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

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INTRODUCTION

- The REVEAL Adolescent and Adult study (NCT05606614), a first-in-human, open-label trial of TSHA-102 gene therapy,[1] is currently enrolling females with Rett syndrome (RS), a childhood-onset X-linked neurologic disorder seen in ~1:10,000 girls.[2]
- TSHA-102 is a pre-authorisation, investigational product.
- Here, we report initial clinical observations on the first two participants enrolled in this study, based on scheduled safety and preliminary efficacy evaluations for Participant 1 (P1) and P2

METHODS

- Immunoprophylaxis (sirolimus plus oral prednisolone) is initiated on Day –7. On Day 0, 5.7×10^{14} vector genomes (vg) are injected intrathecally via lumbar puncture, under anesthesia.
- Prespecified safety monitoring (through Week 20 [P1] or Week 6 [P2]):
  - Laboratory evaluation: blood and cerebrospinal fluid (CSF), renal/ liver function tests, urinalysis
  - Spinal and brain MRI
  - Sensory nerve action potential (SNAP) analysis
  - Adverse events (AEs) and severe AEs (SAEs).
- Viral shedding was evaluated in saliva, stool, urine, and whole blood.
- Efficacy endpoints (through Week 12 (P1) or Week 4 (P2), except as noted):
  - Clinical Global Impression (CGI), including static severity (CGI-S) and CGI improvement (CGI-I), plus Parental (i.e., caregiver) Global Impression (PGI-I)[3]
  - Revised Motor Behavior Assessment (R-MBA), rated by clinician: 24 items comprising 5 subscales
  - Rett Syndrome Behavior Questionnaire (RSBQ), rated by caregiver: 45 items/8 subscales[4]
  - Seizure activity documented through Week 20 (P1) or Week 5 (P2)
  - Rett Syndrome Hand Function Scale (RSHFS),[5] rated by a hand function specialist.

RESULTS

STUDY PARTICIPANTS

- P1 is a 20-year-old female carrying a 3.8 kb *MECP2* deletion, diagnosed with RS at age 3. She could sit without support at 8 months and learned a few words from 11 months onwards. She never crawled, walked independently, or developed a pincer grip.
  - Unable to sit or stand without support since age 8
  - Lost ability to reach or grasp around age 6.5
  - Seizures began at age 3 and are generally well controlled on clobazam and phenytoin; breakthrough seizures seen with phenytoin <100 µmol/L
- P2 is a 21-year-old female carrying the p.Arg133Cys *MECP2* missense mutation (R133C). She was able to stand and walk at 13 months; could run, swim, and climb. At 2 years, she could speak short sentences. Following regression (age 2–3), she developed hand stereotypies, became non-verbal, and stopped running.
  - In her late teens, motor control worsened, and she developed parkinsonian symptoms with bradykinesia.
  - Walks with prompting; requires a leg brace for stability
  - Seizures began at age 10 and are generally well controlled on levetiracetam and topiramate; breakthrough seizures typically 2–3 seizures per week, occurring in clusters of 2–3 seizures in a day.

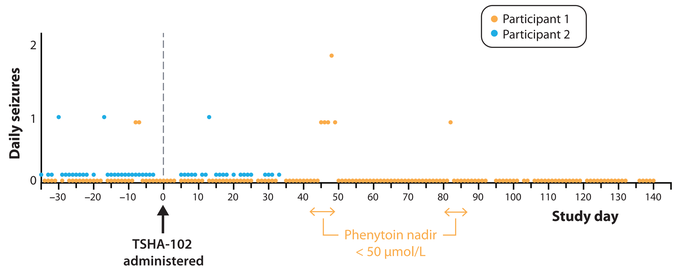
SAFETY DATA TO WEEK 20 (P1) OR WEEK 6 (P2)

- No SAEs or dose-limiting toxicities occurred for either Participant

Key assessments

- No clinically significant ECG or Echo changes. SNAP analysis showed no evidence of worsening pathology. Brain MRIs showed no change at Week 4 for either Participant.
- Seizure frequency before and after treatment is shown in Figure 1.

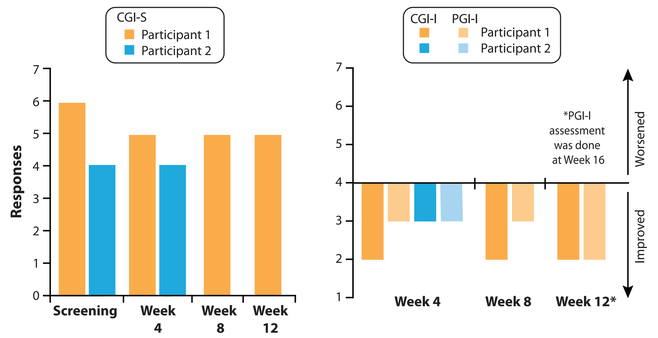
Figure 1.
Seizure activity reported in Participants' seizure diaries before and after TSHA-102 treatment, from Screening to Day 140 (P1) or Day 33 (P2). Post-treatment seizures for P1 corresponded to phenytoin nadir <50 µmol/L.



EFFICACY OUTCOMES

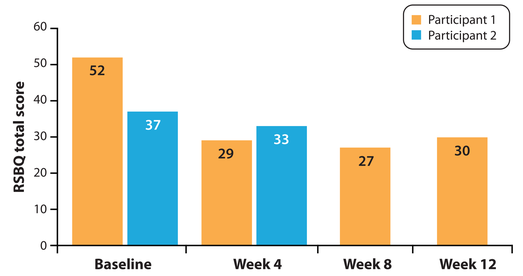
- Clinician and caregiver global impression scores are shown in **Figure 2.**
- On the 7-point CGI-S scale, the Participants' overall RS severity was rated:
  - P1: 6 (severely ill) at Screening and 5 (markedly ill) at later time points through Week 12
  - P2: 4 (moderately ill) at Screening; unchanged at Week 4.
- Clinical improvement evaluated by clinicians and caregivers (CGI-I and PGI-I, respectively) was rated:
  - P1: CGI-I 2 and PGI-I 2 (much better) at Weeks 12 and 16, respectively
  - P2: CGI-I 3 and PGI-I 3 (a little better) at Week 4.

Figure 2.
CGI and PGI scores for Participants 1 and 2.



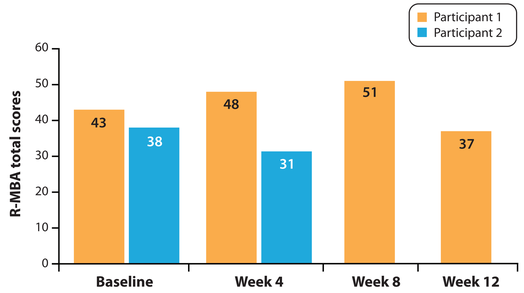
- Total RSBQ Score changes are shown in **Figure 3**.
- P1 showed marked improvement, noted first at Week 4. By Week 12, she had attained a 22-point reduction, driven by improvements in hand behaviors, night-time behavior, breathing problems and facial expressions
- P2 showed modest improvement, with a 4-point reduction by Week 4, driven by improvements in body rocking/facial expressions, walking/ standing and improvements in breathing abnormalities.

Figure 3.
Rett Syndrome Behavior Questionnaire total scores 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).



- Hand use, assessed by the RSHFS, showed that:
  - P1 experienced steady improvement in non-dominant hand function between Baseline and Week 11; now shows some active grasping, with support
  - P2 shows no change in RSHFS score at Week 4. However, clinicians noted that her hand posture has relaxed and stereotypies (e.g., hand wringing) are less frequent and less vigorous.
- R-MBA total score changes are shown in **Figure 4**:
  - P1 attained a 6-point improvement by Week 12, notably on the Social Skills and Motor Dysfunction subscales
  - P2 attained a 7-point improvement by Week 4, notably on the Social Skills and Respiratory Behaviors subscores

Figure 4.
Change in Revised Motor Behavior Assessment (R-MBA).



Functional changes in Participants, noted by physicians and caregivers

- For both Participants, breathing dysrhythmia and autonomic dysfunction are reduced:
  - Breath holding and bouts of hyperventilation, previously multiple times per hour, are now rare and brief
  - Hands and feet, usually cold and blue before, are now warm, with normal color.
- In addition, at Week 12 P1 shows:
  - Evident improvement in ability to sleep peacefully, with normal breathing and free of crying/screaming spells. This change was first noted by Week 2
  - Increased social engagement: Now interested in stories and all interactions; refuses to be positioned on her back where she would be unable to see people. Now vocalizes, hums, grunts, and says "mama" regularly
  - Improved gross and fine motor control: Can now sit for up to 15 minutes without support for the first time in >10 years. Able to open her hands and dissociate her fingers and hold a toy, touch a communication screen, scratch an itch, and pet a dog.
- At Week 4 P2 also shows increased alertness and improved motor control:
  - Now shows increased interest in interactions around her
  - Turns quickly when addressed, and follows conversations
  - Walks more stably
  - Now able to transfer objects between her hands, for the first time since infancy.

CONCLUSIONS

- **The first two Participants have contrasting RS disease histories.**
  - **P1, who carries a probable null allele of *MECP2*, is more severely affected than P2, who carries the R133C mutation, a well-characterized mild missense allele.[6]**
  - **Overall severity is reflected in their different Baseline CGI-S ratings (severely ill and markedly ill, respectively).**
- **Despite differences, both Participants showed functional improvement beginning in the early weeks following TSHA-102 treatment. Early notable improvements affecting activities of daily living include:**
  - **Social interest**
  - **Gross motor function, e.g., improved gait and ability to sit up**
  - **Fine motor function, e.g., hand posture and function**
  - **Restful sleep (P1)**
  - **Autonomic function, including normalized breathing and improved hand/foot circulation.**
- **By Week 12 and Week 4, respectively, P1 and P2 show numerical improvement on:**
  - **R-MBA and CGI-I scales (Clinician-assessed)**
  - **RSBQ and PGI-I scales (Caregiver-assessed).**
- **Seizure frequency for P1 is comparable relative to baseline through Week 20, seizures now appear to be confined to periods where phenytoin level declines to <50 µmol/L (previously <100 µmol/L). Seizure events for P2 through Day 33 are reduced relative to baseline, based on caregiver reports.**
- **There were no SAEs, irrespective of causation, and neither Participant experienced dose-limiting toxicities from the treatment.**

Presented at the BPNA 2024 Annual Conference, 24–26 January 2024, Bristol, UK

REFERENCES

1. Sinnett SE, Boyle E, Lyons C, Gray SJ. *Brain*. 2021; 144(10):3005–3019.
2. Laurvick CL, de Klerk N, Bower C, et al. *J Pediatr* 2006; 148(3):347–52.
3. Neul J, Glaze DG, Percy AK et al. *J Child Neurol* 2015; 30(13):1743–1748.
4. Mount RH, Charman T, Hastings RP et al. *J Child Psychol Psychiatry* 2002; 43(8):1099–110.
5. Downs J, Wong K, Drummond C, Leonard H. *J Pediatr* 2021; 237:244–249.
6. Leonard H, Colvin L, Christodoulou J et al. *J Med Genet* 2003; 40:E52.