Early safety and efficacy observations following the first use of TSHA-102 gene therapy in a patient with Rett Syndrome

E Rossignol,[1] I Meijer,[1] J Downs,[2] N Devidze,[3] E Squiers,[3] B Seremula,[4] V Oswald,[3] E Tesfaye,[3] R Haque-Ahmed,[3] B Maru,[3] S Nagendran[3]

[1]Départements de neurosciences et pédiatrie, Université de Montréal, Québec, Canada; [2]Telethon Kids Institute, Centre for Child Health Research, University of Western Australia, Nedlands, Australia: [3]Taysha Gene Therapies, Dallas, TX, USA; [4]Atorus Research Inc., Newtown Square, PA, USA.

INTRODUCTION

- Rett syndrome (RS), linked to defects in the X-linked *MECP2* gene, is a childhood-onset neurologic disorder seen in ~5 – 10 per 100,000 girls and women:[1]
  - Progression of RS is marked by impaired motor and cognitive developmental defects, including regression of previously attained motor and speech skills
  - Among the most burdensome signs and symptoms are loss of communication, breathing abnormalities, and loss of purposeful hand use (accompanied by hand-motion stereotypies).[2]
- Gene therapy for RS has been explored in animals, including mouse models that recapitulate signs and symptoms of the human disease.[3]
  - The REVEAL Adult study (NCT05606614), a first-in-human trial of TSHA-102 gene therapy,[4] is currently enrolling women ≥18 years old with Rett Syndrome (RS)
  - Here, we report initial clinical observations on the first participant enrolled in this study– the first individual ever to receive gene therapy for RS.

METHODS

- Immunoprophylaxis was initiated on Day –7 and administered at the study site in Montréal
  - Sirolimus (blood trough: 4 – 8 ng/mL)
  - Oral prednisolone.
- On Day 0, 5.7 x 10^{14} viral genomes (vg) Taysha-102 was injected intrathecally in the lumbar spine, with general anesthesia. Vital signs were monitored before and after treatment, with clinical observation and regular blood draws. The Participant was discharged on Day 1.
- Prespecified safety monitoring included:
  - Laboratory evaluation: blood and cerebrospinal fluid, renal and liver function tests, urinalysis
  - Electrocardiogram and electroencephalogram findings
  - Total and neutralizing antibody titer to the gene therapy vector
  - Spinal cord and brain MRI
  - Sensory nerve action potential (SNAP) analysis.
- Efficacy endpoints evaluated by the clinician or caregivers included:
  - Clinical Global Impression (CGI), including static severity (CGI-S) and CGI improvement (CGI-I)[5]
  - Parental (i.e., caregiver) Global Impression (PGI-I)
  - Rett Syndrome Behavior Questionnaire (RSBQ; 45 items, rated by caregiver), comprising 8 subscales[6]
  - Revised Motor Behavior Assessment (R-MBA; 24 items, rated by clinician), comprising 5 subscales
  - Seizure activity
  - Rett Syndrome Hand Function Scale score.
- The first scheduled safety evaluation by the Independent Data Monitoring Committee (IDMC) was based on clinical data captured by Day 42, including efficacy data evaluated at Day 28 (Week 4) and safety data up to Day 42. Seizure activity recorded by caregivers was evaluated to Day 35.

RESULTS

PARTICIPANT 1: CLINICAL HISTORY

- The Participant is a 20-year-old woman diagnosed with RS at age 3:
  - Could sit at 6 months and learned a few words from 11 months onwards, which she eventually lost
  - Never crawled, walked independently, or developed a pincer grip
  - Hand stereotypies developed after age 2
  - Unable to stand without support since age 6; stopped reaching or grasping around age 7.
- Seizures began at age 3:
  - Refractory to multiple medications
  - Over the last 10 years, have been generally well-controlled with daily clobazam and phenytoin
  - Breakthrough seizures during viral infections or when phenytoin <100 µmol/L.
- Chronic elevation of gamma-glutamyl transferase (GGT) is attributed to treatment with phenytoin. Ongoing clinical challenges include persistent constipation, recurrent pneumonia, scoliosis (surgically treated), osteopenia, and a benign thyroid nodule (identified January 2023).

PERI- AND POST-SURGICAL OBSERVATIONS

- At baseline, the Participant:
  - Was wheelchair-bound, with no purposeful hand motion, and was mostly non-verbal.
  - Was generally alert during the day, with moderate interest in conversations or activities; often dozed off when unstimulated
  - Experienced frequent bouts of hyperventilation and breath-holding, sometimes with cyanosis
  - Had cold, occasionally bluish hands and feet.
- Prior to the procedure, she was alert, and her vital signs were unremarkable. Oximetry confirmed good tissue perfusion at all times.
- Baseline blood laboratory values at Day –43 showed elevated liver enzymes and extended prothrombin time (**Table 1**).
  - Scheduled monitoring showed that liver enzyme excursions occurred within the first two weeks after treatment but generally had resolved by Day 28
  - GGT followed a similar trajectory, declining below the Participant's baseline at Day 28, while remaining above the normal range
  - A transient increase in serum cholesterol, seen in Week 2, was expected during sirolimus titration
  - Out-of-range hematology findings were considered clinically non-significant; the decline in lymphocyte count at Day 1 was an expected effect of immunoprophylaxis.

Table 1. Blood chemistry and hematology values falling outside the normal range (bolded values), observed before or after treatment of Participant 1 with TSHA-102. Note that her GGT elevation results from long-term phenytoin treatment (initiated in 2008). INR, International normalized ratio; MCHC, mean corpuscular hemoglobin concentration

Test (units)	Normal Range	Day –43	Day 1	Day 9	Day 15	Day 28
Blood chemistry						
Alanine Aminotransferase (U/L)	10 – 33	**39**	**54**	**42**	**38**	12
Alkaline Phosphatase (U/L)	30 – 115	137	110	97	99	78
Aspartate Aminotransferase (U/L)	10 – 36	26	30	33	**40**	21
Gamma Glutamyl Transferase (U/L)	5 – 32	**104**	**138**	**212**	**173**	**85**
Total Cholesterol (mg/dL)	125 – 200	153	146	**221**	**209**	183
Prothrombin Time (s)	9.4 – 12.5	**14.9**	**13.0**	11.8	12.1	12.2
Prothrombin Time – INR (s)	0.9 – 1.1	**1.3**	1.1	1.0	1.0	1.0
Hematology						
Hematocrit (%)	33 – 47	**45.6**	43.7	NA	NA	**51.8**
Lymphocytes (%)	12 – 46	**39.2**	**4.5**	NA	NA	26.4
MCHC (g/dL)	31 – 36	31.1	**30.4**	NA	NA	**29.2**
Neutrophils (%)	34 – 71	48.4	**86.3**	NA	NA	67.7

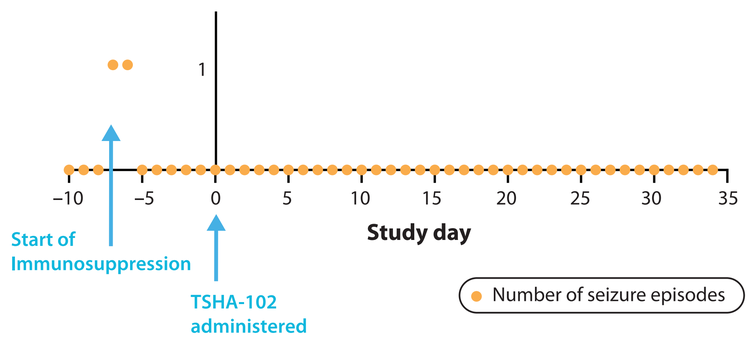
SAFETY

- Five non-serious adverse events (AEs) were observed, including three deemed unrelated to the treatment:
  - GGT elevation
  - A vertebral hemangioma (identified after consent, but 6 weeks before treatment)
  - A suspected urinary tract infection, treated with cefixime, resolving within 11 days.
- In addition, the Participant experienced two non-serious treatment-related AEs:
  - Mild pyrexia on Day 1, treated with acetaminophen and resolving on the same day (attributed to TSHA-102)
  - Irritability, starting Day 5 and resolving on Day 12 (attributed to prednisolone).

SEIZURE ACTIVITY

- The Participant experienced seizures on Days –7 and –6. There has been no seizure activity in the first 35 days post-treatment (**Figure 1**).

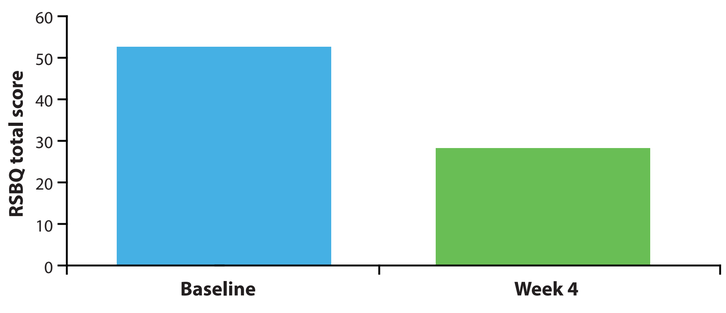
Figure 1. Seizure activity reported in the Participant's seizure diary before and after TSHA-102 treatment.



EFFICACY OUTCOMES

- Based on language and communication abilities, ambulation, hand use, attentiveness, eye contact, seizures and autonomic function, the Participant's overall RS severity was rated at 6 (severely ill) and 5 (markedly ill) on the 7-point CGI-S scale at baseline and Week 4, respectively.
- Clinical improvement was evaluated as:
  - PGI-I 3 (a little better) by caregivers
  - CGI-I 2 (much improved) by clinicians.
- Total RSBQ Score showed marked improvement with a 23-point reduction by Week 4 (**Figure 2**). Of 8 subscales, 6 showed numerical improvement, including:
  - A 7-point improvement (from 12 to 5) on the hand-use subscale
  - A 4-point improvement (from 8 to 4) in general mood
  - A 3-point decrease (from 3 to 0 (normal)) on the night-time behavior subscale.

Figure 2. Rett Syndrome Behavior Questionnaire total score at baseline and Week 4, as assessed by caregivers. The scale consists of 8 subscales with a total of 45 questions, each rated from 0 (not true) to 2 (very true).



- A 2-point rise in the Participant's fear/anxiety subscore, despite her generally improved mood, may be related to her increased ability and desire to engage in social interactions.
- Normalization of night-time behavior reflects the absence of uncontrollable crying and screaming incidents:
  - Caregivers report that the Participant has slept peacefully for the first time in their recollection
  - Breathing patterns during sleep have also improved
- Conversely, no significant change was noted in R-MBA or in any of the 6 R-MBA subscores by Week 4 (**Figure 3**).
- Clinical and caregiver observations (**Table 2**) suggest that the Participant experienced notable reduction in disease burden, beginning within the first 2 weeks after TSHA-102 treatment, with continued progress in the following weeks.

Figure 3. Change in Revised Motor Behavior Assessment (R-MBA) and R-MBA subscores. Note that the rise in the Respiratory Behaviors subscore reflects an increase in bruxism (tooth grinding), rather than a change in respiratory patterns.

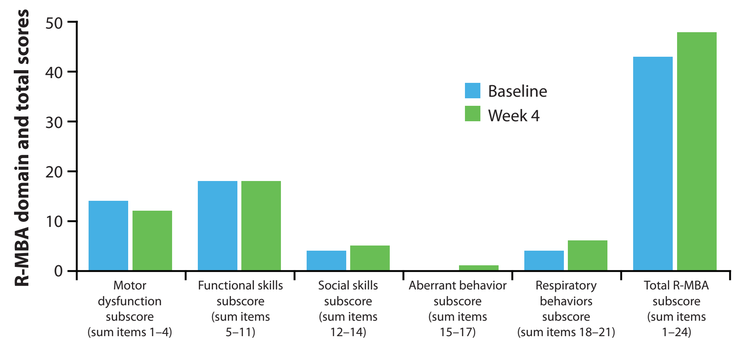


Table 2. Improvements in function in Participant 1, noted by physicians and caregivers within 2 weeks of TSHA-102 treatment

Parameter	Prior history	Change after treatment
Sleep disturbance	Never slept throughout the night.	Now sleeps peacefully for the full night.
Breathing dysfunction	Breath-holding spells with cyanosis and hyperventilation episodes multiple times an hour.	Very infrequent and brief (<5 minutes) breath-holding, occurring when Participant is anxious. Improved breathing patterns while asleep.
Communication ability	Rarely used words (on occasions could say "Mama"); could indicate choices by directing her gaze.	Now calls "Mama" many times per day, in addition to greatly increased use of non-verbal sounds (e.g., grunts and hums).
Social interest	Passive; usually sleepy, with little apparent interest in watching family's activities or listening to stories.	Eager to engage and hear stories. Cries when positioned on her back; when sitting up, she shows interest in all activity around her.
Limb movement and tone	Unable to sit up, turn her torso, or stand.	Makes efforts to sit up on her own; still unsuccessful, but she appears to be gaining strength and control.
Gross motor skills	Constant hypertonia/ rigidity, flexion contractures in wrists/ elbows/knees. Unable to move legs; adopted a frog-legged position.	Limb muscle tone greatly improved; moves arms frequently and rests with legs straight. Able to scratch her head/neck with the back of her arm; able to hold her head up and sit with light support on a hospital plinthe.
Fine motor skills	Generally unable to grip or reach for toys or other objects; some ability to hold a spoon.	Able to grasp a wider range of objects; able to hold a toy (>3 minutes); uses finger to interact with a touchscreen.

CONCLUSIONS

- **Participant 1 is the first individual with RS to undergo gene therapy. The procedure went smoothly, with no clinically significant changes in vital signs.**
- **In a pre-specified safety evaluation 42 days after treatment with TSHA-102, Participant 1 experienced 2 non-serious treatment-emergent adverse events (mild pyrexia and mild irritability). These were attributed to TSHA-102 and prednisolone treatment, respectively.**
- **There were no serious adverse events, irrespective of causation.**
- **At baseline, the patient was markedly ill with RS, as assessed by physicians. Improvements in function were noted within 2 weeks in various parameters that affect the Participant and her caregivers.**
- **Early observations show an improvement in Participant 1's RSBQ score, notably on the Hand Behavior, General Mood and Night-time Behavior subscales. However, no improvements have been noted yet on the R-MBA scale.**
- **Because Participant 1 experienced no dose-limiting toxicities from her treatment, the IDMC approved the treatment of two more adults with RS, using the same dose of 5.7 x 10^{14} vg TSHA-102.**

References

1. Petriti U, Dudman DC, Scosyrev E, Lopez-Lyon S. *Syst Rev* 2023; 12(1):5.
2. https://rettpfdd.org/site/assets/files/1/2022-rett-syndrome-voice-of-the-patient-report.pdf, accessed August 2023.
3. Gadalla KK, Ross PD, Riddell JS et al. *PLoS One* 2014; 9(11):e112889.
4. Sinnett SE, Boyle E, Lyons C, Gray SJ. *Brain*. 2021; 144(10):3005–3019.
5. Neul J, Glaze DG, Percy AK et al. *J Child Neurol* 2015; 30(13): 1743–1748.
6. Mount RH, Charman T, Hastings RP et al. *J Child Psychol Psychiatry* 2002; 43(8):1099–110.

Presented at the Rett Syndrome Research Trust Meeting, Sept 13–15, 2023, Boston MA, USA