TSHA-102 Investigational Gene Therapy for Rett Syndrome: First-cohort Data from the REVEAL Adolescent/Adult and Pediatric Studies

Friday, October 4, 2024

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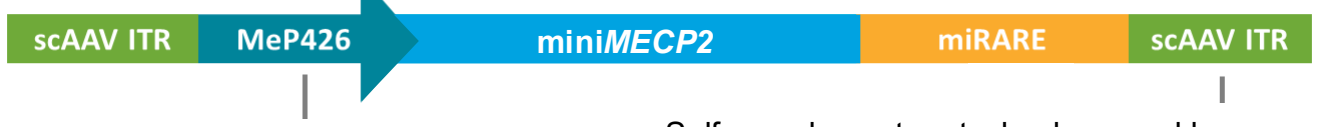
TSHA-102: An Investigational, One-time Gene Therapy For Rett Syndrome that is Designed to Regulate *MECP2* on a Cell-by-Cell Basis

AAV9 capsid
Clinically and commercially proven across multiple CNS indications

miniMECP2 allows for packaging of miRARE technology for sophisticated regulatory control in a self-complementary design[1,2]



MeP426 promoter drives primarily neuronal expression, capitalizing on endogenous transcriptional regulation in the brain

Self-complementary technology enables more rapid transgene expression due to ability to bypass the rate-limiting second-strand synthesis in host cells[3]

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AAV9, adeno-associated virus serotype 9; CNS, central nervous system; ITR, inverted terminal repeat; *MECP2, methyl CpG-binding protein 2*; miRARE, microRNA-responsive autoregulatory element; scAAV, self-complementary AAV

1. Tillotson R, Selfridge J, Koerner MV, et al. *Nature*. 2017;550(7676):398-401. 2. Sinnett SE et al. A New Approach for Designing a Feedback-Enabled AAV Genome Improves Therapeutic Outcomes of MiniMeCP2 Gene Transfer in Mice Modeling RTT. *23rd Annual meeting for the American Society of Gene & Cell Therapy*; April 28,2020. 3. McCarty DM. *Mol Ther*. 2008;16(10):1648-1656.

REVEAL Phase 1/2 Adolescent and Adult Trial

Interim Results

REVEAL Phase 1/2 Adolescent and Adult Trial in U.S. and Canada

Open-label, dose-escalation and dose-expansion, randomized, multi-center trial for TSHA-102

Study Overview

Objectives

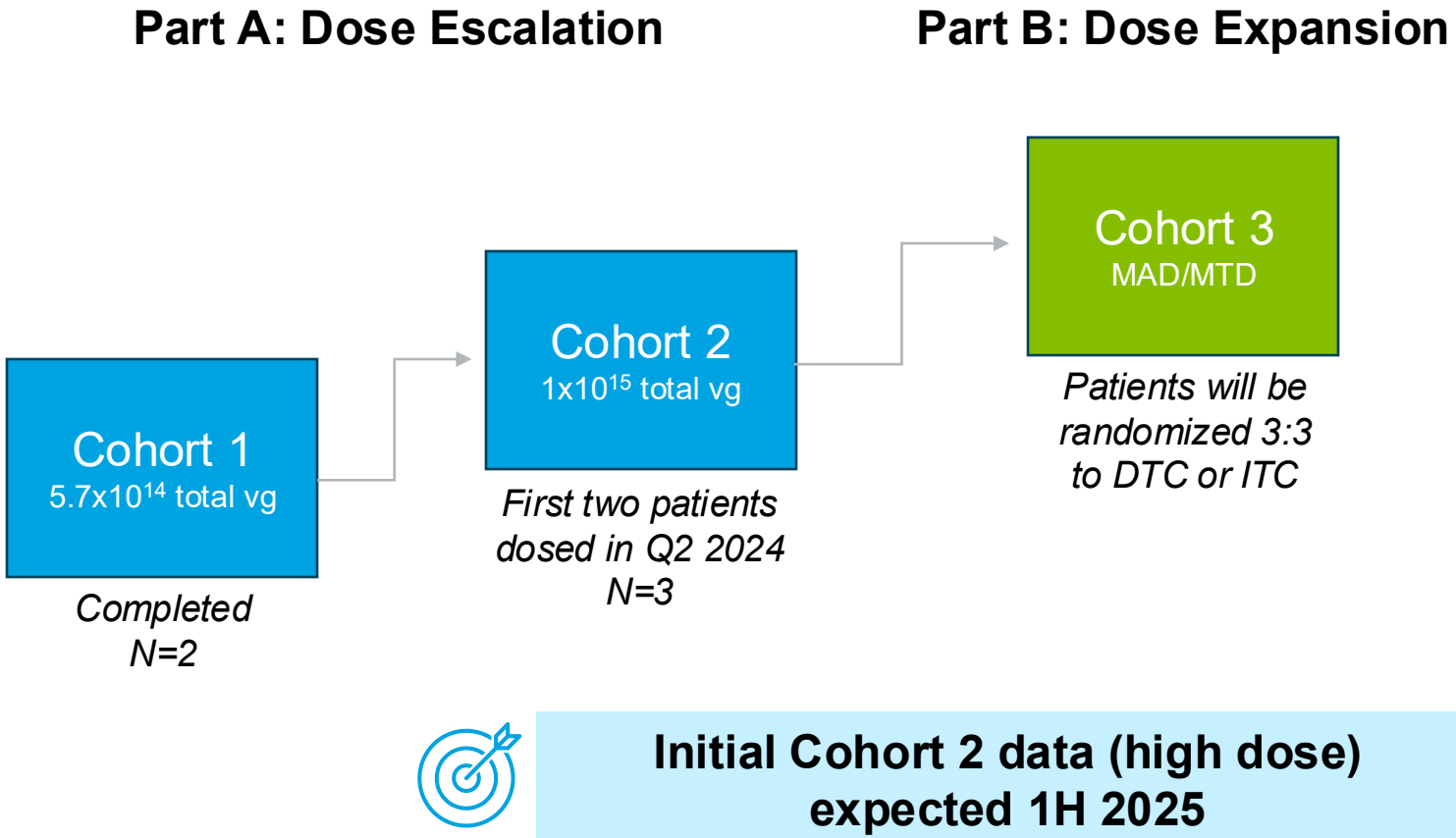
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels (n=2 low dose, n=3 high dose); if possible, establishes MAD or MTD
- **Part B**: evaluates the MAD or MTD

Key Inclusion Criteria

- Females aged 12+ with pathogenic confirmation of *MECP2* mutation
- CGI-S score of ≥4 at screening

Key Clinical Assessments

- R-MBA
- CGI-S and CGI-I
- PGI-I
- RSBQ
- RSHFS



Initial Cohort 2 data (high dose) expected 1H 2025

CGI-S, Clinical Global Impression Scale-Severity; CGI-I, Clinical Global Impression Scale-Improvement; DTC, delayed treatment cohort; ITC, immediate treatment cohort; MAD, maximum administered dose; *MECP2*, *methyl-CpG-binding protein 2*; MTD, maximum tolerated dose; PGI-I Parental Global Impressions Scale-Improvement; R-MBA, Revised Motor Behavior Assessment Scale; RSHFS, Rett Syndrome Hand Function Scale; RSBQ, Rett Syndrome Behavior Questionnaire; vg, total vector genomes

Taysha Gene Therapies Inc. REVEAL Adult Study. ClinicalTrials.gov Identifier: NCT05606614. Updated November 28, 2023, Accessed February 2024. https://clinicaltrials.gov/ct2/show/NCT05606614.

First Two Adult Patients Have Stage Four Rett Syndrome with Different Genetic Mutation Severity and Phenotypic Expression

Patient 1	Patient 2
Diagnosed with stage four “late motor deterioration muscle wasting” RTT	
20-year-old female at the time of dosing	21-year-old female at the time of dosing
Large *MECP2* deletion affecting exons 3 and 4	Missense *MECP2* mutation (R133C)
Severe phenotype	**Milder** phenotype
“Severely ill” – CGI-S Baseline score of 6	“Moderately ill” – CGI-S Baseline score of 4

• **Motor Skills:** Loss of hand function by age 6.5
  • Complete loss of ambulation and wheelchair-bound by age 8
• **Communication/Socialization**: Mostly non-verbal by age 6
• **Autonomic Function**: Frequent apnea and hyperventilation by age 3
• **Seizures**: Seizures at age 5 (2-4 per year at Baseline)
	• **Motor Skills:** Partial loss of ambulation by age 2
	  • Walks with impaired gait and balance by age 18
	  • Hand stereotypies with weak grasping by age 3
	• **Communication/Socialization**: Mostly non-verbal by age 2
	• **Autonomic Function**: Frequent hyperventilation by age 3
	• **Seizures**: Seizures by age 10 (2-4 per week at Baseline)

Baseline characteristics based on pre-treatment observations, Baseline assessments, prescreening visits and patient’s medical history.
CGI-S, Clinical Global Impressions-Severity; *MECP2, methyl-CpG-binding protein 2*; RTT, Rett Syndrome

TSHA-102 Safety Data in the Adult/Adolescent REVEAL Trial

- TSHA-102 has been generally well tolerated.
- No SAEs related to TSHA-102 or dose limiting toxicities in Patient One as of Week 52 and Patient Two as of Week 36.
- All TEAEs were mild-to-moderate in severity.*

Patient 1

- 9 TEAEs
- No SAEs
- Two nonserious events related to TSHA-102 (mild: pyrexia, CSF protein increase)
- Two nonserious adverse events were related to immunosuppression (mild: irritability, stress fracture)

Patient 2

- 13 TEAEs
- No SAEs
- Two nonserious events related to TSHA-102 (mild: CSF protein increase, clonus)
- Eight nonserious events were related to immunosuppression (mild: vomiting (2), dermatitis acneiform, Cystatin C increase, blisters, myopathy) (moderate: chronic renal disease, myopathy)

*Listing 5.1 TSHA-102-CL-101, 05/10/2024 An event may have more than 1 causality reported.

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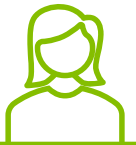
CSF, cerebrospinal fluid; SAEs, serious adverse events; TEAEs, treatment emergent adverse events

For more information on safety outcomes, please visit our poster.

At One Year and 6 Months, Improvements in Multiple Clinical Domains for Both Adult Patients Based on Clinical Evaluation

Patient 1; Week 52

Steroid taper completed Week 36, sirolimus taper completed Week 43



Patient 2; Week 25

Steroid taper completed Week 25, sirolimus taper completed Week 31

	Patient 1; Week 52	Patient 2; Week 25
Gross and Fine Motor Skills	• Improved hand function, with hands more open • Gained ability to sit unassisted and move legs, for the first time in over a decade	• Improved hand stereotypies for the first time since regression at age three, and improved posture and stability
Communication/ Socialization	• Improved social interest, vocalization, and use of eye-driven communication device	• Improved social interest and increased response to words and eye contact
Autonomic Function	• Improved breathing patterns and circulation • Normalized sleep quality/duration • Able to sleep through night for the first time in 20 yrs	• Improved breathing patterns and circulation
Seizures	• Stable seizure events with lower levels of anti-seizure medication, relative to Baseline	• Seizure-free for 8.5 months following TSHA-102, compared to 2-4 seizures per week pre-treatment • Significantly reduced seizure events with 25% lower levels of anti-seizure medication, relative to Baseline*
Overall change	+	+

*Seizure data for adult patient two is based on Seizure Diary and caregiver reports as of Week 36 post-TSHA-102 treatment.
Clinical observations made by the Principal Investigator are based on post-treatment assessments, pre-treatment observations, Baseline assessments, pre-screening visits and patient's medical history. Subject to change as the trial progresses.

Global Impression Scores in Adolescent/Adult Patients 1 and 2

	Static Measure of Severity of Illness		Dynamic Measures Assessing Symptom Improvement			
	CGI-S		**CGI-I, *with Rett anchors***		**PGI-I**	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**
Screening, Baseline	6 Severely ill	4 Moderately ill	–	–	–	–
Week 4	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better
Week 8	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better
Week 12	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	2 Much better*	3 A little better
Week 25	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	2 Much better	3 A little better
Week 52	5 Markedly ill	–	3 Minimally improved	–	1 Considerably better	–
Overall Change	**+**	**=**	**+**	**+**	**+**	**+**

- Baseline disease severity improved for Patient 1
- Global impressions show early (Week 4) improvement for both patients sustained through Week 52 for Patient 1 and Week 25 for Patient 2 as evaluated by clinicians and caregivers, respectively

Data presented reflects current data in the Electronic Data Capture System (EDC); this is an ongoing study, and these data are subject to change in EDC
*PGI-I Week 12 assessment was captured at Week 16.
+ indicates improvement from Baseline; = indicates no change from Baseline.

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; P1, Patient 1; P2, Patient 2; PGI-I, Patient Global Impression-Improvement;

For more information on efficacy outcomes, please visit our poster.

Baseline assessment prior to treatment with TSHA-102

Adult/Adolescent Patient 1

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Week 6 assessment following treatment with TSHA-102

Adult/Adolescent Patient 1

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Week 35 assessment following treatment with TSHA-102

Adult/Adolescent Patient 1

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REVEAL Phase 1/2 Pediatric Trial

Interim results

REVEAL Phase 1/2 Pediatric Trial in the U.S. and U.K.

Open-label, dose-escalation and dose- and age-expansion, randomized, multi-center trial

Study Overview

Objectives

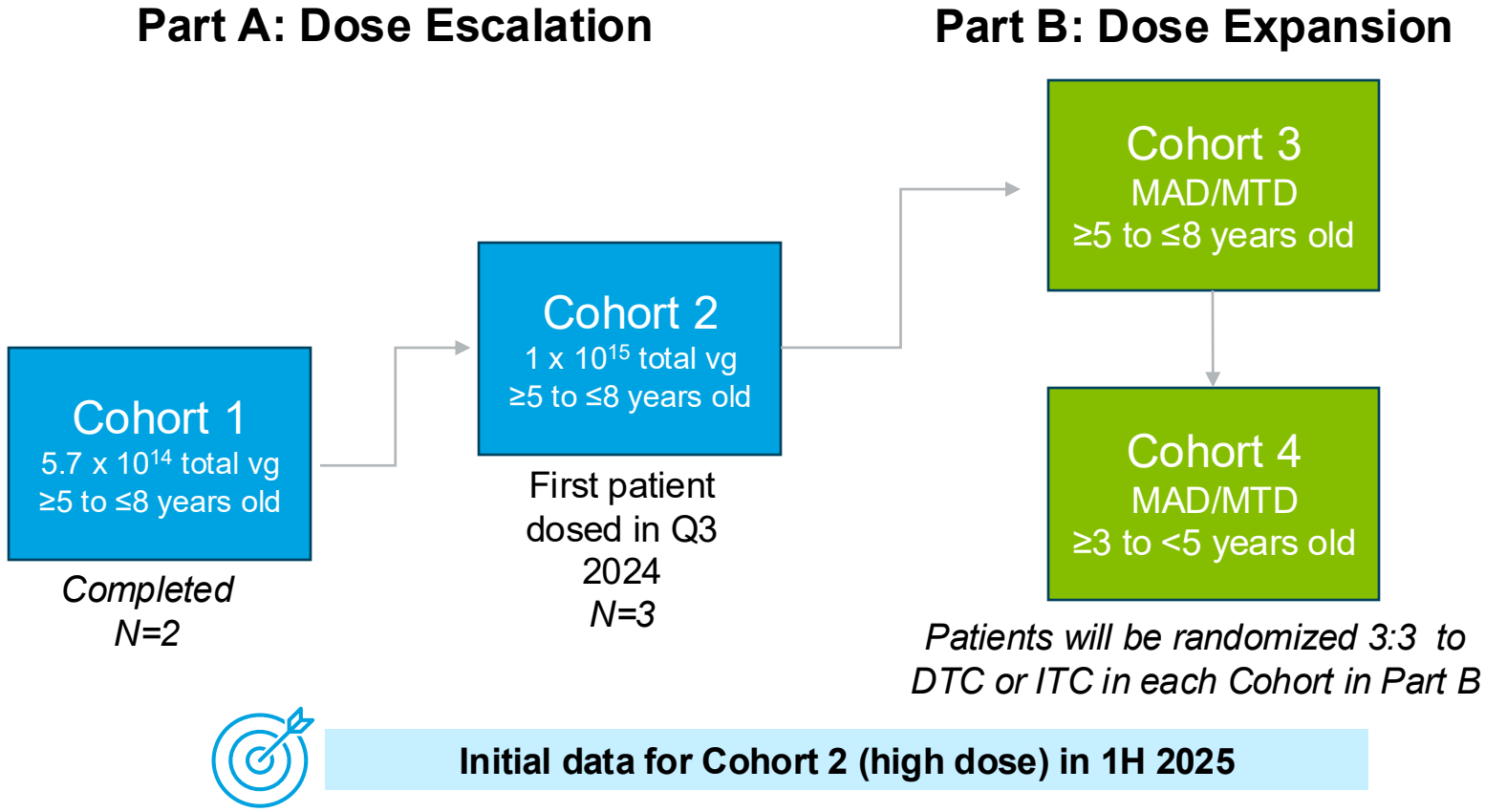
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels (n=2 low dose; n=3 high dose); if possible, establishes the MAD or MTD
- **Part B**: evaluates the MAD or MTD in two age cohorts

Key Inclusion Criteria

- Females 3-8 years old with pathogenic confirmation of *MECP2* mutation (Part A)
- CGI-S score of ≥4 at screening

Key Clinical Assessments

- R-MBA
- CGI-S and CGI-I
- PGI-I
- RSBQ
- MSEL-A



Initial data for Cohort 2 (high dose) in 1H 2025

CGI-S, Clinical Global Impression Scale-Severity; CGI-I, Clinical Global Impression Scale-Improvement; DTC, delayed treatment cohort; ITC, immediate treatment cohort; MAD, maximum administered dose; *MECP2*, *methyl-CpG-binding protein 2*; Adapted Mullen Scales for Early Learning, MSEL-A; MTD, maximum tolerated dose; PGI-I Parental Global Impressions Scale-Improvement; R-MBA, Revised Motor Behavior Assessment Scale; RSBQ, Rett Syndrome Behavior Questionnaire; vg, total vector genomes

Taysha Gene Therapies Inc. REVEAL Pediatric Study. ClinicalTrials.gov Identifier: NCT06152237. Updated February 14, 2024, Accessed February 2024. https://clinicaltrials.gov/study/NCT06152237.

First Two Pediatric Patients with Stage Three Rett Syndrome in Cohort 1 had Different Genetic Mutation Severity and Phenotypic Expression

Baseline characteristics of first two pediatric patients

Pediatric Patient 1	Pediatric Patient 2
Diagnosed with stage three “pseudo stationary” Rett Syndrome	
6-year-old female at the time of dosing	7-year-old female at the time of dosing
Nonsense *MECP2* mutation (R255X)	Missense *MECP2* mutation (R306C)
Moderate phenotype	**Milder** phenotype
“Markedly ill” – CGI-S Baseline score of 5	“Moderately ill” – CGI-S Baseline score of 4

• **Motor Skills:** Non-ambulatory
  • Sits unassisted for 30 seconds/stands with support by age 3
  • Impaired hand function with lost pincer grasp by age 1.5
• **Communication:** Mostly non-verbal by age 2
• **Autonomic Function:** Breath holding by age 4
• **Seizures:** Seizures by age 3 (1 seizure every 3 months)
	• **Motor Skills:** Partial loss of ambulation by age 1.5
	  • Stands independently by age 2
	  • Impaired hand function by age 1
	• **Communication:** Mostly non-verbal by age 1
	• **Autonomic Function:** Frequent hyperventilation by age 4
	• **Seizures:** Seizures by age 4 (2-4 seizures daily)

Baseline characteristics based on pre-treatment observations, Baseline assessments, pre-screening visits and patient’s medical history.
CGI-S, Clinical Global Impressions-Severity; *MECP2, methyl-CpG-binding protein 2*; RTT, Rett Syndrome

TSHA-102 has been Generally Well-tolerated to Date in the Pediatric REVEAL Trial

- TSHA-102 has been generally well-tolerated to date in both pediatric patients.
  - Both patients had challenging side-effects related to immunosuppressant treatment.
- No SAEs related to TSHA-102, no dose limiting toxicities.

Pediatric Patient 1

- Six TEAEs
- Four events related to TSHA-102 (3 mild: irritability, pyrexia, vomiting; 1 moderate: lethargy)
- One adverse event related to immunosuppression (1 mild: irritability)

Pediatric Patient 2

- Five TEAEs
- Two events related to TSHA-102 (both mild: seizure, lethargy)
- One serious adverse event, (severe, grade 3: change in seizure presentation) unrelated to TSHA-102, related to pre-existing disease and urine infection with multiple confounders (e.g., anesthesia, sleep deprivation)
  - Overall, she has experienced a decrease in seizure events, compared to Baseline
- After cut off for TEAE listing, PedP2 experienced a second SAE (moderate: constipation, grade 2) unrelated to TSHA-102. Patient was admitted for irritability and had a medical history of chronic constipation and concurrent non-serious event of parainfluenza virus, which may have been contributory

Listing 5.1 TSHA-102-CL-101 and TSHA-102-CL-102, 05/10/2024. An event may have more than 1 causality reported. Causality assessments updated per communication from investigator on 06/11/2024.

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SAEs, serious adverse events; PedP1, Pediatric Patient1; PedP2, Pediatric Patient 2; TEAEs, treatment emergent adverse events

For more information on safety outcomes, please visit our poster.

Overall Improvements Seen Across Multiple Clinical Domains in Both Pediatric Patients Based on Clinical Evaluation

	Patient 1; Week 12 *Steroid taper started Week 17*	Patient 2; Week 8 *Steroid taper to be initiated*
Gross and Fine Motor Skills	• Improved hand function and grasping with ability to hold object up to three-minutes vs 12 seconds at Baseline • Improved truncal stability and balance; gained ability to move her leg and to take a step with assistance and sit unassisted for longer duration	• Improved gait and balance when walking; new abilities of walking up a stair and standing up from a chair • Improved hand function, with ability to reach and grab/swat at objects
Communication/ Socialization	• Improved communication and use of eye-driven communication device, with new words communicated using device	• Improved social interest and eye contact*
Autonomic Function/ Oral Motor	• Improved breath holding, swallowing and oral intake relative to gastrostomy tube feeding	• Improved breathing patterns
Seizures	• Stable seizure events, relative to Baseline	• Increase in seizure-free days, relative to historical seizure frequency; although phenobarbital was added to regimen at Week 4 due to event of increased seizures**
Overall change	+	+

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*Has experienced irritability thought to be secondary to immunosuppression. **Increased seizure frequency SAE, resolved, unrelated to TSHA-102.
Clinical observations made by the Principal Investigator are based on post-treatment assessments, pre-treatment observations, Baseline assessments, pre-screening visits and patient's medical history. Subject to change as the trial progresses.

Global Impression Scores in Pediatric Patients 1 and 2

	Static Measure of Severity of Illness		Dynamic Measures Assessing Symptom Improvement			
	CGI-S		CGI-I, with Rett anchors		PGI-I	
	P1	P2	P1	P2	P1	P2
Screening, Baseline	5 Markedly ill	4 Moderately ill	–	–	–	–
Week 4	5 Markedly ill	4 Moderately ill	3 Minimally improved	3 Minimally improved	3 A little better	3 A little better
Week 8	5 Markedly ill	4 Moderately ill	3 Minimally improved	2 Much improved	3* A little better	2 Much better
Week 12	5 Markedly ill	–	3 Minimally improved	–	3 A little better	–
Overall Change	=	=	+	+	+	+

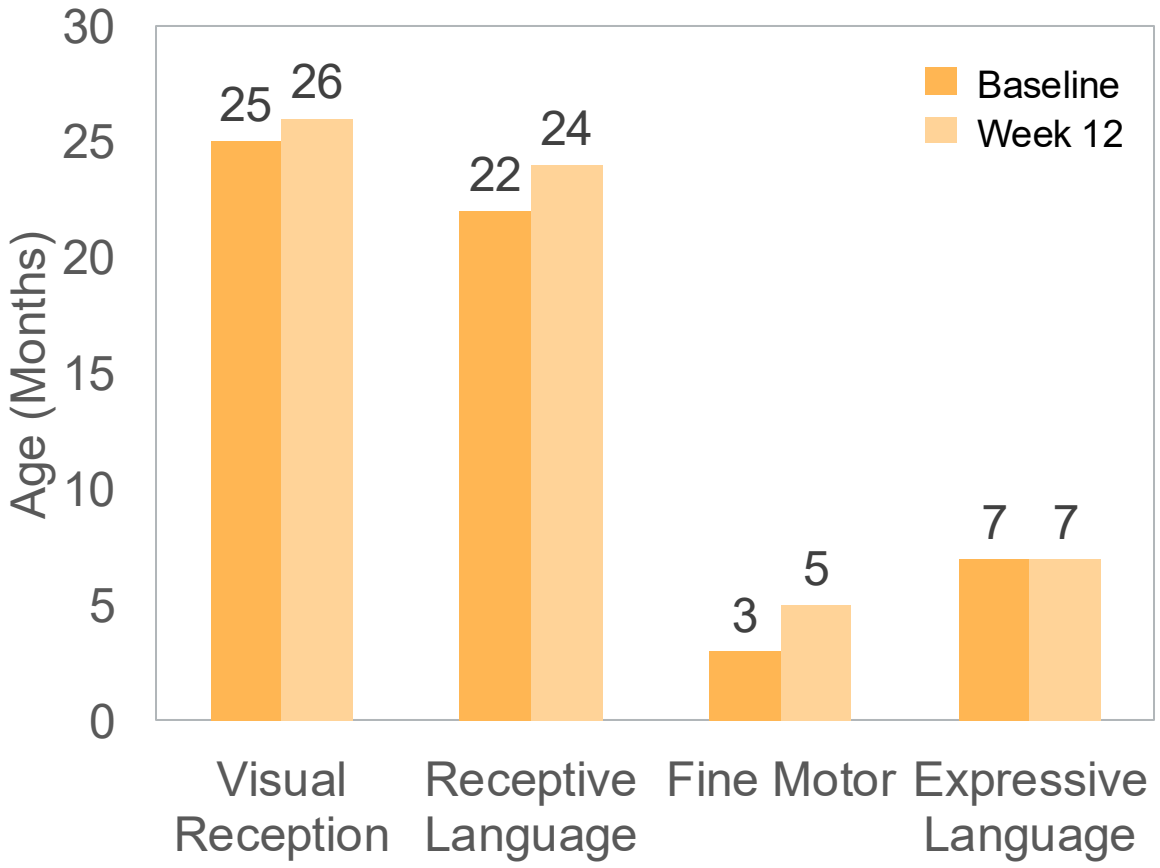
Global impressions show improvement for Patient 1 at Week 12 and Patient 2 at Week 8 as judged by clinicians and caregivers

*PGI-I Week 8 assessment was captured at Week 11
+ indicates improvement from Baseline; = indicates no change from Baseline

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; P1, Patient 1; P2, Patient 2; PGI-I, Patient Global Impression-Improvement

For more information on efficacy outcomes, please visit our poster.

Developmental Age Equivalent Adapted Mullen Scores in Pediatric Patient 1 at Week 12



- Examples of Week 12 functional improvements reflected in these MSEL-A scores include:
  - VR: gained ability to identify an object from memory
  - RL: gained ability to follow two unrelated commands and identify the function of objects and action words
  - FM: gained ability to use refined thumb grasp
- Based on the MSEL-A Baseline assessment and caregiver history, the patient was not able to demonstrate the above gained functional improvements before treatment

Adapted Mullen Scales for Early Learning, MSEL-A; FM, fine motor; RL, receptive language; VR, visual reception

For more information on efficacy outcomes, please visit our poster.

Baseline assessment prior to treatment with TSHA-102

Pediatric Patient 1

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Week 4 and 8 assessment following treatment with TSHA-102

Pediatric Patient 1

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Week 12 assessment following treatment with TSHA-102

Pediatric Patient 1

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Baseline assessment prior to treatment with TSHA-102

Pediatric Patient 2

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Week 8 assessment following treatment with TSHA-102

Pediatric Patient 2

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Safety Overview Across Studies – Non-serious Adverse Events

Overall TEAEs and Causality of Events Related to TSHA-102

Event (MedDRA PT)	Total Events (Patients)	Relatedness Assessments*			
		TSHA-102	Pre-existing Disease	Immuno-suppression	Other Cause/ None
Any TEAE	34 (4)	10	6	13	9
Pyrexia	2 (2)	2	0	0	0
CSF protein increased	2 (2)	2	0	0	0
Lethargy	2 (2)	2	1	0	1
Vomiting	5 (2)	1	0	3	0
Irritability	4 (2)	1	1	2	0
Clonus	1	1	0	0	0
Seizures	1	1	1	0	0

*more than 1 causality may be noted per event relatedness assessment, additional events unrelated to TSHA-102 in poster

- TSHA-102 has been well tolerated with a total of 34 TEAEs as 05/10/2024. Of these, 33 were mild or moderate
- The most common AE overall was vomiting (5 TEAEs), a known risk of sirolimus
- Two serious adverse events have also been reported for PedP2 (one after 05/10/2024 cut off), both unrelated to TSHA-102
- Seizure frequency by patient is consistent or improved over Baseline via seizure diary data
- Clinicians have reported qualitative improvement (from non-triggered seizures events to only triggered events)

Listing 5.1 TSHA-102-CL-101 and TSHA-102-CL-102, 05/10/2024. An event may have more than 1 causality reported. Causality assessments updated per communication from investigator on 06/11/2024.

CSF, cerebrospinal fluid; TEAEs, treatment emergent adverse events

Encouraging Safety Profile and Clinical Improvements Observed in both REVEAL Studies Strongly Support the Potential of TSHA-102

Generally well-tolerated	No SAEs related to TSHA-102 or dose limiting toxicities observed
Improvements across key efficacy measures	Early improvements observed across key efficacy measures in all patients and sustained at longer-term assessments, including following completion of immunosuppressant taper in one patient
Improvements across multiple clinical domains	Clinical improvements observed across motor skills, communication/ socialization, autonomic function (i.e., improved sleep, breathing and GI function), and seizures

In this first–in-human clinical trial, improvements were observed across clinical domains and efficacy measures, regardless of type of *MECP2* mutation, Baseline severity, and clinical presentation

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GI, gastrointestinal; *MECP2, methyl-CpG-binding protein 2*; SAE, severe adverse event

Thank you

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