UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 18, 2024

Taysha Gene Therapies, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-39536**	**84-3199512**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

3000 Pegasus Park Drive, Suite 1430 **Dallas, Texas**	**75247**
(Address of Principal Executive Offices)	**(Zip Code)**

(214) 612-0000
(Registrant's telephone number, including area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.00001 par value	TSHA	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On June 18, 2024, Taysha Gene Therapies, Inc. (the "***Company***") issued a press release entitled "Taysha Gene Therapies Announces Positive Clinical Data Across Adult and Pediatric Patients from Low Dose Cohort in Ongoing REVEAL Phase 1/2 Trials Evaluating TSHA-102 in Rett Syndrome". The press release provides certain updates on positive longer-term clinical data from the Company's ongoing REVEAL Phase 1/2 adolescent and adult trial and initial clinical data from the REVEAL Phase 1/2 pediatric trial evaluating TSHA-102 in Rett Syndrome. The full text of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K and incorporated herein by reference.

On June 18, 2024, the Company also made available a presentation to be used to discuss the clinical data from the REVEAL Phase 1/2 adolescent and adult trial and REVEAL Phase 1/2 pediatric trial. A copy of the presentation will be available by 8:00 a.m. ET on the Events & Presentations page of the Investors section of the Company's website, and a copy is attached as Exhibit 99.2 to this Current Report on Form 8-K. The information contained in, or that can be accessed through, the Company's website is not a part of this filing.

The information in this Item 7.01 of this Current Report on Form 8-K (including Exhibit 99.1 and Exhibit 99.2) is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "***Exchange Act***"), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated June 18, 2024.
99.2	Corporate presentation, dated June 18, 2024.
104	Cover Page Interactive Data File (the cover page XBRL tags are embedded within the inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Taysha Gene Therapies, Inc.

By: /s/ Kamran Alam
Kamran Alam
Chief Financial Officer

Date: June 18, 2024

Exhibit 99.1

Taysha Gene Therapies Announces Positive Clinical Data Across Adult and Pediatric Patients from Low Dose Cohort in Ongoing REVEAL Phase 1/2 Trials Evaluating TSHA-102 in Rett Syndrome

Durable improvements across consistent clinical domains in both adult and pediatric patients, including motor skills, communication/socialization, autonomic function, seizures, and an encouraging safety profile seen across adult (up to 52 weeks) and pediatric (up to 22 weeks) patients with different genetic mutation severity

Longer-term data from both adult patients showed sustained and new improvements across multiple efficacy measures and clinical domains following the completion of steroid taper (patient one: sat unassisted for first time in over a decade, normalized sleep, stabilized seizures; patient two: improved hand stereotypies and breathing, seizure-free for 8.5 months at 25% lower anti-seizure medication)

Initial data from first two pediatric patients showed improvements across multiple efficacy measures and clinical domains, with early evidence of developmental gains (patient one: improved hand function, grasp and gross motor coordination, gained visual reception and receptive language skills; patient two: gained ability to stand up from chair and walk up a stair, increase in seizure-free days)

IDMC approved Company's request for early advancement to cohort two (high dose) in the REVEAL pediatric trial; dosing expected in Q3 2024 following IDMC review of initial safety data from the first high dose patient in the adolescent and adult trial

Company will host webcast today at 8:00 AM Eastern Time

DALLAS – June 18, 2024 – Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a clinical-stage biotechnology company focused on advancing adeno-associated virus (AAV)-based gene therapies for severe monogenic diseases of the central nervous system (CNS), today announced positive longer-term clinical data from the ongoing REVEAL Phase 1/2 adolescent and adult trial and initial clinical data from the REVEAL Phase 1/2 pediatric trial evaluating TSHA-102 in Rett syndrome.

"We are highly encouraged by the safety profile and broad clinical response observed across multiple domains in both the adult and pediatric patients with different genetic mutation severity treated with the low dose of TSHA-102," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "The longer-term follow up data indicate a durable response with sustained and new improvements across multiple clinical domains in both adult patients, and importantly, both pediatric patients showed initial improvements across consistent clinical domains, with early evidence of developmental gains following treatment with TSHA-102. We believe these improvements in adult and pediatric patients further reinforce the potential of TSHA-102 to be transformative for a broad range of patients with Rett syndrome."

Elsa Rossignol, M.D., FRCP, FAAP, Associate Professor in Neuroscience and Pediatrics at the Université de Montréal and Principal Investigator of the REVEAL adolescent and adult trial at the CHU Sainte-Justine added, "TSHA-102 was well-tolerated in both adult patients treated, with no serious adverse events or dose-limiting toxicities as of week 52 and week 36 post-treatment for the first and second patient, respectively. It's encouraging that we continue to see improvements across multiple clinical domains in the longer-term assessments with no diminution of effect. The first adult patient sustained improvements at week 52 post-treatment after the completion of her steroid and sirolimus taper, including regaining movement in her legs, the gained ability to sit unassisted for the first time in over a

decade and gained function in her non-dominant hand. She continues to show vastly increased interest in social communication and activities, as well as improvements in breathing dysrhythmia and normalized sleep behaviors for the first time in 20 years. The second adult patient showed sustained improvements following the completion of her steroid taper at week 25 post-treatment, including reduced hand stereotypies for the first time since regression at age three, sustained improvements in breathing dysrhythmia and a significant reduction in seizures, as she has been seizure-free for 8.5 months relative to experiencing 2-4 seizures per week pre-treatment. Additionally, the patient showed improvement in posture and stability at week 25 post-treatment. We believe these longer-term clinical data support the durability and broad clinical benefits of TSHA-102 in adult patients with the most advanced stage of Rett syndrome."

REVEAL Phase 1/2 Adolescent and Adult Trial (Canada and U.S.): a first-in-human, open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in adolescent and adult females aged 12 years and older with Rett syndrome due to *MECP2* loss-of-function mutation. TSHA-102 is administered as a single lumbar intrathecal injection. Dose escalation will evaluate two dose levels of TSHA-102 sequentially. The maximum tolerated dose (MTD) or maximum administered dose (MAD) established in Part A will then be administered during dose expansion in Part B of the study.

- Completed dosing in cohort one (low dose, n=2) of $5.7x10^{14}$ total vg
- Dosed first patient in cohort two (high dose, n=3) of $1x10^{15}$ total vg in the second quarter of 2024
- Initial available safety and efficacy data from cohort two expected in the second half of 2024

Longer-term data from the first adult patient (20 years old; large *MECP2* deletion; associated with severe phenotype) and second adult patient (21 years old; missense *MECP2* mutation; associated with milder phenotype) with late motor deterioration, stage four Rett syndrome dosed with TSHA-102 in the low dose cohort:

- Generally well-tolerated with no serious adverse events (SAEs) related to TSHA-102 or dose-limiting toxicities (DLTs) as of 52-week assessment post-treatment for patient one and 36-week assessment post-treatment for patient two
- Sustained and new improvements observed across multiple clinical domains relative to baseline, as of 52-weeks post-treatment for patient one, based on clinical observations reported by the Principal Investigator (PI), including:
  - **Motor skills**: improved hand function and gained ability to sit unassisted for first time in over a decade and move legs (patient one), and improved hand stereotypies for the first time since regression at age three and improved posture and stability (patient two)
  - **Communication/Socialization**: improved social interest, vocalization and ability to use eye-gaze driven communication device (patient one), and improved social interest with increased response to spoken words and eye contact (patient two)
  - **Autonomic function**: improved breathing patterns, normalized sleep quality/duration for first time in 20 years and improved circulation (patient one), and improved breathing patterns and circulation (patient two)
  - **Seizures**: stable seizure events (patient one), and significantly reduced seizure events (patient two)

- Seizure Diary and caregiver reports:
  - **Patient one at week 52 post-treatment**: stable seizure events at lower levels of anti-seizure medication relative to baseline
  - **Patient two at week 36 post-treatment**: significantly reduced seizure events at 25% lower levels of anti-seizure medication relative to baseline (2-4 seizures per week), with 8.5 months reported seizure-free
- Clinical improvements seen across multiple efficacy measurements relative to baseline include:
  - **Patient one at week 52 post-treatment**: Sustained improvement in Clinical Global Impression–Improvement (CGI-I), Clinical Global Impression–Severity (CGI-S) and Seizure Diaries, with new improvement in Revised Motor Behavior Assessment (R-MBA), Parental Global Impressions–Improvement (PGI-I) and Rett Syndrome Behavior Questionnaire (RSBQ) following completion of steroid and sirolimus taper
  - **Patient two at week 25 post-treatment**: Sustained improvement in CGI-I and PGI-I, with new improvement in R-MBA and Seizure Diaries following completion of steroid taper

Colleen Buhrfiend, M.D., Assistant Professor of Pediatrics at RUSH University Medical Center said, "Following treatment with TSHA-102, both pediatric patients with different genotypes and disease severity had challenging side effects related to immunosuppressant treatment but showed a well-tolerated safety profile with no SAEs or DLTs related to TSHA-102 as of week 22 and week 11 post-treatment for the first and second pediatric patient, respectively, as well as some initial improvements across multiple clinical domains and early evidence of new developmental gains. Specifically, at week 12 post-treatment, the first patient's truncal stability and balance improved, which enabled her to sit unassisted for a longer duration and move her leg on her own to better take a step with assistance. Her hand function improved, and she was able to hold an object for three minutes following treatment compared to up to 12 seconds pre-treatment. Additionally, she communicated new words using an eye-gaze driven communication device and gained the ability to identify object functions for the first time. At week eight post-treatment, the second pediatric patient's gait, speed and stability improved, resulting in the ability to walk longer distances. Her hand function showed initial improvement, and she gained some new skills that were previously lost, including the ability to stand up from a chair and walk up a stair. The initial improvements observed across multiple areas of disease in both pediatric patients are encouraging early signs of possible benefit."

REVEAL Phase 1/2 Pediatric Trial (U.S. and U.K.): an open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in pediatric females with Rett syndrome due to *MECP2* loss-of-function mutation. TSHA-102 is administered as a single lumbar intrathecal injection. Part A of the study will focus on determining MAD and MTD in patients aged 5 to 8 years old. Part B is the dose expansion phase and will evaluate TSHA-102 at the MAD or MTD in two age cohorts (5 to 8 years and 3 to 5 years).

- Completed dosing in cohort one (low dose, n=2) of $5.7x10^{14}$ total vg
- Received IDMC approval of Company's request to advance early to cohort two (high dose, n=3) evaluating $1x10^{15}$ total vg, with dosing to occur following IDMC review of the 42-day safety data from the first high dose patient in the adolescent and adult trial
- Dosing of first pediatric patient in cohort two expected in the third quarter of 2024
- Initial available safety and efficacy data from cohort two expected in the second half of 2024

Initial results from the first pediatric patient (6 years old; *MECP2* deletion; associated with moderate phenotype) and second pediatric patient (7 years old; missense *MECP2* mutation; associated with milder phenotype) with pseudo stationary symptoms, stage three Rett syndrome dosed with TSHA-102 in the low dose cohort:

- Generally well-tolerated with no SAEs related to TSHA-102 or DLTs as of 22-week assessment post-treatment for patient one and 11-week assessment post-treatment for patient two; 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 resolved
    - Significant challenges with AEs dues to immunosuppressive regimen
- Initial improvements observed across multiple clinical domains relative to baseline as of 12-weeks post-treatment for patient one and 8-weeks post-treatment for patient two, based on clinical observations reported by the PI:
    - **Motor skills**: improved hand function with the ability to hold an object for three minutes vs up to 12 seconds at baseline, improved truncal stability and balance with the gained ability to move her leg on her own to better take a step with assistance and sit unassisted for a longer duration, and improved swallowing and oral intake relative to gastrostomy tube feeding (patient one), and improved hand function and gait, speed and stability when walking with some new skills gained, including standing up from a chair and walking up a stair (patient two)
    - **Communication/Socialization**: improved communication and ability to use eye-gaze driven communication device and gained visual reception and receptive language skills (patient one), and improved social interest and eye contact (patient two)
    - **Autonomic function**: reduced breath holding (patient one), and improved breathing patterns (patient two)
    - **Seizures**: stable seizure events (patient one), and increase in days reported seizure-free since dosing (patient two)
- Seizure Diary and caregiver reports:
    - **Patient one at 22-weeks post-treatment**: stable seizure events relative to baseline
    - **Patient two at 11-weeks post-treatment**: increase in days reported seizure-free since dosing relative to baseline (2-4 seizures daily), although a new anti-seizure medication was added to patient two's regimen at week four, which she has maintained through week 11 post-treatment
- Clinical improvements seen across multiple efficacy measurements relative to baseline include:
    - **Patient one at 12-weeks post-treatment**: CGI-I, PGI-I, R-MBA, Adapted Mullen Scales of Early Learning (MSEL-A) and Seizure Diaries
    - **Patient two at 8-weeks post-treatment**: CGI-I, PGI-I, RSBQ, R-MBA and Seizure Diaries

Presentation with additional details and accompanying figures are available through Taysha's website here.

Conference Call and Webcast Information

Taysha management will hold a conference call and webcast today at 8:00 a.m. ET to discuss these clinical data for TSHA-102 in Rett syndrome. Participants can register for the live webcast here. The live webcast and replay will be available through Taysha's website here.

2024 IRSF Rett Syndrome Scientific Meeting Presentation Details

These data will also be presented by Elsa Rossignol, M.D., FRCP, FAAP, Principal Investigator of the REVEAL adolescent and adult trial at CHU Sainte-Justine and Colleen Buhrfiend, M.D., of RUSH University Medical Center at the 2024 International Rett Syndrome Foundation (IRSF) Rett Syndrome Scientific Meeting during a poster presentation on Tuesday, June 18 at 5:15 p.m. MT and during an oral presentation on Wednesday, June 19 at 11:00 a.m. MT.

About TSHA-102

TSHA-102 is a self-complementary intrathecally delivered AAV9 investigational gene transfer therapy in clinical evaluation for Rett syndrome. Designed as a one-time lumbar intrathecal treatment, TSHA-102 aims to address the genetic root cause of the disease by delivering a functional form of *MECP2* to cells in the CNS. TSHA-102 utilizes a novel miRNA-Responsive Auto-Regulatory Element (miRARE) technology designed to mediate levels of *MECP2* in the CNS on a cell-by-cell basis without risk of overexpression. TSHA-102 has received Regenerative Medicine Advanced Therapy, Fast Track and Orphan Drug and Rare Pediatric Disease designations from the FDA, Orphan Drug designation from the European Commission and Innovative Licensing and Access Pathway designation from the Medicines and Healthcare products Regulatory Agency.

About Rett Syndrome

Rett syndrome is a rare neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene encoding methyl CpG-binding protein 2 (MeCP2), which is essential for regulating neuronal and synaptic function in the brain. The disorder is characterized by loss of communication and hand function, slowing and/or regression of development, motor and respiratory impairment, seizures, intellectual disabilities and shortened life expectancy. Rett syndrome progression is divided into four key stages, beginning with early onset stagnation at 6 to 18 months of age followed by rapid regression, plateau and late motor deterioration. Rett syndrome primarily occurs in females and is one of the most common genetic causes of severe intellectual disability. Currently, there are no approved disease-modifying therapies that treat the genetic root cause of the disease. Rett syndrome caused by a pathogenic/likely pathogenic *MECP2* mutation is estimated to affect between 15,000 and 20,000 patients in the U.S., EU, and U.K.

About Taysha Gene Therapies

Taysha Gene Therapies (Nasdaq: TSHA) is a clinical-stage biotechnology company focused on advancing adeno-associated virus (AAV)-based gene therapies for severe monogenic diseases of the central nervous system. Its lead clinical program TSHA-102 is in development for Rett syndrome, a rare neurodevelopmental disorder with no approved disease-modifying therapies that address the genetic root cause of the disease. With a singular focus on developing transformative medicines, Taysha aims to address severe unmet medical needs and dramatically improve the lives of patients and their caregivers. The Company's management team has proven experience in gene therapy development and commercialization. Taysha leverages this experience, its manufacturing process and a clinically and commercially proven AAV9 capsid in an effort to rapidly translate treatments from bench to bedside. For more information, please visit www.tayshagtx.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipates," "believes," "expects," "intends," "projects," "plans," and "future" or similar expressions are intended to identify forward-looking statements. Forward-looking statements include, but are not limited to, statements concerning the potential of TSHA-102 and Taysha's other product candidates, to positively impact quality of life and alter the course

of disease in the patients Taysha seeks to treat, its research, development and regulatory plans for its product candidates, including the anticipated timelines for reporting data for the TSHA-102 REVEAL trials and the trial design of the TSHA-102 REVEAL trials, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed and the potential market opportunity for Taysha's product candidates. Forward-looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding Taysha's business are described in detail in its SEC filings, including in Taysha's Annual Report on Form 10-K for the full-year ended December 31, 2023, which is available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that Taysha makes from time to time with the SEC. These forward-looking statements speak only as of the date hereof, and Taysha disclaims any obligation to update these statements except as may be required by law.

Company Contact:
Hayleigh Collins
Director, Head of Corporate Communications, and Investor Relations
Taysha Gene Therapies, Inc.
hcollins@tayshagtx.com

Media Contact:
Carolyn Hawley
Inizio Evoke
Carolyn.hawley@inizioevoke.com

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

Taysha GENE THERAPIES

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

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

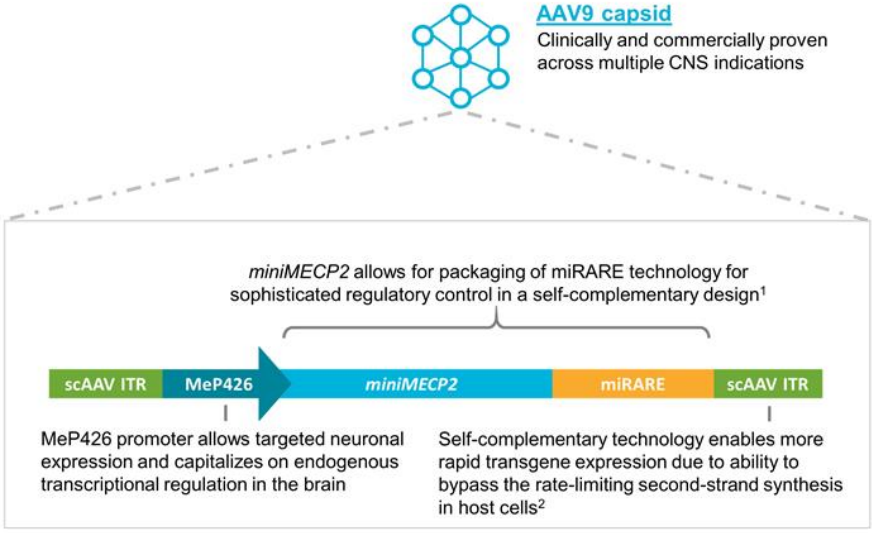
- Estimated prevalence of typical Rett syndrome caused by a *MECP2* mutation is between **15,000 and 20,000** patients in major global markets (U.S., EU+U.K.)[3]
- Rett syndrome occurs worldwide in **1 of every 10,000** female births[3]

Taysha GENE THERAPIES

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



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

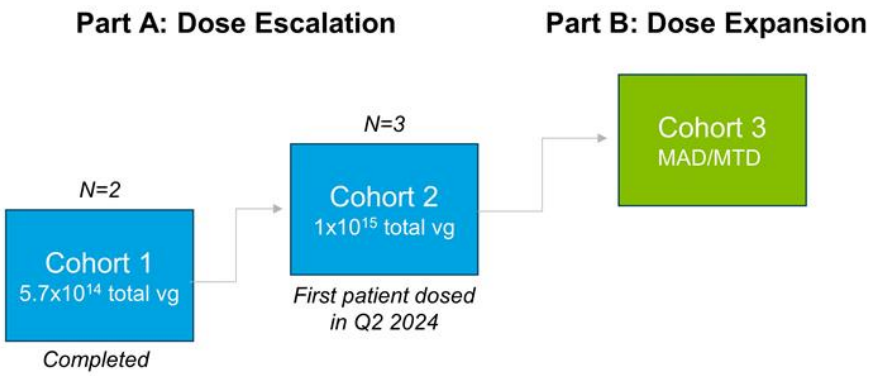
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels; if possible, establishes MAD or MTD
- **Part B**: evaluates the MAD or MTD

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

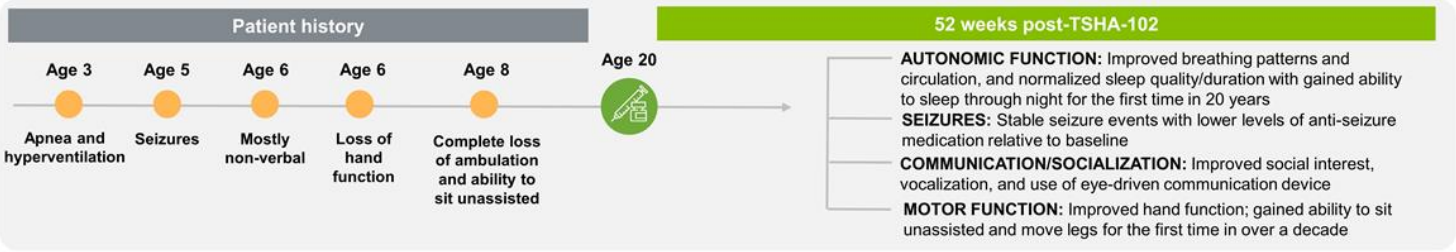
Clinical Domain Improvements	Adult Patient One 52 weeks post-treatment *Completed steroid taper week 36 and sirolimus taper week 43*	Adult Patient Two 25 weeks post-treatment *Completed steroid taper week 25 and sirolimus taper week 31*
Motor skills	○ Improved hand function and gained ability to sit 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)



Adult Patient Two

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

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

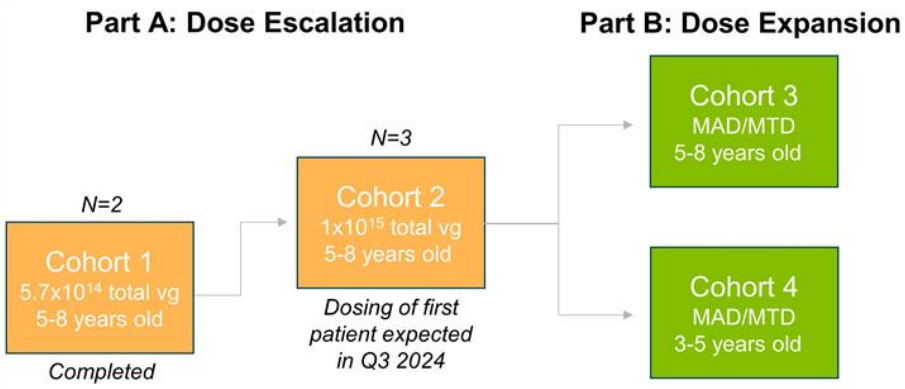
- Safety and preliminary efficacy of TSHA-102
- **Part A**: evaluates two dose levels; if possible, establishes the MAD or MTD
- **Part B**: evaluates the MAD or MTD in two age cohorts

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)



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

*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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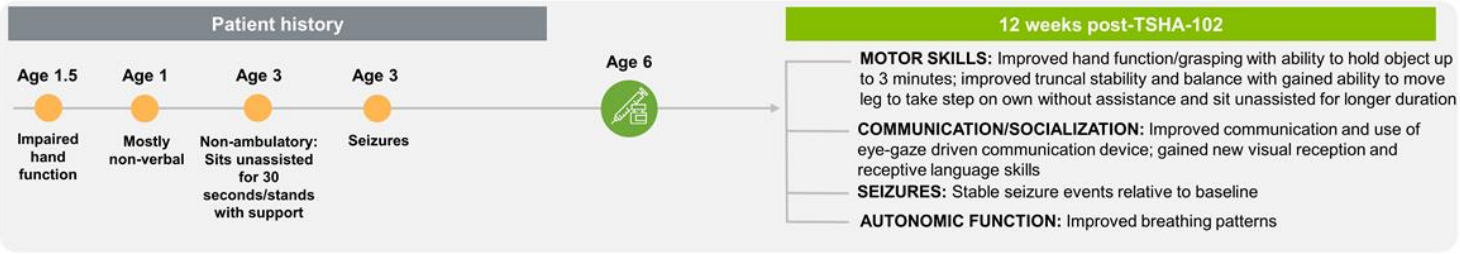
Clinical observations made by the Principal Investigator are based on post-treatment assessments, pre-treatment observations, baseline assessments, pre-screening visits and patient's medical history. Subject to change as the trial progresses.

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

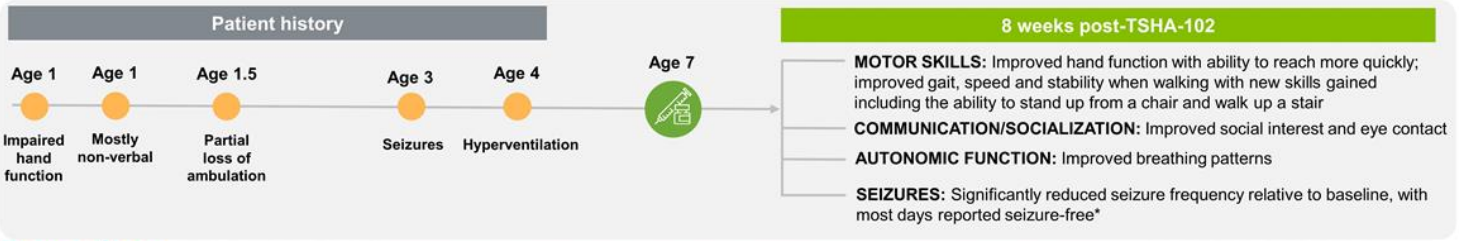
Pediatric Patient One

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



Pediatric Patient Two

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



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

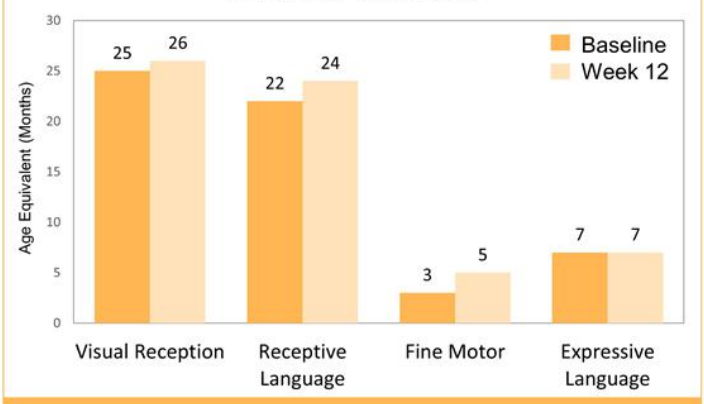
Clinical improvements demonstrated across multiple efficacy measures in both pediatric patients treated with TSHA-102 (low dose, $5.7x10^{14}$ total vg)

	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

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

*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

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Thank You

investors@tayshagtx.com

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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