TSHA-102 in clinical evaluation for Rett syndrome: Cohort one data from the REVEAL Phase 1/2 Adolescent-Adult and Pediatric trials

June 18, 2024

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Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, prospects, plans and objectives of management, the potential of TSHA-102, the anticipated timelines for reporting data for the TSHA-102 REVEAL trials and the trial design of the TSHA-102 REVEAL trials are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2023, and our other filings with the SEC, which are available on the SEC’s website at www.sec.gov . We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

Key Takeaway: Encouraging safety profile and improvements across consistent clinical domains in all four patients treated with the low dose of TSHA-102 support the transformative potential of TSHA-102

Generally well-tolerated

No serious adverse events (SAEs) related to TSHA-102 or dose-limiting toxicities (DLTs) observed

Improvements across multiple efficacy measures

Early improvements demonstrated, and sustained through longer-term assessments

Improvements across multiple clinical domains

Motor skills

Communication/socialization

Autonomic function

Seizures

Improvements across consistent clinical domains in adult and pediatric patients with different genetic mutation severity support broad treatment potential of TSHA-102

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Adolescent/adult trial: based on week 52 safety and efficacy data for patient one, and week 36 safety data and week 25 efficacy data for patient two. Pediatric trial: based on week 22 safety data and week 12 efficacy data for patient one, and week 11 safety data and week 8 efficacy data for patient two.

Rett syndrome: a rare, progressive neurodevelopmental disease with high unmet medical need

- Caused by mutations in the X-linked gene encoding MeCP2[1]
- Primarily occurs in females
- Symptoms and severity vary due in part to random X-inactivation[2]
- Leads to impaired brain development and function

Significant market opportunity

- Estimated prevalence of typical Rett syndrome caused by a *MECP2* mutation is between **15,000 and 20,000** patients in major global markets (U.S., EU+U.K.)[3]
- Rett syndrome occurs worldwide in **1 of every 10,000** female births[3]

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Sources: [1]Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet. 1999;23(2):185-188. [2]Braunschweig D, Simcox T, Samaco RC, LaSalle JM. X-Chromosome inactivation ratios affect wild-type MeCP2 expression within mosaic Rett syndrome and Mecp2-/+ mouse brain. Hum Mol Genet. 2004;13(12):1275-1286. [3]IRSF; NORD; Amir RE, Van den Veyver IB, Wan M, et al. Rett Syndrome Is Caused by Mutations in X-Linked Mecp2, Encoding Methyl-Cpg-Binding Protein 2. Nat Genet 232:185-188. 1999.

TSHA-102: an investigational one-time gene therapy for Rett syndrome that is designed to regulate *MECP2* on a cell-by-cell basis

- TSHA-102 delivers a functional form of *MECP2* to cells in the central nervous system (CNS)
- Equipped with novel miRNA-responsive target sequence (miRARE) designed to mediate levels of *MECP2* in the CNS on a cell-by-cell basis to minimize risk of overexpression
  - Senses transgene and endogenous *MECP2* levels to provide a superior therapeutic profile to that of unregulated *MECP2* gene replacement[3]
- Delivered via intrathecal (IT) administration to target key CNS regions and minimize viral load using a routine, minimally invasive procedure in an outpatient setting

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]

MeP426 promoter allows targeted neuronal expression and capitalizes 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[2]

Sources: [1]Tillotson R et al. 2017 *Nature;* 550:398-401; 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. [2]McCarty DM. Self-complementary AAV vectors: Advances and applications. Mol Ther. 2008;16(10):1648-1656. [3]Haque E et al. The microRNA-responsive autoregulatory element from TSHA-102 for Rett Syndrome modulates therapeutic transgene expression in response to cellular MeCP2 in mouse and human cell lines. 30th Annual Congress of the European Society for Gene and Cell Therapy, 24–27 Oct 2023, Brussels, Belgium. Poster #P435.

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

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

Study Overview

Objectives

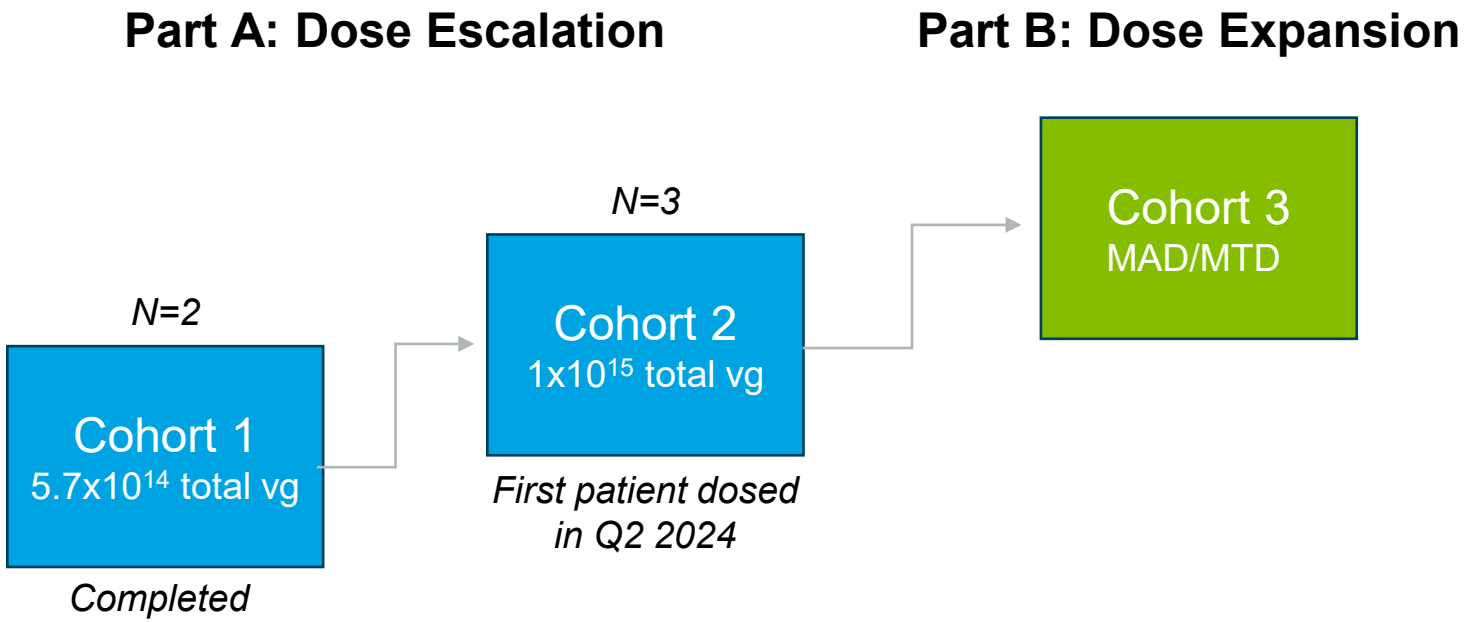
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels; if possible, establishes MAD or MTD
- **Part B**: evaluates the MAD or MTD

Key inclusion criteria

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

Key clinical assessments

- Revised Motor Behavior Assessment Scale (R-MBA)
- Clinical Global Impression Scale-Severity and Improvement (CGI-S and CGI-I)
- Parental Global Impressions Scale-Improvement (PGI-I)
- Rett Syndrome Behavior Questionnaire (RSBQ)
- Rett Syndrome Hand Function Scale (RSHFS)



Clinical trial: NCT05606614; MAD: maximum administered dose; MTD: maximum tolerated dose

Encouraging safety profile and improvements across consistent clinical domains observed through longer-term assessments in both adult patients in low dose cohort

Generally well-tolerated	No SAEs related to TSHA-102 or DLTs as of week 52 assessment (patient one) and week 36 assessment (patient two)
Improvements across multiple efficacy measures	Sustained and new improvements at week 52 (patient one) and at week 25 (patient two) following completion of steroid taper
Improvements across multiple clinical domains	Principal Investigator reported sustained and new improvements across multiple domains including motor skills, communication/socialization, autonomic function and seizures at week 52 (patient one) and at week 25 (patient two) following completion of steroid taper

Continued improvements observed in both adult patients with different genetic mutation severity and phenotypic expression support the durable response of TSHA-102

Both adult patients dosed in low dose cohort had stage four Rett syndrome with different genetic mutation severity and phenotypic expression

Baseline Characteristics

Adult Patient One	Adult Patient Two
Diagnosed with stage four "late motor deterioration muscle wasting" Rett syndrome	
20 year-old female	21 year-old female
Large *MECP2* deletion	Missense *MECP2* mutation
Severe phenotype	**Milder** phenotype
"Severely ill" – CGI-S baseline score of 6	"Moderately ill" – CGI-S baseline score of 4
Motor Skills: Complete loss of ambulation and ability to sit unassisted; wheelchair-bound by age 8 Loss of hand function by age 6 **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)

Source: Company data | baseline characteristics based on pre-treatment observations, baseline assessments, pre-screening visits and patient's medical history.

Sustained and new improvements seen across multiple clinical domains in both adult patients based on clinical observations reported by Principal Investigator

Clinical Domain Improvements	Adult Patient One 52 weeks post-treatment *Completed steroid taper week 36 and sirolimus taper week 43*	Adult Patient Two 25 weeks post-treatment *Completed steroid taper week 25 and sirolimus taper week 31*
Motor skills	○ Improved hand function and 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-gaze driven communication device	○ Improved social interest, including increased response to spoken words and eye contact
Autonomic function	○ Improved breathing patterns and circulation, and normalized sleep quality/duration with gained ability to sleep through night for the first time in 20 years	○ Improved breathing patterns and circulation
Seizures	○ Stable seizure events with lower levels of anti-seizure medication relative to baseline	○ Significantly reduced seizure events with 25% lower levels of anti-seizure medication relative to baseline ○ Seizure free for 8.5 months post-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.
*Seizure data for adult patient two is based on Seizure Diary and caregiver reports as of week 36 post-TSHA-102

Sustained and new improvements seen across multiple clinical domains in both adult patients based on clinical observations from Principal Investigator

Adult Patient One

20-year-old female (large MECP2 deletion; severe phenotype)

Patient history

- **Age 3:** Apnea and hyperventilation
- **Age 5:** Seizures
- **Age 6:** Mostly non-verbal
- **Age 6:** Loss of hand function
- **Age 8:** Complete loss of ambulation and ability to sit unassisted
- **Age 20**

52 weeks post-TSHA-102

- **AUTONOMIC FUNCTION:** Improved breathing patterns and circulation, and normalized sleep quality/duration with gained ability to sleep through night for the first time in 20 years
- **SEIZURES:** Stable seizure events with lower levels of anti-seizure medication relative to baseline
- **COMMUNICATION/SOCIALIZATION:** Improved social interest, vocalization, and use of eye-driven communication device
- **MOTOR FUNCTION:** Improved hand function; gained ability to sit unassisted and move legs for the first time in over a decade

Adult Patient Two

21-year-old female (missense MECP2 mutation; milder phenotype)

Patient history

- **Age 2:** Partial loss of ambulation, mostly non-verbal
- **Age 3:** Hand stereotypies with weak grasp
- **Age 3:** Frequent hyperventilation
- **Age 10:** Seizures
- **Age 18:** Bradykinesia, walks with impaired gait and balance
- **Age 21**

25 weeks post-TSHA-102

- **MOTOR FUNCTION:** Improved hand stereotypies for the first time since regression at age three and improved posture and stability
- **COMMUNICATION/SOCIALIZATION:** Improved social interest
- **AUTONOMIC FUNCTION:** Improved breathing patterns and circulation
- **SEIZURES:** Significantly reduced seizure events with 25% lower levels of anti-seizure medication relative to baseline; seizure free for 8.5 months*

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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.
*Seizure data for adult patient two is based on Seizure Diary and caregiver reports as of week 36 post-TSHA-102

Clinical improvements demonstrated across multiple efficacy measures in both adult patients treated with TSHA-102 (low dose, $5.7x10^{14}$ total vg)

	CGI-S		CGI-I, with Rett anchors		PGI-I		RSBQ		R-MBA		RSHFS	
Scale Description	Clinician-reported 7-point assessment of illness severity 1=*normal* 7=*among the most extremely ill*		Clinician-reported 7-point assessment of overall improvement 1=*very much improved* 7=*very much worse*		Caregiver-reported 7-point assessment of overall improvement 1=*considerably better* 7=*very much worse*		Caregiver-reported 45-item questionnaire to assess Rett syndrome characteristics *Higher scores indicate greater severity*		Clinician-reported 24-question scale measuring disease behaviors of Rett syndrome *Higher scores indicate greater severity*		Clinician-reported assessment of hand function in Rett syndrome by an independent experienced physical therapist, being reported as best score for large objects 1=*no active grasping* 4=*independent grasp*	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**
Screening, Baseline	6 Severely ill	4 Moderately ill	-	-	-	-	52	37	43	38	DH: 3 NH: NA*	DH: NE* NH: 1
Week 4	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better	29	33	48	31		DH: NE* NH: 1
Week 8	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	3 A little better	3 A little better	27	33	51	24	DH: 2 NH: 1	DH: 4 NH: 1
Week 12	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	2 Much better*	3 A little better	30	35	37	21	DH: 3 NH: 3*	DH: NE* NH: 1
Week 25	5 Markedly ill	4 Moderately ill	2 Much improved	3 Minimally improved	2 Much better	3 A little better	22	39	42	15	DH: 3 NH: 2	DH: 4 NH: 1
Week 52	5 Markedly ill		3 Minimally improved		1 Considerably better		17		26			
Overall Change	+	=	+	+	+	+	+	–	+	+	+	=

DH = dominant hand; NH = non-dominant hand; = not assessed; NE = not evaluable = improvement from baseline = no change from baseline = decline from baseline

**PGI-I week 12 assessment for patient one was captured at week 16; RSHFS week 12 assessment for patient one was captured on week 11; RSHFS assessment for patient one was not conducted at baseline; RSHFS assessment for patient two's DH was not conducted as defined in the guidelines at baseline, week 4 and week 12, therefore the data is not evaluable at these time points.*

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Data presented reflects current data in the Electronic Data Capture System, subject to change

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

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

Study Overview

Objectives

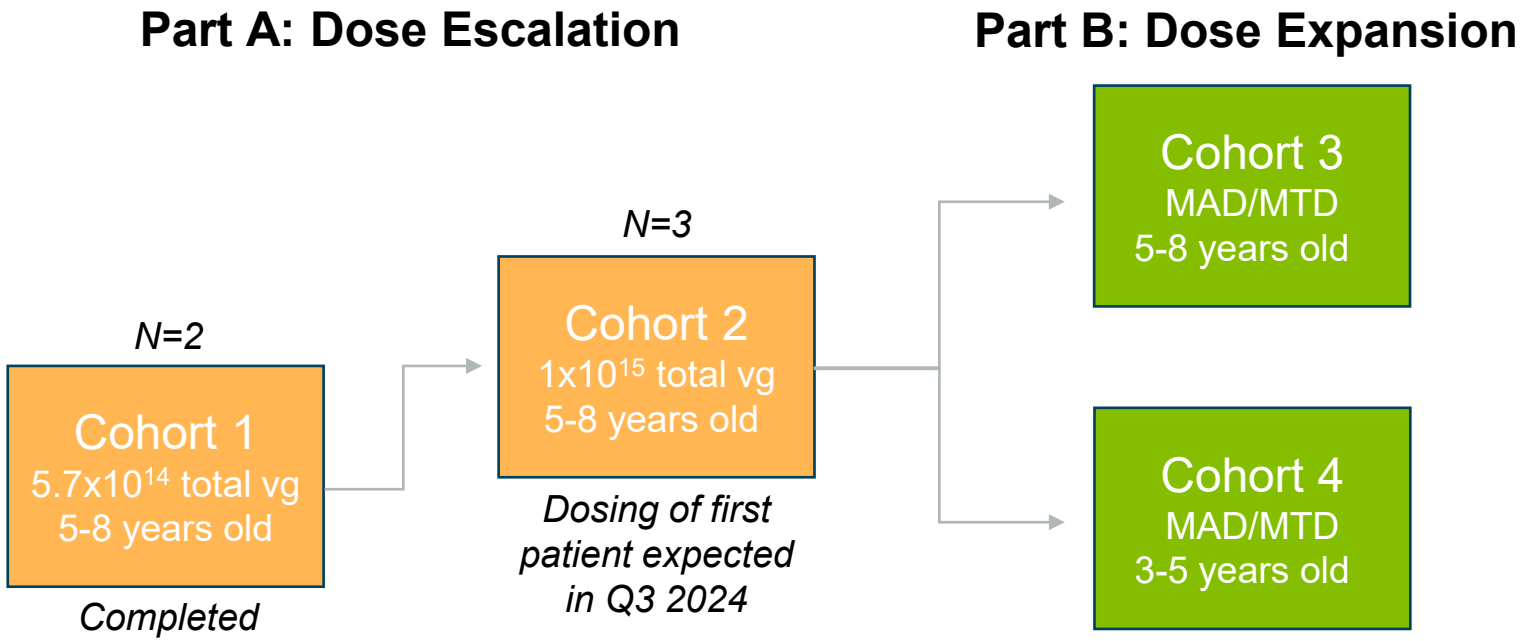
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels; if possible, establishes the MAD or MTD
- **Part B**: evaluates the MAD or MTD in two age cohorts

Key inclusion criteria

- Females 5-8 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
- Adapted Mullen Scales for Early Learning (MSEL-A)



Clinical trial: NCT06152237

Encouraging safety profiles and initial clinical improvements observed across multiple domains in first two pediatric patients dosed in low dose cohort

Generally well-tolerated	No SAEs related to TSHA-102 or DLTs as of week 22 assessment (patient one) and week 11 assessment (patient two)*
Improvements across multiple efficacy measures	Early improvement demonstrated across multiple efficacy measures at week 12 (patient one) and at week 8 (patient two)
Improvements across multiple clinical domains	Principal Investigator reported improvements across multiple domains including motor skills, communication/socialization, autonomic function and seizures at week 12 (patient one) and at week 8 (patient two)

Early improvements observed in similar areas of disease with early evidence of developmental gains in pediatric patients with different genetic mutation severity and phenotypic expression

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*There were two SAEs reported in the second pediatric patient that were not deemed treatment-related – both were related to underlying disease, and one was also attributed to immunosuppression, and have both resolved.

First two pediatric patients with stage three Rett syndrome in low dose cohort had different genetic mutation severity and phenotypic expression

Baseline Characteristics

Pediatric Patient One	Pediatric Patient Two
Diagnosed with stage three "pseudo stationary" Rett syndrome	
6 year-old female	7 year-old female
MECP2 deletion	Missense *MECP2* mutation
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 by age 1.5 **Communication/Socialization:** Mostly non-verbal by age 1 **Autonomic Function:** Breath holding **Seizures:** Seizures by age 3 (1 seizure every 3 months at baseline)	**Motor Skills:** Partial loss of ambulation by age 1.5 Impaired hand function by age 1 **Communication/Socialization:** Non-verbal by age 1 **Autonomic Function:** Frequent hyperventilation by age 4 **Seizures:** Seizures by age 3 (2-4 seizures daily at baseline)

Source: Company data | baseline characteristics based on pre-treatment observations, baseline assessments, pre-screening visits and patient's medical history.

Improvements seen across multiple clinical domains in both pediatric patients based on clinical observations reported by Principal Investigator

Clinical Domain Improvements	Pediatric Patient One 12 weeks post-treatment	Pediatric Patient Two 8 weeks post-treatment
Motor skills	○ Improved hand function and grasping with ability to hold object up to 3 minutes vs 12 seconds at baseline ○ Improved truncal stability and balance with gained ability to move her leg on her own to better take a step with assistance and sit unassisted for longer duration ○ Improved swallowing and oral intake relative to gastrostomy tube feeding	○ Improved hand function with ability to reach more quickly ○ Improved gait, speed and stability when walking with new skills gained including the gained ability to stand up from a chair and walk up a stair
Communication / Socialization	○ Improved use of eye-gaze driven communication device with new words communicated and gained ability to string multiple words together and identify object functions through device ○ New skills gained in visual reception and receptive language	○ Improved social interest and eye contact
Autonomic function	○ Improved breathing patterns	○ Improved breathing patterns
Seizures	○ Stable seizure events relative to baseline	○ Increase in days reported seizure-free since dosing; a new anti-seizure medication was added to regimen week 4, which has been maintained through week 11

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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.

Early evidence of developmental gains in both pediatric patients based on clinical data and observations from Principal Investigator

Pediatric Patient One

6-year-old female (MECP2 deletion; moderate phenotype)

Patient history

- **Age 1.5** — Impaired hand function
- **Age 1** — Mostly non-verbal
- **Age 3** — Non-ambulatory: Sits unassisted for 30 seconds/stands with support
- **Age 3** — Seizures
- **Age 6**

12 weeks post-TSHA-102

- **MOTOR SKILLS:** Improved hand function/grasping with ability to hold object up to 3 minutes; improved truncal stability and balance with gained ability to move leg to take step on own without assistance and sit unassisted for longer duration
- **COMMUNICATION/SOCIALIZATION:** Improved communication and use of eye-gaze driven communication device; gained new visual reception and receptive language skills
- **SEIZURES:** Stable seizure events relative to baseline
- **AUTONOMIC FUNCTION:** Improved breathing patterns

Pediatric Patient Two

7-year-old female (missense MECP2 mutation; milder phenotype)

Patient history

- **Age 1** — Impaired hand function
- **Age 1** — Mostly non-verbal
- **Age 1.5** — Partial loss of ambulation
- **Age 3** — Seizures
- **Age 4** — Hyperventilation
- **Age 7**

8 weeks post-TSHA-102

- **MOTOR SKILLS:** Improved hand function with ability to reach more quickly; improved gait, speed and stability when walking with new skills gained including the ability to stand up from a chair and walk up a stair
- **COMMUNICATION/SOCIALIZATION:** Improved social interest and eye contact
- **AUTONOMIC FUNCTION:** Improved breathing patterns
- **SEIZURES:** Significantly reduced seizure frequency relative to baseline, with most days reported seizure-free*

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.
*A new anti-seizure medication was added to patient two's regimen week 4, which has been maintained through week 11

Clinical improvements demonstrated across multiple efficacy measures in both pediatric patients treated with TSHA-102 (low dose, $5.7x10^{14}$ total vg)

	CGI-S		CGI-I, with Rett anchors		PGI-I		RSBQ		R-MBA		MSEL-A	
Scale Description	Clinician-reported 7-point assessment of illness severity 1=*normal* 7=*among the most extremely ill*		Clinician-reported 7-point assessment of overall improvement 1=*very much improved* 7=*very much worse*		Caregiver-reported 7-point assessment of overall improvement 1=*very much improved* 7=*very much worse*		Caregiver-reported 45-item questionnaire to assess Rett syndrome characteristics *Higher scores indicate greater severity*		Clinician-reported 24-question scale measuring disease behaviors of Rett syndrome *Higher scores indicate greater severity*		Clinician-reported 4 subscale scores to assess cognitive function for visual reception (VR), receptive language (RL), expressive language (EL) and fine motor (FM) *Higher score indicates improvement*	
	P1	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**	**P1**	**P2**
Screening, Baseline	5 Markedly ill	4 Moderately ill	–	–	–	–	37		40	41	VR: 22 RL: 21 EL: 8 FM: 5	VR: 33 RL: 15 EL: 8 FM: 9
Week 4	5 Markedly ill	4 Moderately ill	3 Minimally improved	3 Minimally improved	3 A little better	3 A little better	41	50	35			
Week 8	5 Markedly ill	4 Moderately ill	3 Minimally improved	2 Much improved	3 A little better*	2 Much better	36*	37*	30	30		
Week 12	5 Markedly ill		3 Minimally improved		3 A little better		44		36		VR: 23 RL: 27 EL: 8 FM: 9	
Overall Change	=	=	+	+	+	+	–	+	+	+	+	

= *not assessed* = *improvement from baseline* = *no change from baseline* = *decline from baseline*

**Patient one's RSBQ and R-MBA week 8 assessment was collected week 11; patient two's RSBQ improvement at week 8 is compared to week 4 score as baseline RSBQ was not captured*

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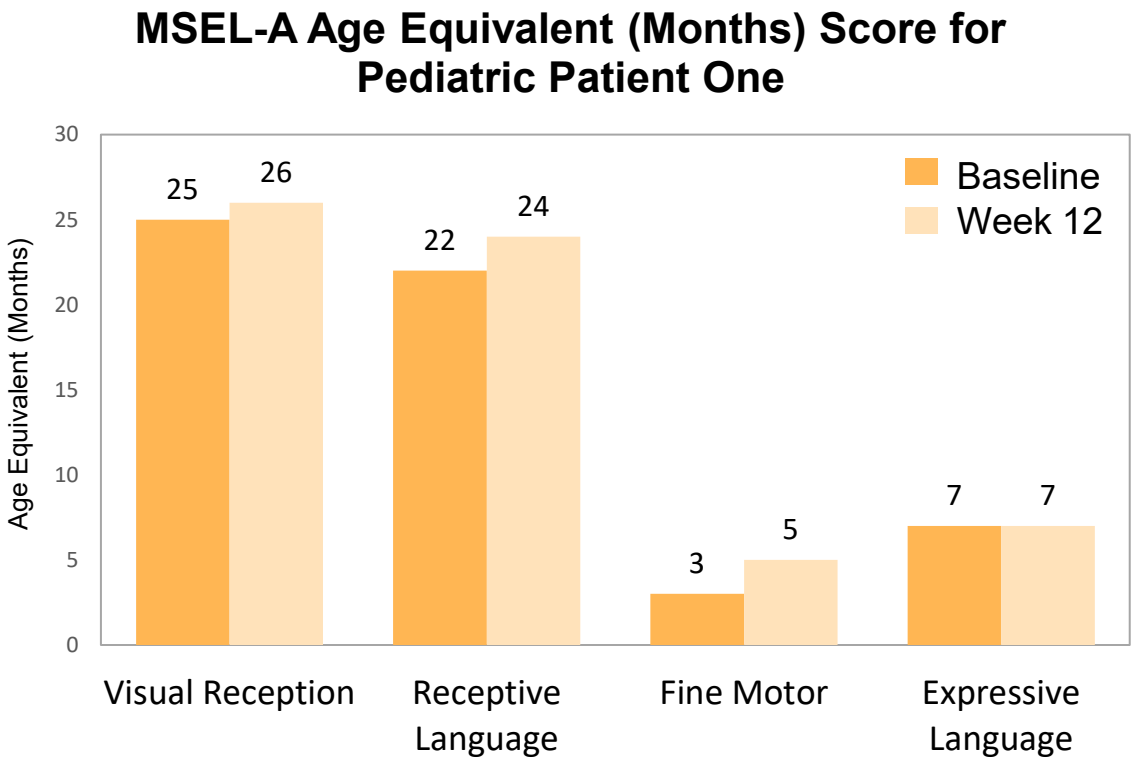
Data presented reflects current data in the Electronic Data Capture System, subject to change

MSEL-A: Pediatric patient one showed new developmental gains in visual reception, receptive language and fine motor skills at week 12



Improvement in age equivalence of skills demonstrated in visual reception (VR), fine motor (FM) and receptive language (RL) at week 12 post-TSHA-102

Adapted Mullen Scales of Early Learning (MSEL-A):

- Standardized cognitive developmental assessment adapted for patients with Rett syndrome that functionally evaluates skills compared to developmental milestones

New developmental gains demonstrated at week 12 post-TSHA-102:

- **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 a refined thumb grasp

Per medical history and as reported by caregiver, the patient was not able to demonstrate these skills before treatment.

Clarkson T, LeBlanc J, DeGregorio G, Vogel-Farley V, Barnes K, Kaufmann WE, Nelson CA. Adapting the Mullen Scales of Early Learning for a Standardized Measure of Development in Children With Rett Syndrome. Intellect Dev Disabil. 2017 Dec;55(6):419-431. doi: 10.1352/1934-9556-55.6.419. PMID: 29194024.

Improvements across consistent clinical domains in all patients treated with low-dose TSHA-102 based on clinician and caregiver assessments and video evidence

Adult Patient One (week 52)
Severe phenotype

- Gained **motor skills** with ability to sit unassisted and move legs for first time in over a decade
- Improved **communication** with gained ability to use eye-gaze driven communication device
- Improved **autonomic function** including normalized sleep behaviors for first time in 20 years
- **Stabilized seizures** at lower level of anti-seizure medication

Adult Patient Two (week 25)
Milder phenotype

- Improved **motor skills,** with reduced hand stereotypies for first time since regression at age 3 and improved posture and stability
- Improved **social interest** with increased response to words and eye contact
- Improved **autonomic function** including breathing patterns
- **Seizure-free for 8.5 months** at 25% lower levels of anti-seizure medication relative to baseline (2-4 per week)

Pediatric Patient One (week 12)
Moderate phenotype

- Improved **motor skills** including hand function and grasping with ability to hold object up to 3 minutes vs. 12 seconds pre-treatment
- Improved **communication** and use of eye-driven communication device with new words communicated using device
- Improved swallowing and oral intake relative to gastrostomy tube feeding
- **Stabilized seizures**

Pediatric Patient Two (week 8)
Milder phenotype

- Gained new **motor skills** of standing up from a chair walking up a stair
- Improved **social interest** and eye contact
- Improved **autonomic function** including breathing patterns
- Increase in **seizure-free** days since dosing (a new anti-seizure medication was added to patient two's regimen at week 4)

Progress in clinical-stage TSHA-102 program supports clinical evaluation across a broad range of ages and stages of Rett syndrome

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

- ✓ Completed dosing of Cohort 1 (low dose, n=2); encouraging longer-term safety and efficacy data*
- ✓ Expanded trial to include patients ≥12 years of age
- ✓ Dosed first patient in cohort two (high dose) following IDMC approval of Company's request to dose escalate early
- ✓ RMAT, ODD, RPDD and FTD from U.S. FDA

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

- ✓ Completed dosing of Cohort 1 (low dose, n=2); encouraging initial safety and efficacy data*
- ✓ IDMC approved Company's request to dose escalate early with dosing of first pediatric patient in cohort two (high dose) to follow IDMC review of initial safety data from first high dose patient in adolescent/adult trial
- ✓ RMAT, ODD, RPDD and FTD from U.S. FDA, ODD from E.U. EMA and ILAP designation from U.K. MHRA

2024: expect significant clinical data in adult, adolescent and pediatric patients at low and high dose across multiple geographies

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*Adolescent/adult trial: based on week 52 safety and efficacy data for patient one, and week 36 safety data and week 25 efficacy data for patient two. Pediatric trial: based on week 22 safety data and week 12 efficacy data for patient one, and week 11 safety data and week 8 efficacy data for patient two.
IDMC=Independent Data Monitoring Committee; RMAT=regenerative medicine advanced therapy designation; ODD=Orphan Drug designation; RPDD=Rare Pediatric Disease designation; FTD=Fast Track designation; FDA=Food and Drug Administration; E.U.=European Union; EMA=European Medicines Agency; ILAP=Innovative Licensing and Access Pathway designation; U.K.=United Kingdom; MHRA=Medicines and Healthcare products Regulatory Agency

Anticipated TSHA-102 2024 program milestones

Third quarter of 2024	Dose first patient in cohort two (high dose, n=3) of $1x10^{15}$ total vg in REVEAL Phase 1/2 pediatric trial
Second half of 2024	Report initial safety and efficacy data from cohort two (high dose) of $1x10^{15}$ in both REVEAL trials

Q&A

Thank You

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Taysha GENE THERAPIES

Appendix

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Safety summary and relatedness assessments

In these clinical trials, TSHA-102 has been well-tolerated, with a total of 34** treatment-emergent adverse events (TEAEs). Of these, 33 were mild or moderate.

- One serious adverse event (SAE), seizure (severe, grade 3), has been reported, unrelated to TSHA-102. This patient has a medical history of seizures requiring hospitalization for anti-epileptic loading, as occurred during this event; with multiple confounders (e.g., anesthesia, urinary tract infection (UTI), sleep deprivation). Overall, she has experienced an increase in seizure-free days since dosing.
- One SAE (constipation, moderate, grade 2) unrelated to TSHA-102 was reported after TEAE listing cut off. Patient was admitted for irritability and had a medical history of constipation and concurrent non-serious event of parainfluenza virus, which may have been contributory.
- The most common AE overall was vomiting (5 TEAEs), a known risk of sirolimus.

Laboratory Measures

Liver Function. Patients have experienced no clinically significant liver or cardiac abnormalities. Laboratory evaluations have shown some excursions, particularly in patients with high liver enzyme values (GGT/ALT/AST and AP) at Baseline. Two patients had abnormal liver enzymes at Baseline, consistent with concomitant medication. One patient showed mild (<1.5 x ULN) transient and self-limited ALT and AST elevations, that were not assessed at TEAEs.

Neurofilament light chain (NfL) levels. All four patients have experienced transient NfL increase, consistent with the NfL increase after LP alone, as reported in nonhuman primates in the absence of gene therapy and in a small human study.[5-7]

- NfL increases through Week 4, declining after week 12.
- MRI Brain and Spine: No findings of inflammation or damage.
- SNAPs: No clinically significant changes from Baseline
- No observed functional changes or clinical correlation with TEAEs.

Table 2: TEAEs causality and events related to TSHA-102

		Relatedness Assessments*			
Event (MedDRA PT)	Total Events (Patients)	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

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. The following TEAEs unrelated to TSHA-102, were also reported: Myopathy, Agitation, Aphthous Ulcer, Blister, chronic kidney disease, Cystatin C increased, Dermatitis acneiform, Epilepsy, Escherichia UTI, Gastroenteritis, Infection, Papular rash, Seizure, Skin ulcer, Stress fracture, Ureteric dilatation