Early and Sustained Clinically Meaningful Gross Motor Improvements in a Phase 1/2 Study of NGN-401, a Novel Regulated AAV9 Gene Therapy, in Rett Syndrome

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Poster 14

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INTRODUCTION

- Rett syndrome (RTT) is an X-linked disorder occurring in 1 in 10,000 females globally and is caused by loss-of-function variants in the *MECP2* gene encoding MeCP2, a protein critical for normal function in the brain and nervous system.
  - Hallmark features include developmental regression, impaired gross motor function, and limited acquisition of complex motor skills.[1–4]
- Caregivers report that even modest gains in motor function can enhance patient autonomy, reduce complications, and ease caregiving burden.[2]
- 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 administered intracerebroventricularly for the treatment of Rett sydrome.[5]
- The data presented here show changes in gross motor function over time in participants who received NGN-401 in the Phase 1/2 trial.

METHODS

- The Phase 1/2 open-label trial (NCT05898620) in females with classic RTT, age ≥4, with a baseline Clinical Global Impression – Severity (CGI-S) score of 4–6, is evaluating the safety, tolerability, and efficacy of NGN-401.[6]
- 10 participants received 1E15 vg NGN-401 (age 4–10 cohort, n=8; age ≥11 cohort, n=2).
- The data cutoff was June 16, 2026, yielding a minimum of 12 months and up to 30 months of follow-up across the 10 participants.
- Gross motor function is assessed in 2 ways:
  - Through acquisition of developmental milestones based on the criteria in Embolden.[7]
  - The Rett Syndrome Gross Motor Scale (RSGMS),[8] a validated clinical tool assessing 15 gross motor tasks for RTT (**Figure 1**). Tasks are grouped into three subdomains – sitting, standing/walking, and challenge skills. A higher RSGMS score indicates better gross motor function (**Figure 1**).

Figure 1. The RSGMS assesses gross motor abilities

Assessing 15 Key Gross Motor Abilities
Evaluates movements ranging from sitting and standing to walking and "challenge" skills.

Higher Scores Indicate Better Function
A higher total score reflects ability to perform tasks with less physical assistance.

Increase in 3+ Points Signals Meaningful Improvement
An increase of 3+ points is considered a meaningful gain in motor ability.

Each of the 15 items is scored on a scale of 0–3, for a possible total score of 45

Score	0	1	2	3
Description	Maximal assistance*	Moderate assistance	Minimal assistance	No assistance

*Item is also scored 0 if a participant is unable to perform.

RSGMS analysis

- RSGMS testing was videotaped in clinic, and scores were assessed by central independent raters.
- Replicable and best attained scores were assessed relative to baseline, to account for variability across visits (e.g., fatigue, illness, attention, apraxia) and align with established responder frameworks in rare neurological diseases.[9–10]
- Reproducibility of best score was confirmed via ≥2 documented central ratings and/or centrally reviewed videos performed outside the assessment. Repeat confirmation was not required when the best score occurred at the most recent assessment as it was deemed an emergent skill.

Table 1. Phase 1/2 baseline participant demographics

Characteristic	All participants (N=10)
Age at dosing, years, range	4–18
Baseline CGI-S score*	4–6
Genetic variant severity	mild to severe
Time post-dosing	12–30 months
Baseline ambulatory status	Ambulatory: 60% Non-ambulatory: 40%

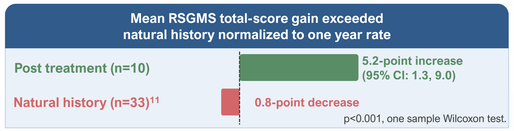
*Score of 4 indicates 'Moderately ill'; score of 5 indicates 'Markedly ill'; score of 6 indicates 'Severely ill'".
CGI-S, Clinical Global Impression – Severity scale.

RESULTS

- **Mean RSGMS score increased by 6 points**, from 20.5 (range 9–37) at baseline to 26.5 (range 13–42) post-treatment.
- When normalized to a one-year rate, NGN-401 treatment resulted in statistically significant gain vs. a decline in natural history (**Figure 2A**).
  - Ambulatory participants had a mean **8.3-point increase** in post-treatment total scores; non-ambulatory participants had a **2.5-point increase**.
  - Ambulatory participants demonstrated improvement across RSGMS fundamental and complex motor tasks (**Figure 2B**), while non-ambulatory participants had gains primarily in seated balance, standing duration, and sit to stand (**Figure 2C**).
  - **All participants** achieved independent sitting following treatment (**Figure 2B, 2C**).

Figure 2. RSGMS score improvements

A



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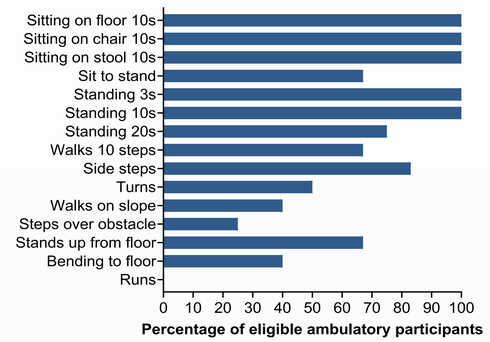

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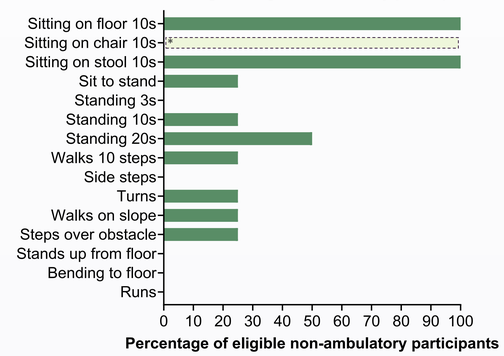


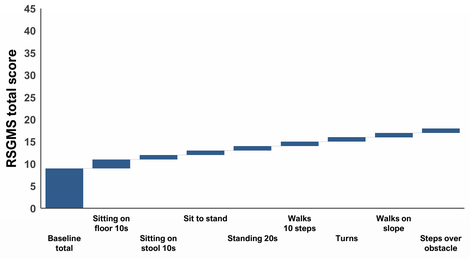
*All participants were able to complete this task with no assistance at baseline.
A gain is defined as a 1 point or more increase in the item from Baseline to any visit. Eligible participants are defined as those who could not perform with full independence at baseline.
RSGMS, Rett Syndrome Gross Motor Scale; S, seconds.

SAMPLE VIGNETTES

Total scores: Example responders below showed gains in strength, postural control, motor planning, and independence (Figures 3–5).

Figure 3. Pt:3 (non-ambulatory at baseline)

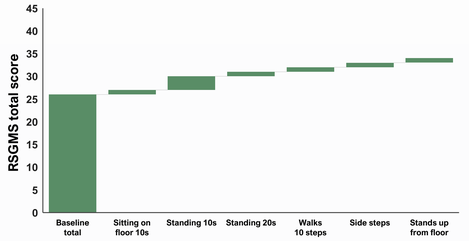
Increased functional mobility has led to substantially less support required for activities



Pt, participant; RSGMS, Rett Syndrome Gross Motor Scale; s, seconds.

Figure 4. Pt:10 (adolescent, ambulatory at baseline)

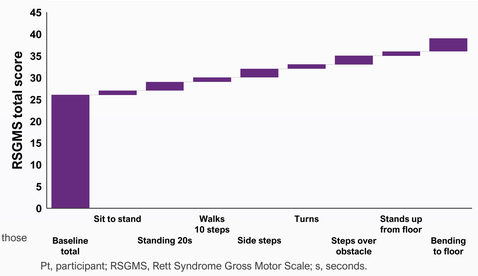
Advancement of functional mobility has led to greater independence



Pt, participant; RSGMS, Rett Syndrome Gross Motor Scale; s, seconds.

Figure 5. Pt:2 (ambulatory at baseline)

Acquired higher-order transitional skills and improved navigation of environment observed



Pt, participant; RSGMS, Rett Syndrome Gross Motor Scale; s, seconds.

KEY CONCLUSIONS

1. Treatment with NGN-401 resulted in a **mean RSGMS increase of 6 points**, representing a clinically meaningful improvement on a scale that declines over time in Rett syndrome natural history.[11–13]
2. **Skill gains followed a hierarchical pattern** tied to baseline status: **More advanced skills** in ambulatory participants and **core postural control improvements** in non-ambulatory participants.
3. Both groups showed transition skill gains, pointing to **enhanced motor planning, coordination, and execution, abilities typically impaired in RTT**.
4. RSGMS gains translated into **new functional skills, developmental milestone acquisition, and greater daily independence**, consistent with caregiver-defined clinically meaningful outcomes and a potential reduction in caregiver burden.[14]

TRANSITION SKILL GAINS

5/7 improved

SIT TO STAND: Gains reduce physical burden on caregiver and enhance independence

n=7 could not independently perform at baseline.

Pt:3: Sit to stand with less assistance

BASELINE: Non-ambulatory, required maximum support (RSGMS score = 0) to transition from sitting to standing and the support of 2 people to maintain standing

POST TREATMENT: Improved functional mobility, requiring only moderate assistance (RSGMS score = 1) for sit-to-stand transfers and the support from a single individual to maintain standing

5/6 improved

STANDS UP FROM FLOOR: Complex motor planning allows for greater autonomy and reduced caregiver physical burden

n=6 ambulatory participants could not independently perform at baseline.

2/5 achieved full independence

BENDING TO FLOOR: Enables picking up toys on own and exploring the world at ground level without help

n=5 ambulatory participants could not independently perform at baseline.

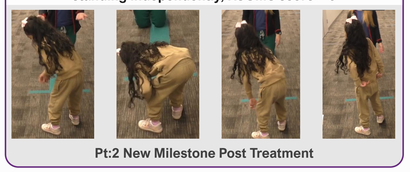
Pt:8: Standing up from floor independently RSGMS score = 3

Baseline: Ambulatory, needed moderate assistance to stand up from floor, RSGMS score = 1

Pt:8 New Milestone Post Treatment

Pt:2: Bends to floor and recovers to standing independently RSGMS score = 3

Baseline: Ambulatory, unable to bend to floor and recover to standing independently, RSGMS score = 0

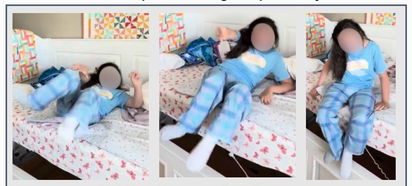


Pt:2 New Milestone Post Treatment

REAL-WORLD IMPACT

Pts:4, 7, 1: Real-world impact of improved gross motor function translates to increased participation in family routines

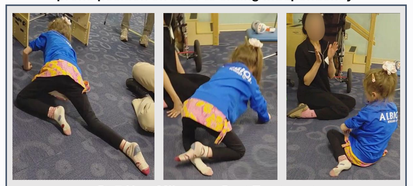
Baseline: Non-ambulatory, unable to transition from supine to sitting independently



Pt:4 New Milestone Post Treatment

Sitting up in bed independently: Self-initiated transitioning from supine to sitting up position on caregiver request; demonstrating motor planning, self-initiated routine, improved postural control, increased autonomy, and increased engagement with her surroundings.

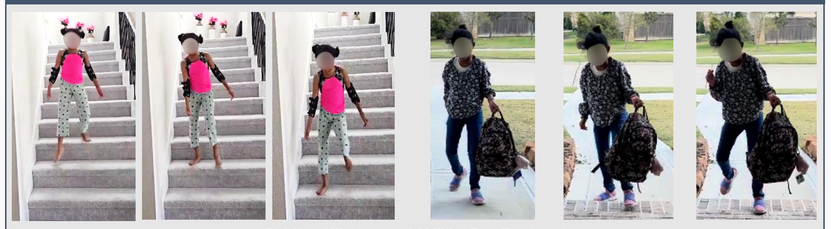
Baseline: Ambulatory, unable to transition from prone position on floor to sitting independently



Pt:7 New Milestone Post Treatment

Transition from lying to sitting independently: Self-initiated repositioning from the floor into sitting as caregiver applauds, demonstrating improved motor planning, postural control, increased autonomy, and increased engagement with her surroundings.

Pt:1: Baseline: Ambulatory, unable to ascend/descend stairs independently, impaired hand function, dropped items quickly



Pt:1 New Milestone and Abilities Post Treatment

Descending stairs independently: Autonomous navigation of stairs with appropriate motor planning, balance, and postural control as caregiver waits at the bottom, demonstrating safe and independent home mobility.

Coming home from school: Able to navigate walkway and stairs up to house while carrying school backpack; meaningful routine requiring complex motor planning, balance, grip strength, and functional independence.

Pt, participant.

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