Safety and Efficacy Results from the REVEAL Part A Phase 1/2 Trial of TSHA-102 in Pediatric and Adolescent/Adult Cohorts

Poster 59

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Aims

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

Background

- RTT disease presentation and progression is highly heterogeneous, with inter-individual variability in the timing and pattern of lost or missed developmental milestones (DM), impacting activities of daily living[1–4]
- A recent analysis of Natural History Study (NHS) data demonstrated that patients reach a developmental plateau at ≥6 years of age[4], with a <6.7% likelihood of gaining new or regaining lost developmental milestones among a defined list of 28 (Figure 1)[5]
- Gaining or regaining a DM would not be expected from individuals in the developmental plateau population
- While current care aims to manage symptoms, there are no approved disease-modifying strategies that address the genetic root cause of RTT (loss of function mutation in the methyl-CpG-binding protein 2 [*MECP2*] gene)[6]
- 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)[7,8]
- The REVEAL pivotal trial is investigating TSHA-102 for adolescent/adult (NCT05606614) and pediatric (NCT06152237) individuals with RTT[9,10]
- Here, we present longer-term safety and efficacy data from REVEAL Part A, including all 12 patients with ≥12 months of follow-up, with data extending up to 30 months for the earliest treated patient

Figure 1: Rigorous analysis of the Rett Natural History Study demonstrated likelihood of gaining/regaining any of the 28 defined DMs is predictable in patients ≥6 years of age

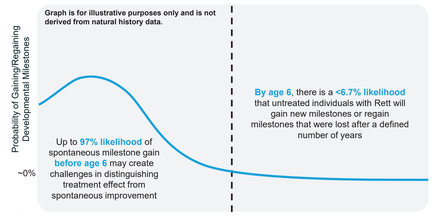
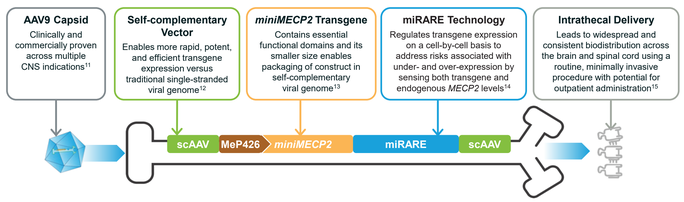


Figure 2: TSHA-102 construct: An investigational one-time gene therapy designed to regulate *MECP2*



Methods

- REVEAL is an ongoing Phase 1/2, open-label, dose-escalation (Part A) and dose-expansion (Part B), registrational, multi-center trial, using each patient as their own control; ≥12-month Part A data is reported here (Figure 3)[9,10]
- Safety monitoring included clinical/laboratory evaluations
- Primary evidence of efficacy (DM gain or regain): Applied rigorous evaluation criteria to available video-evidenced DM data that enabled a reliable, objective assessment of TSHA-102 efficacy (Figure 4)
- Supportive evidence of functional gain: 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 4)

Figure 3: REVEAL Part A study overview[9,10]

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
- Developmental Milestones Gain/regain
- R-MBA
- ORCA
- MSEL-A
- CGI-S
- CGI-I

Figure 4: Rigorous evaluation criteria applied to Part A data enabled reliable, objective assessment of TSHA-102 efficacy

Primary Evidence of Efficacy	*Additional evidence of functional gain*
Developmental Milestones (DM)	**Additional Skills and Improvements**
The functional gain of ≥one of the **28 DMs defined in the natural history study** assessed via rigorous video-evidenced evaluation	Functional gain or improvement in a core disease characteristic **beyond the 28 natural history defined DMs** assessed via rigorous video-evidenced evaluation and validated scales
Evaluation Criteria:	**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%	✓ **Adapted Mullen Scales of Early Learning (MSEL-A)**: Centrally rated video-recorded evaluation assessing expressive / receptive language skills
✓ **Post-treatment**: Video-documentation of milestone demonstration	✓ **Observer-Reported Communication Ability (ORCA)**: Caregiver-reported structured evaluation assessing communication skills
✓ **Evaluation method**: Determined by multiple independent central raters based on prespecified definitions of achievement for each milestone	✓ **Revised Motor Behavior Assessment (R-MBA)**: Clinician-reported video evaluation assessing frequency, severity or independence of Rett syndrome characteristics

n=8 patients with ORCA data, n=7 with MSEL-A data, and n=12 with R-MBA data.

Results

Baseline characteristics
- As of May 2026 data cut, 12 patients (low dose, N=4; high dose, N=8) had received TSHA-102. Patients were 6–21 YOA, with diverse clinical histories, broad disease severity (CGI-S 4 to 6), and varied *MECP2* mutations to reflect a real-world population

Safety
- TSHA-102 was generally well tolerated at the low and high dose, with no treatment-related serious adverse events (SAEs) or dose-limiting toxicities (DLT) (Table 1)
- All TEAEs considered related to TSHA-102 were mild-moderate in severity, with the most common being elevated liver enzymes* (n=4, 33%), CSF protein increased (n=3, 25%) (clinically insignificant), pyrexia (n=3, 25%)
- Seizures have generally been well controlled following TSHA-102

*Includes preferred terms: Gamma-glutamyltransferase increased, Hypertransaminasaemia, Liver function test increased, Transaminases increased.

Table 1: Events across the 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	17	5	20	9	37
Serious TEAE Unrelated to TSHA-102	3	9	4	8	7	17
Serious TEAE Related to TSHA-102	**0**	**0**	**0**	**0**	**0**	**0**

Efficacy

Table 2: All 12 pediatric, adolescent, and adult patients across a broad range of disease severity gained/regained ≥one developmental milestone post-TSHA-102*

	Age at dosing (years)	Baseline CGI-S Score	Post-treatment follow-up (months)	DM gain post-TSHA-102
Low Dose $5.7x10^{14}$ vg	20	6	30	✓
	21	4	30	✓
	6	5	24	✓
	7	4	24	✓
High Dose $1x10^{15}$ vg	15	5	18	✓
	21	5	18	✓
	8	5	18	✓
	15	5	12	✓
	16	5	12	✓
	6	4	12	✓
	7	6	12	✓
	6	5	12	✓

Developmental milestone gains and regains were assessed by multiple independent central raters through video evidence.*Incidence models derived from NHS data; accessed from 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.

- TSHA-102 delivered consistent and clinically meaningful treatment benefit across pediatric and adolescent/adult patients with RTT
  - 16 DMs in pediatric (n=6) and 15 DMs in adolescent/adult (n=6) patients support the broad treatment potential of TSHA-102

Figure 5: Rapid and robust response rate in REVEAL Part A supports the pivotal trial is well-powered to establish efficacy

REVEAL Part A data exceeded FDA-aligned response rate threshold for pivotal trial success

Supports potential for 6-month REVEAL pivotal trial interim analysis to enable BLA submission

REVEAL Phase 1/2 Part A Data

Response Rate = the % of patients who gain or regain ≥1 developmental milestone from a list of 28.

Figure 6: 31 total developmental milestones achieved across core disease domains post-TSHA-102 reflect meaningful improvements in daily living

Communication
- 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

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

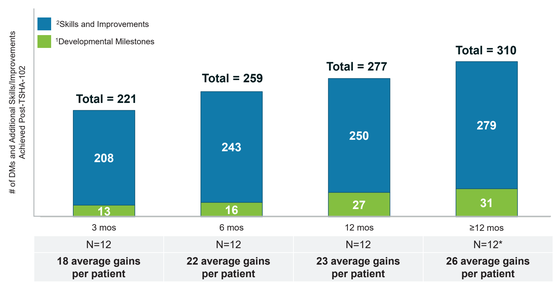
Fine Motor
- Used utensils to eat without assistance
- Used utensils to eat with assistance
- Finger fed
- Transferred an object from one hand to another
- Used a pincer grasp
- Reached for a toy
- Holds bottle unpropped

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

Gross Motor
- Walked with support
- Climbed down stairs with support
- Stood while holding on
- Pulled to standing
- Sat without support

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

Figure 7: Patients achieved durable, clinically meaningful skill gains and improvements that accumulated over time in addition to developmental milestones



†Gain/regain of ≥one of the 28 natural history-defined developmental milestones from the REVEAL pivotal trial primary endpoint. ‡Skill gains/improvements derived from MSEL-A, R-MBA and ORCA: N=8 patients with ORCA data, N=7 with MSEL-A data, and N=12 with R-MBA data. *N=7 patients with data >12 months post-TSHA-102, N=5 patients with 12-month data.

- ~26 functional gains per patient across core disease domains reflect the broad functional impact demonstrated post-TSHA-102

Figure 8: TSHA-102 delivers durable, multi-domain functional gains that enable activities of daily living

Communication improvements

Pre-TSHA-102	Post-TSHA-102
Non-verbal	Speaks in phrases/sentences with meaning
Understood simple words	Engages in conversations and play/activity with others
Made choices <10% of time using eye gaze	Makes choices 100% of time by pointing
Rarely responds to spoken words	Follows directions and responds to questions

Fine motor improvements

Pre-TSHA-102	Post-TSHA-102
Required caregiver-assisted feeding	Finger feeds and uses utensils to eat independently
No purposeful hand use	Plays with toys and self-feeds
Stereotypies 76-100% of time	Stereotypies 1-25% of time
Limited hand function	Holds a bottle unpropped

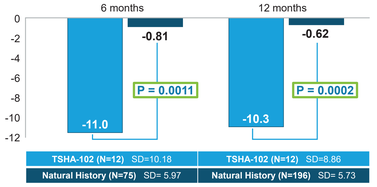
Gross motor improvements

Pre-TSHA-102	Post-TSHA-102
Non-ambulatory	Walks with support
Unable to use stairs	Climbs down stairs with support
Needed caregiver assistance	Pulls self to standing position and stands while holding on
Most severe dystonia (fixed positional deformity)	No dystonia

Autonomic/Other improvements

Pre-TSHA-102	Post-TSHA-102
Unable to eat by mouth and required a g-tube	Eats/drinks by mouth
Weekly to monthly seizure episodes	Seizure-free ≥6 months
Hyperventilating/breath holding 26-50% of time	Absent or reduced hyperventilating/ breath holding
Feeding took >30 minutes	No feeding difficulties

Figure 9: R-MBA score mean change from baseline in patients ≥6 years: REVEAL low and high-dose patients vs natural history*, indicating a reversal in the disease trajectory



Average score ≥18 months post-TSHA-102:
- -15.7 in high dose cohort
- -7.8 in low dose cohort

N=12 at 6 and 12 months, N=7 at ≥18 months post-TSHA-102. Statistical analyses are based on May 2026 data cutoff (N=12). †R-MBA assessed in Rett syndrome NHS at ~6 and ~12 months; 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.

Table 3: Robust and clinically meaningful responses at 6 and ≥12 months support potential for BLA submission based on the 6-month interim analysis from REVEAL pivotal trial

Endpoint		6 months *N=12*	12 months *N=12*	≥18 months *N=7*
Functional Gains	% of Patients Gained/Regained ≥One Developmental Milestone	**83%**	**100%**	**100%**
	Average Functional Gains Per Patient	**22** gains per patient	**23** gains per patient	**26** gains per patient
R-MBA*	Statistically Significant Mean Score Improvement vs Natural History	**-11.0** P = 0.0011	**-10.3** P = 0.0002	**-11.0** P = 0.0046
CGI-I	% of Patients with CGI-I Score ≤3 at Multiple Post-treatment Assessments	**100%**	**100%**	**100%**
CGI-S**	% of Patients with CGI-S Total Score Improvement	**25%**	**25%**	**57%**

*R-MBA mean score change post-TSHA-102 is relative to baseline; lower score=improvement from baseline. **CGI-S: a clinician-assessed scale ranging from 1 to 7, assessing severity of illness.

Conclusions

- No treatment-related SAEs or DLTs observed in any patients, with all patients having ≥12 months of follow-up
- 100% of patients (N=12, 6-21 years) in developmental plateau population of gained/regained ≥one DM
- Longer follow-up demonstrates a durable and deepening treatment effect across all patients, with additional functional gains continuing to accumulate over time ≥12 months
  - DM gains increased by 69% from 6 to 12 months and by 94% from 6 to ≥12 months post TSHA-102
  - Patients with longest follow-up at 30 months continue to demonstrate functional gains/improvements
- Broad functional impact consistently demonstrated across core disease domains post-TSHA-102 regardless of age, disease severity or genotype
  - At ≥12 months post-TSHA-102, a total of 310 functional gains and improvements were observed (~26 per patient), comprising 31 DMs and 279 additional skill gains/improvements
  - Durable, multi-domain gains enable independent engagement in daily activities, reduce caregiver burden and enhance social engagement
- Robust, clinically meaningful responses at 6 and ≥12 months exceed FDA-aligned minimum threshold for efficacy and support potential for BLA submission based on REVEAL pivotal trial 6-month interim analysis

Key takeaway

- **TSHA-102 continues to be generally well-tolerated in pediatric, adolescent, and adult patients with RTT**
- **Longer-term follow-up showed a durable and deepening treatment effect ≥12 months post-TSHA-102, with functional gains accumulating over time across core disease domains**
- **310 total functional gains demonstrated ≥12 months post-TSHA-102 (~26 per patient), comprising 31 developmental milestones and 279 additional skill gains/improvements**
- **Robust and clinically meaningful responses at both 6 and ≥12 months in REVEAL Part A further support potential for BLA submission based on REVEAL pivotal trial 6-month interim analysis**

The authors wish to thank all patients and caregivers, as well as the study staff who make this research possible

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Acknowledgments: Studies funded by Taysha Gene Therapies. Medical writing support for this poster was provided by Leigh O'Connor-Jones, PhD and Lauren Batt, PhD, of Avalere Health US Inc., funded by Taysha Gene Therapies
Disclosures: ER: Consultancy with Acadia Pharmaceuticals, CACNA1A Foundation, Canadian Pediatric Epilepsy Network, Canadian Association for Neurosciences, and Taysha Gene Therapies; Clinical Trials with Ionis Pharmaceuticals and Taysha Gene Therapies; Grants from CACNA1A Foundation; Canada Foundation for Innovation; Canadian Institutes of Health Research, Canada Research Chairs; CHU Saint-Justine, Ontario Rett Syndrome Association; CHUSJ-SickKids Precision in Child Health Partnership (PCHP); Université de Montréal.

Abbreviations: AAV9, adeno-associated virus serotype 9; BLA, biologics license application; 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; E, number of events; *MECP2*, *methyl-CpG-binding protein 2*; miRARE, microRNA autoregulatory element; MSEL-A, Adapted Mullen Scales of Early Learning; N, number of patients; NHS, Natural History Study; ORCA, Observer-Reported Communication Ability; R-MBA, Revised Motor Behavior Assessment; RTT, Rett syndrome; SAE, serious adverse event; sc, self-complementary; SD, standard deviation; TEAE, treatment-emergent adverse event; vg, vector genome; YOA, years of age

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