Design of the REVEAL Pediatric study of TSHA-102 gene therapy for Rett Syndrome

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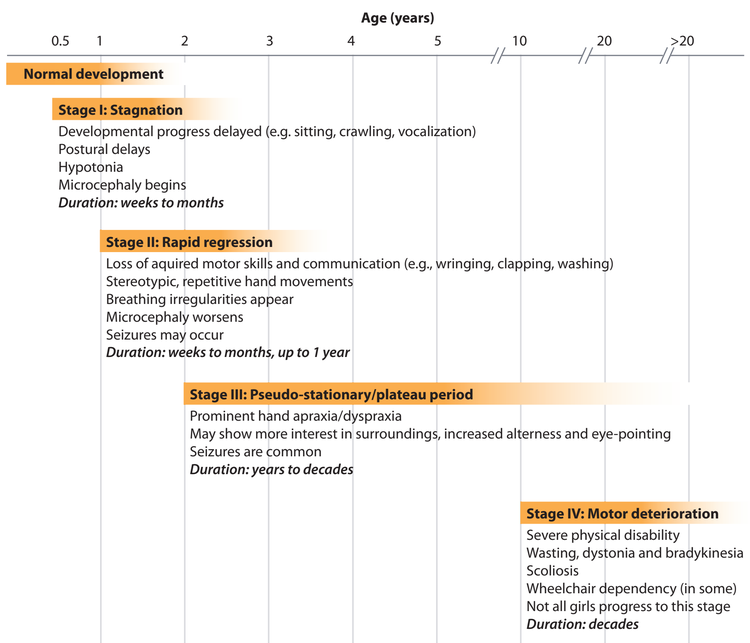
INTRODUCTION

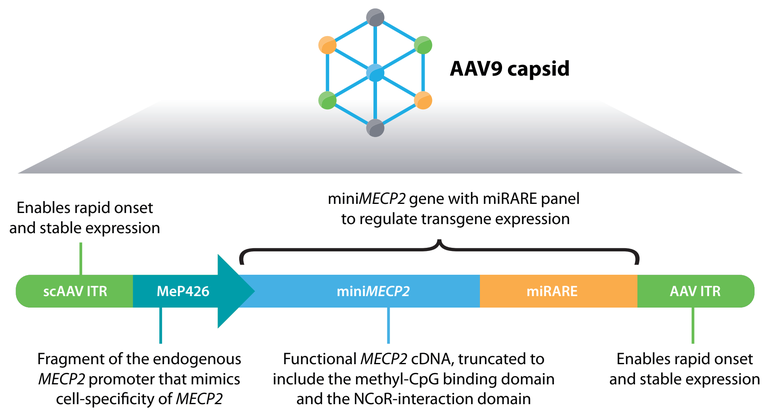
- Rett Syndrome (RS), associated with mutation of the X-linked *MECP2* gene, is a progressive neurological disorder that is characterized by 4 stages of progression (**Figure 1**).[1,2,3]
- In females with RS (*MECP2*$^{-/+}$ heterozygotes), *MECP2* expression is silenced in a random and cell-autonomous manner due to X chromosome inactivation.[4]
- Rett syndrome represents a challenging case for human gene therapy because the therapeutic window for *MECP2* transgene expression is narrow; as with *MECP2* deficiency, *MECP2* gene duplication leads to serious neurodevelopmental disease.[5,6]

Figure 1. Rett Syndrome Disease Progression[1]



- One approach to safe therapeutic reversion of RS is to engineer post-transcriptional feedback repression into a therapeutic *MECP2* transgene, mitigating risk of MeCP2 overexpression.
- TSHA-102 (**Figure 2**) is a human-ready adeno-associated virus- (AAV-) based gene therapy construct for use in RS. This construct contains:[6]
  - A truncated but functional *MECP2* cDNA (mini*MECP2*)[7] under control of a *MECP2* promoter fragment (MeP426)
  - A microRNA- (miRNA-) responsive autoregulatory element (miRARE), designed to regulate expression of mini*MECP2* in the CNS.
- TSHA-102 was recently granted fast-track designation by the FDA (August, 2023).

Figure 2. Schematic of TSHA-102



RATIONALE FOR THIS STUDY

- The US FDA has recently cleared an Investigational New Drug application, allowing Taysha Gene Therapies to initiate the REVEAL Pediatric study, the first trial of TSHA-102 gene therapy for girls under age 18 with RS.
- Safety and efficacy of TSHA-102 were first tested in animal models, which have provided evidence of the potential efficacy of TSHA-102 as a treatment for RS in a mouse model of RS (*Mecp2*$^{-/y}$ males), with an adequate margin of safety in wild-type, heterozygous female (*Mecp2*$^{-/+}$) mice, rats, and nonhuman primates.
- TSHA-102 is also under clinical evaluation in the REVEAL Adult study (NCT05606614) and preliminary findings from the first participant dosed have been promising.
- Compared to adult treatment, gene therapy in early childhood may have greater potential to transform the lives of RS patients, e.g., delaying loss of ambulation or other irreversible outcomes.

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STUDY DESIGN

The REVEAL Pediatric study will be a Phase 1/2, multicenter, open-label, dose-escalation study and a randomized dose-expansion study (Parts A and B, respectively) to evaluate the safety, tolerability and preliminary efficacy of a single intrathecal (IT) administration of TSHA-102 via lumbar puncture in 3–8-year-old (yo) girls with RS and a documented pathogenic or likely pathogenic classified mutation in the *MECP2* gene.

- Part A is an open-label, single-arm dose-escalation study evaluating 2 doses of TSA-102 and is intended to define a maximum tolerated or maximum administered dose (MTD or MAD) (**Figure 3**). Immunoprophylaxis will begin at Day –7 and will be tapered from Week 17 to Week 25 (oral prednisolone) and starting from Week 38 (sirolimus).
- In Cohort 1 (n=3), participants 5–8 yo will receive a single IT dose of 5.0 x 10^{14} viral genomes (vg).
  - Independent Data Monitoring Committee (IDMC) safety evaluation, scheduled 42 days after the first and third participant treatments, will identify any dose-limiting toxicities (DLTs).
  - Finding of 1 DLT will trigger expansion of Cohort 1 to 6 participants; should two DLTs occur in Cohort 1, the initial dose will have surpassed the MTD.
- Otherwise, Cohort 2 (n=3) will be treated with 1.0 x 10^{15} vg, and safety evaluation will occur as above.
  - Should 0/3 (or 1/6) Cohort 2 participants experience DLTs, the MAD of 1.0 x 10^{15} vg will be applied in Part B.
- All Part A efficacy outcomes will be evaluated with descriptive statistics, relative to each participant's baseline data.
- Outcomes will include objective metrics including:
  - Electroencephalography for seizure assessment
  - Auditory and visual evoked potentials; mismatch negativity
  - Whole-body polysomnography
  - Physical, functional, and cognitive scoring by study personnel and caregivers.
- Caregiver-assessed outcomes will capture aspects of RS identified as specifically burdensome in this disease:
  - Communication
  - Hand movement control
  - Breathing
  - Mobility difficulties.
- Prior to commencing Part B, Taysha Gene Therapies will consult with FDA regulators to finalize the design of Part B. Tentatively and subject to FDA approval, Part B will enroll 6 participants (Cohort 3; 5–8 yo), randomized to an immediate and a delayed treatment cohort (ITC and DTC). Following IDMC review, 6 additional participants (Cohort 4; 3–5 yo) will be randomized. (**Figure 4**). Treatment will be with TSHA-102 at the MAD or MTD determined previously.
- Efficacy and safety evaluations will be conducted at prespecified intervals before and ≥2 years after treatment.
  - Weeks 1–12 (Core observation): Conducted by the clinician in clinic; PRO assessments may be done at home.
  - Weeks 13–104 (Initial follow-up observation).
  - For outcomes with potential evaluator bias, participant videos will be assessed by independent experts blinded to participants' treatment status.

Figure 3. Part A Dosing Scheme. DLT, dosage-limiting toxicity; IDMC, Independent Data Monitoring Committee; IT, intrathecal; MAD, maximum applied dose; MTD, maximum tolerated dose; vg, viral genomes.

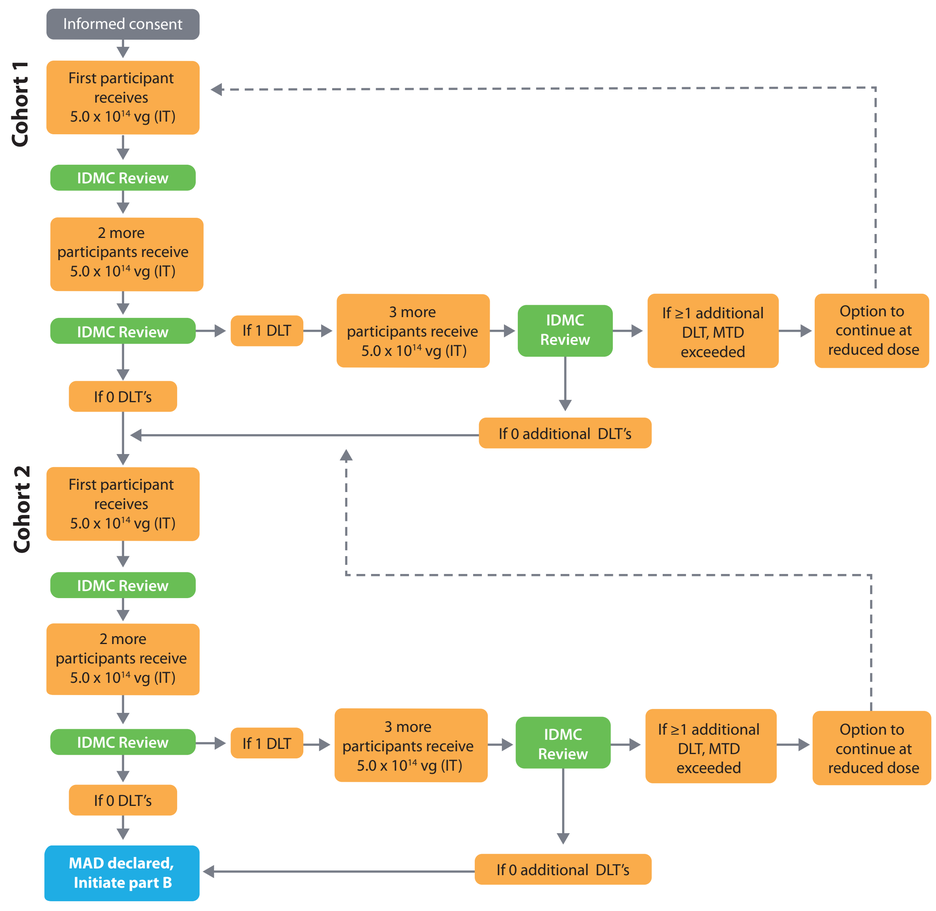
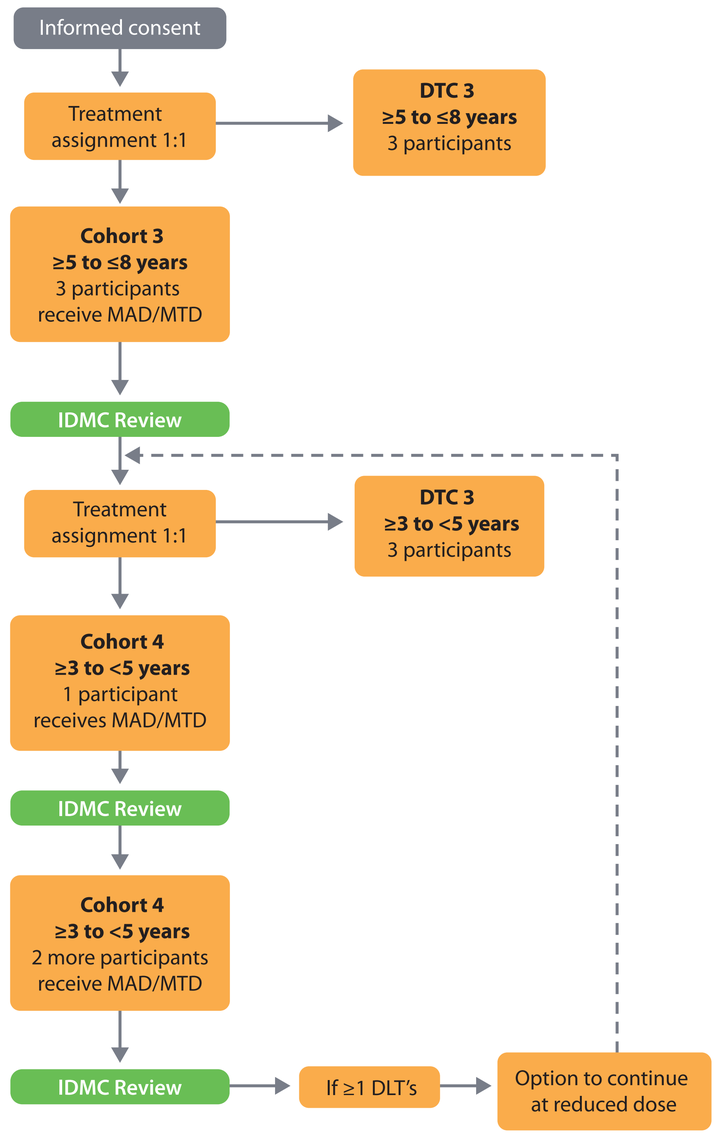


Figure 4. Proposed Dosing Scheme for Part B.
DTC, delayed treatment cohort; other abbreviations as in Figure 3.



SUMMARY AND NEXT STEPS

- **Data from nonclinical and preliminary clinical analyses in adults show promise of TSHA-102 for the treatment of RS.**
- **Given the rapid deterioration of function in RS, therapeutic intervention focused on restoration of MeCP2 early on, when plasticity is at its highest, may allow for more meaningful reversal and/or prevention of symptoms.**
- **Strengths of the current study include its two-part, multicohort design, which allows investigators to proceed systematically to define an MTD or MAD based on the safety record in earlier cohorts; the design also enables treatment for younger patients, who may avoid irreversible effects of RS.**
- **Site identification, review and activation have begun, with the goal of dosing the first pediatric patient by March 2024.**

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