Interim Safety and Efficacy of NGN-401, a Novel Regulated AAV9 Gene Therapy, from a Phase 1/2 Study in Rett Syndrome

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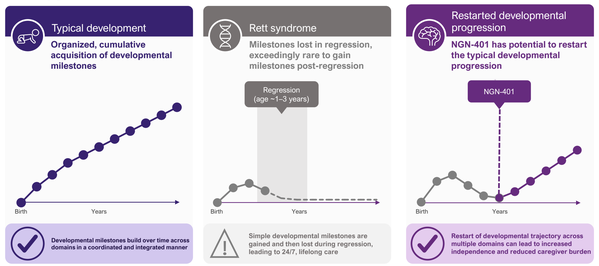
INTRODUCTION

- Rett syndrome (RTT) is a neurodevelopmental disorder caused by loss-of-function variants in the methyl-CpG binding protein 2 (*MECP2)* gene, which encodes for MeCP2, a protein critical for normal function in the brain and nervous system.[1]
- RTT is characterized by regression of acquired developmental milestones and severe impairments in fine motor skills, gross motor abilities, and communication.[2–4]
- NGN-401 is an investigational AAV9 gene therapy that delivers the full-length human *MECP2* transgene incorporating EXACT™ transgene regulation technology designed to enable controlled MeCP2 expression on a cell-by-cell basis and is intracerebroventricularly administered.[1]
- Here, we report interim safety and efficacy results from a Phase 1/2 clinical trial in females with RTT as of the data cutoff date of June 16, 2026.

Restarting developmental progression is the goal for a one-time gene therapy



Frankenburg WK *et al*., Self-administered checklist. In: Denver II. Denver Developmental Materials, Inc.; 1967; May D *et al*. *J Neurodev Disord* 2024; 16 (1): 42.
Graphs for illustrative purposes only.

METHODS

- The Phase 1/2 open-label trial (NCT05898620) is designed to evaluate the safety, tolerability, and efficacy of a one-time 1E15 vg dose of NGN-401 (**Figure 1**).[5]

Figure 1. Phase 1/2 study design

Open-label trial evaluating 1E15 vg NGN-401

Target population / key inclusion criteria:
- Females ages ≥4 to ≤10 y for pediatric cohort or ≥11 y for adult/adolescent cohort with genetically confirmed classic RTT
- CGI-S score of 4–6
- Post-regression stage: ≥6 months since last loss of key milestones in 3 core domains:
  - Hand function
  - Gross motor function
  - Communication

Study endpoints

Safety, tolerability, and efficacy of NGN-401 in RTT
- Efficacy assessments include CGI-I and functional ability in core RTT domains
  - Developmental milestone gains from baseline scored by independent central review using prespecified criteria

CGI, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; y, years.

RESULTS

Baseline Characteristics

- 10 participants (8 in the pediatric cohort and 2 in the adult/adolescent cohort) have been dosed reflecting a broad age range with a wide spectrum of disease severity (**Table 1**).

Table 1. Phase 1/2 baseline characteristics

	Pediatric cohort (N=8)								Adult / adolescent cohort (N=2)	
	Pt:1	Pt:2	Pt:3	Pt:4	Pt:5	Pt:6	Pt:7	Pt:8	Pt:9	Pt:10
Age at dosing (Years)	7	4	6	7	6	4	6	8	18	14
Baseline CGI-S score	4 Moderately ill	5 Markedly ill	5 Markedly ill	5 Markedly ill	6 Severely ill	5 Markedly ill	4 Moderately ill	4 Moderately ill	4 Moderately ill	5 Markedly ill
Genetic variant severity	Mild	Severe	Severe	Severe	Severe	Moderate	Mild-Moderate	Mild-Moderate	Severe	Severe
Follow-up period (months)	30	24	24	24	18	12	12	12	15	12

As of data cutoff date of June 16, 2026.
The CGI-S is scored on a 7-point scale where 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.[6]
CGI-S, Clinical Global Impression – Severity; Pt, participant.

RESULTS

Safety

- NGN-401 remains generally well tolerated at the 1E15 vg dose level in the Phase 1/2 trial.
- All TEAEs related to NGN-401 have been Grade 1 (mild) or Grade 2 (moderate) in severity; the majority are known potential risks of AAV and have resolved or are resolving.
  - Most common related TEAEs: Mild ALT/AST elevation.
- No new treatment-related SAEs reported since last data cutoff date (October 2025).
  - Two previously disclosed Grade 2 SAEs in Pt:5, resolved.
- No cases of HLH.
- No ICV procedure-related AEs.
- No signs or symptoms of MeCP2 overexpression.
- Seizures have remained well controlled following NGN-401.

Table 2. Safety data

Phase 1/2 trial	1E15 vg Dose N = 10	
	n	Events
TEAEs related to NGN-401	9	68
Serious TEAEs Unrelated to NGN-401	3	6
Serious TEAEs Related to NGN-401	1	2

ICV, intracerebroventricular; HLH, hemophagocytic lymphohistiocytosis, TEAE, treatment-emergent adverse event.

Efficacy

- 100% of participants gained ≥1 developmental milestone and improved on CGI-I.
- 47 total milestones gained; 4.7 avg milestones gained per participant.

Figure 2. NGN-401 response over time

Rapid response observed post NGN-401 that deepened over time (**Figure 2**).

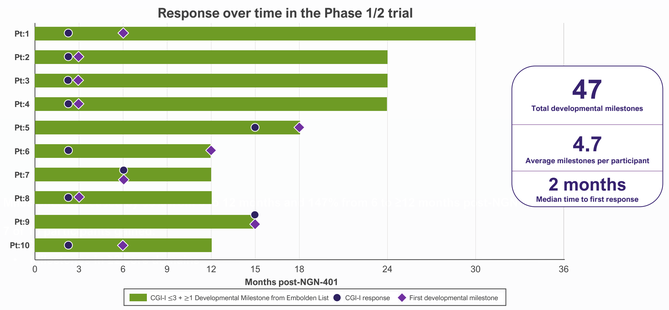
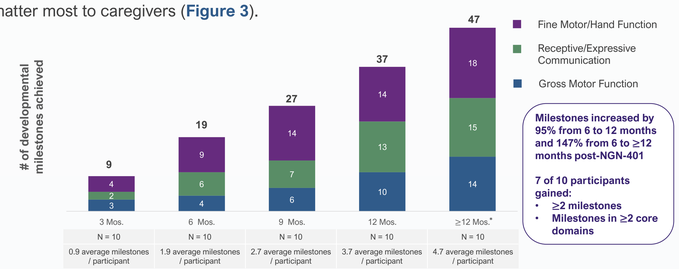


Figure 3. Developmental milestones increased by domain over time post-NGN-401

NGN-401 drove durable accumulation of multi-domain milestones across core domains that matter most to caregivers (**Figure 3**).



Four previously disclosed developmental milestones included are derived from other validated scales and are not included in the Embolden list: Pt.1 – Heel to toe walking – 9 mos.; Pt.2 – Bent down, touched floor and recovered – 9 mos.; Stepped off curb with help – 12 mos.; Pt.8 – Bent down, touched floor and recovered – 3 mos.
*n=6 participants with data > 12 mos. Post-NGN-401 and n=4 participants with 12-month data.

KEY CONCLUSIONS

1. 1E15 vg NGN-401 was generally well-tolerated.
2. NGN-401 was associated with durable, multi-domain developmental milestone gains that accrued and deepened over time for up to 30 months post NGN-401 with no signs of plateauing. The milestones were acquired in a developmentally ordered sequence, mirroring typical trajectory.
3. Real-world impacts of NGN-401 may include increased gains across daily living, increased independence, and reduced caregiver burden.
4. The results from the Phase 1/2 trial suggest potential disease-modifying activity in RTT.

RESTARTED DEVELOPMENTAL PROGRESSION LEADS TO REAL-WORLD IMPACT

- Evidence of developmental progression restarting is demonstrated in the four participants with the longest follow-up. Milestones developed in a sequential, coordinated developmental progression, as exemplified by Pt:1 and Pt:2 (**Figures 4a, 5a**). Coordinated gains across the key domains translated into greater independence and reduced caregiver burden (**Figures 4b, 5b, 6, 7**).

Figure 4a. Pt:1 developmental milestones

At baseline (Age 7):	Impaired hand use, raking, no ability to hold objects	Gross motor impairment, ataxic, unable to climb stairs	Severe communication impairment, unable to follow commands

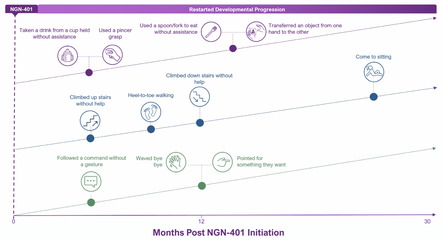


Figure 4b. Pt:1 real-world impact

Gets in/out of bathtub, on/off furniture, & up/down stairs, all without assistance
Shops with Mom, carrying the basket with both hands
Climbs in & out of the car & shuts the door herself
Carries her backpack, takes the stairs, & closes the door – following directions in two languages
Uses hands to select correct colors when asked
Waves hello to greet people on video calls

Figure 5a. Pt:2 developmental milestones

At baseline (Age 4):	Impaired hand use, unable to use hands	Gross motor impairment, ataxic, needs help to stand	Severe communication impairment, unable to follow commands

Figure 5b. Pt:2 real-world impact

Self-feeds & holds own drinks
Bends down to pick up toys & blankets without help
Turns when called, says words with meaning, & follows instructions

Figure 6. Pt:3 real-world impact

Follows directions in two languages and chooses the correct puzzle piece
Requires less physical support to stand and move
Self-feeds using a pincer grasp

Figure 7. Pt:4 real-world impact

Feeds herself with a regular spoon – easier, more independent mealtimes
Pushes herself up from lying down, moves through her day with more freedom
Turns the lights on and off herself, takes charge of her surroundings
Catches a ball with both hands and plays back-and-forth with others
Tells her caregiver what she wants more reliably using her communication device
Shares more moments with family, including giving "high fives"

References

1. Ross PD *et al*. *Sci Transl Med* 2025; 17 (792): eadq3614; PMID: 40173263. **2.** Neul JL *et al*. *Ann Neurol* 2010; 68 (6): 944–950; PMID: 21154482. **3.** Neul JL *et al*. *J Neurodev Disord* 2014; 6 (1): 20; PMID: 25071871. **4.** Einspieler C *et al. Neurosci Biobehav Rev* 2019; 98: 320–332; PMID: 30832924. 5. ClinicalTrials.gov NCT05898620. Available at https://clinicaltrials.gov/study/NCT05898620. Accessed June 2026. 6. Busner J *et al. Psychiatry (Edgmont)* 2007; 4 (7): 28–37; PMID: 20526405.

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