REVEAL Adolescent/Adult and Pediatric Clinical Trial Update: Safety and Efficacy Data on TSHA-102 AAV9 Investigational Gene Therapy in Clinical Evaluation for Rett Syndrome

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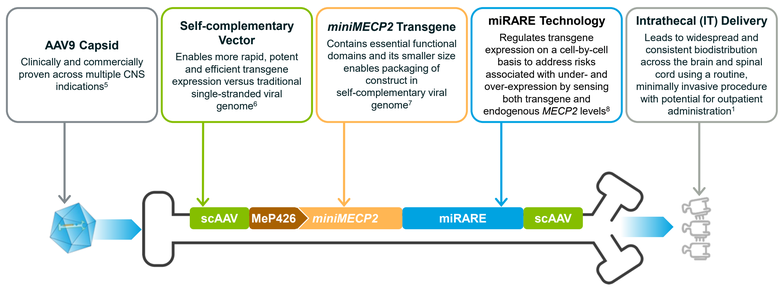
Aim

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

Background

- TSHA-102 is a one-time gene therapy for Rett syndrome, designed to enable optimal and controlled transgene expression of *MECP2* across the CNS following intrathecal administration (Figure 1)[1,2]
- The REVEAL adolescent/adult (NCT05606614) and pediatric (NCT06152237) studies are first-in-human trials of TSHA-102 for individuals with Rett syndrome[3,4]
- As established COAs and CROs are not optimal measures of functional outcomes in small, open-label trials, measuring gain/regain of DMs presents an objective, data-driven way to assess the efficacy of TSHA-102 in a broad Rett syndrome population
- Here, we present the currently available safety and efficacy data (up to 18 months for the first dosed patient) from Part A (dose escalation) of the REVEAL studies

Figure 1: 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), randomized, multi-center trials (Figure 2)[3,4]
- Following immunosuppression initiation at Day −7, a single dose of TSHA-102 was delivered via intrathecal infusion through lumbar puncture on Day 0
- Safety (clinical and laboratory evaluations) and efficacy are being assessed through 18 months
- Taysha's analysis of IRSF's longitudinal Rett syndrome NHS data demonstrated individuals ≥6 YOA have reached a developmental plateau, with an exceedingly low (0% to <6.7%) likelihood of gaining new or regaining DMs that were lost after a defined number of years. (Figure 3)
  - Patient gain/regain of these milestones in Part A was determined by multiple independent central raters based on video-evidenced evaluation according to predefined definitions of achievement for each DM

Figure 2: Study overview[3,4]

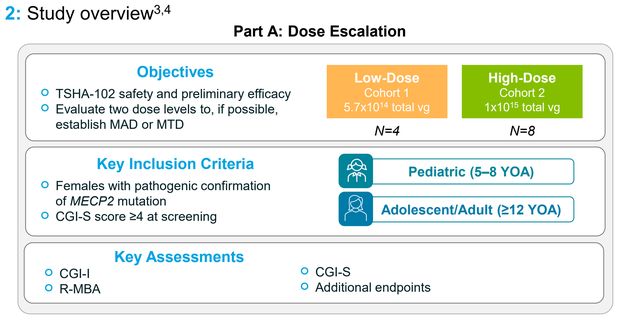


Figure 3: 28 DMs from the NHS that would reflect meaningful functional gains to caregivers, with a ~0% likelihood of being achieved after ≥6 YOA if untreated

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 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

Results

Baseline characteristics

- As of May 20, 2025 (data cut), 12 participants (low dose, N=4; high dose, N=8) have received TSHA-102. The participants are aged 6–21 years, have diverse clinical histories 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 SAEs or DLTs (Table 1)
- All TEAEs related to TSHA-102 were mild-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 experience 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: TSHA-102 TEAEs

Number of Events Across 12 Pediatric, Adolescent, and Adult Participants Dosed in Part A of the 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

Efficacy

- Currently, efficacy data are available for 4 low-dose and 6 high-dose participants (data cut May 19, 2025)
- 100% of participants gained/regained ≥1 milestone by 9 months (high dose) or 12 months (low dose) compared with ~0% of people in the NHS (Figures 4 and 5)
- TSHA-102 demonstrated a statistically significant mean R-MBA score improvement compared with NHS participants at both 6 and 12 months (Figure 6)
- Mean CGI-I score was 1.0 (very much improved) in the high-dose cohort compared with 2.8 in the low-dose cohort at ≥9 months post-TSHA-102 (Table 2)
- There is a clear and consistent dose response, with the high-dose cohort continually outperforming the low-dose cohort across key outcome measures at 6 months post-treatment including in DM gain and regain, R-MBA, and CGI-I (Table 3)

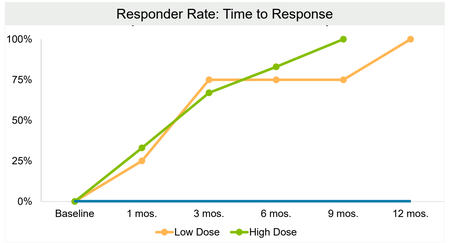
Figure 4: 100% of participants (n=10) gained/regained ≥1 defined DM post-TSHA-102, with a ~0% likelihood of being achieved without treatment based on NHS data[9]

	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.

Figure 5: A) High-dose TSHA-102 achieved 100% responder result at a 25% faster rate compared to low-dose TSHA-102; **B)** Participants gained/regained DMs across the core functional domains of Rett syndrome post-TSHA-102

A) Accelerated functional benefit seen with high-dose TSHA-102



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

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

Early clinical response may increase the likelihood of reversing the disease trajectory and may be predictive of long-term clinical outcomes in Rett syndrome

B) 22 developmental milestones were achieved across 10 participants treated with TSHA-102

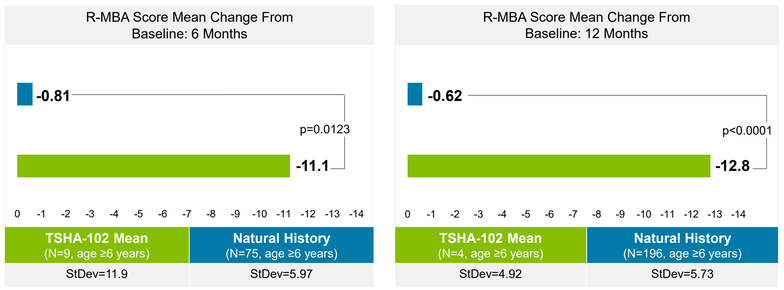
Communication
- Spoke in phrases (2 words or more) with meaning
- Used word(s) with meaning
- Followed a command without a gesture
- Followed a command with a gesture
- Pointed for something they wanted
- Identified body parts

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

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

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 Baseline, 1, and 3 months, N=5 at 6 months, N=2 at 9 months, based on available follow-up. *People ≥6 YOA. Cumulative incidence models of NHS data conducted by third-party statistical partners. Incidence models derived from NHS data[9].

Figure 6: 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 2: TSHA-102 demonstrated early global improvement, with dose-dependent effects deepening over time in mean CGI-I*

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

*Mean CGI-I scores based on latest assessment for each patient. No data available at 12 and 18 months in high-dose cohort.

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%	✓

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 fine motor, gross motor, and communication post-TSHA-102, compared with an ~0% likelihood of DMs being achieved without treatment, based on NHS data
  - A total of 22 DMs were achieved across the 10 participants, as determined by multiple independent central raters based on video-evidenced evaluation according to predefined definitions of achievement for each DM
  - DMs were achieved early post-TSHA-102, with new gains/regains demonstrated over time
  - The 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 R-MBA and CGI-I, which corroborates the DM gains/regains demonstrated post-TSHA-102
- The high-dose cohort outperformed the low-dose cohort across multiple outcome measures 6 months post-treatment, with dose-dependent effects deepening over time (≥9 months post-treatment)

Key takeaway

Pediatric, adolescent, and adult participants in Part A of the REVEAL trials who are in the developmental plateau phase and thus not expected to achieve developmental gains or regains, have all gained or regained developmental milestones that are meaningful to caregivers, families, and clinicians. Based on this safety and efficacy data we plan to initiate pivotal Part B trial activities in Q3 2025

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Abbreviations: AAV9, adeno-associated virus serotype 9; CGI-I, Clinical Global Impression Scale-Improvement; CGI-S, Clinical Global Impression Scale-Severity; CNS, central nervous system; COA, clinical outcomes assessment; CRO, caregiver reported outcomes; CSF, cerebrospinal fluid; DLT, dose-limiting toxicity; DM, developmental milestone; IRSF, International Rett Syndrome Foundation; ITR, inverted terminal repeat; MAD, maximum administered dose; *MECP2*, methyl-CpG-binding protein 2; miRARE, microRNA autoregulatory element; miRNA, microRNA; mos, months; MTD, maximum tolerated dose; NfL, neurofilament light; NHS, Natural History Study; R-MBA, Revised Motor Behavior Assessment Scale; 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
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SCAN ME

2025 IRSF Rett Syndrome Scientific Meeting: June 9–11, Boston MA, USA