Supportive Evidence of Functional Gain A Total of 165 Additional Skills and Improvements Achieved		
- 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	MSEL-A = 34 total gains		
	ORCA = 59 total gains		
	R-MBA = 72 total improvements		
	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)		
	Used gesture to communicate (e.g. point, eye gaze)		
	Understood mood (based on facial expression/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		

*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	Fine Motor Improvements	Gross Motor Improvements	Autonomic/Other Improvements
Enable expression of needs, preferences, emotions, and foster social connections PRE-TREATMENT: Non-verbal POST-TSHA-102: 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	Reflect self-care skills and purposeful hand use that enable independence PRE-TREATMENT: Stereotypies 76–100% of time POST-TSHA-102: 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	Enhance mobility and independence, and reduce the physical burden of caregiving PRE-TREATMENT: Most severe dystonia (fixed postional deformity) POST-TSHA-102: 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	Improve core features of RTT that have a meaningful impact on quality of life PRE-TREATMENT: Hyperventilating/ breath holding 26–50% of time POST-TSHA-102: 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.