



Poster #265

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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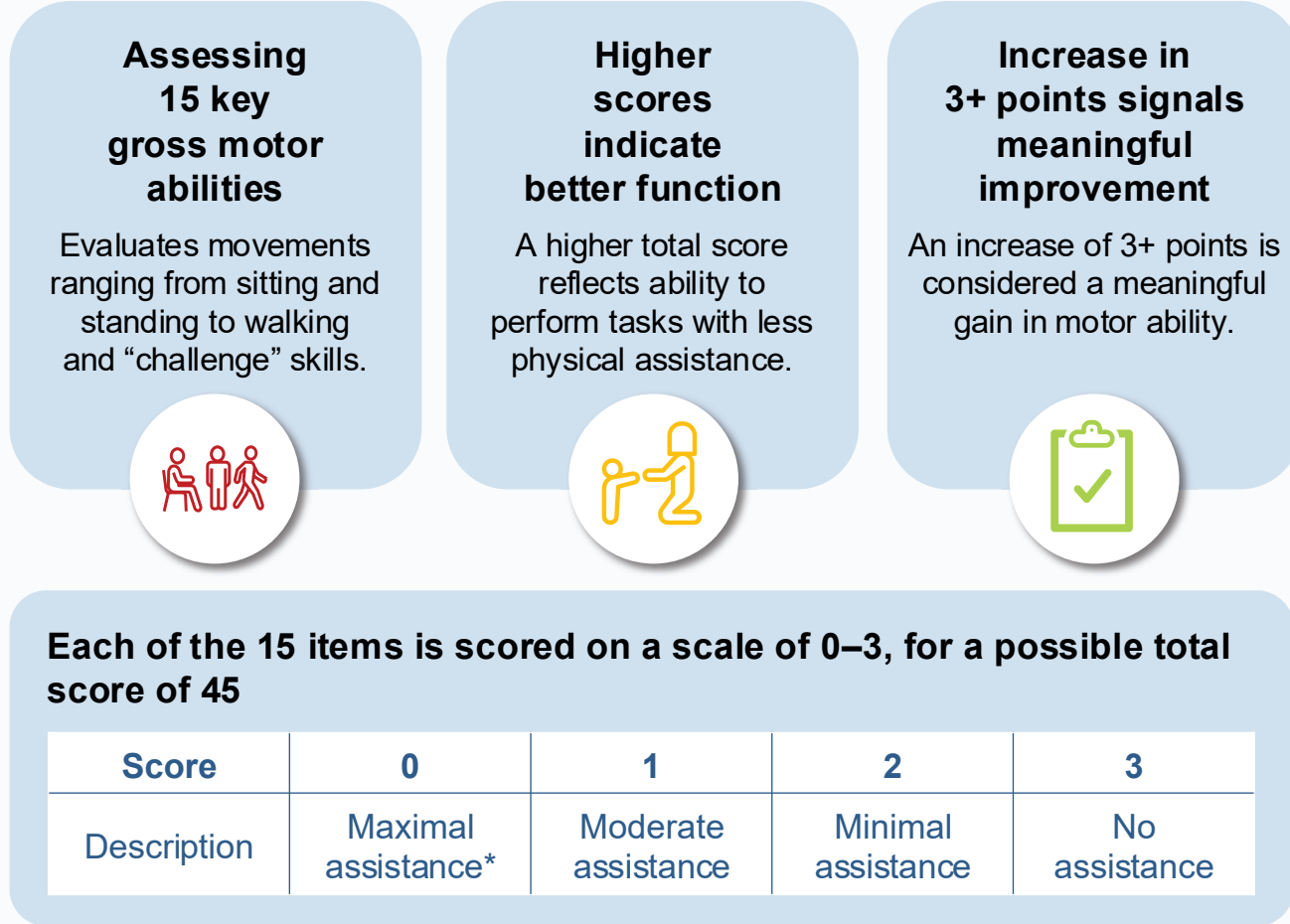
INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disorder caused by loss-of-function variants in the *MECP2* gene encoding MeCP2, a protein critical for normal function in the brain and nervous system.^{1,2}
 - 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.³
- 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 RTT.⁵
- The data presented here show improvement in gross motor function 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 was assessed in 2 ways:
 - Through acquisition of developmental milestones based on the criteria in the Embolden registrational trial evaluating NGN-401.⁷
 - 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. The RSGMS assesses gross motor abilities.



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%

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

References

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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 1-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**.
- Skill level improvement (Figure 2B and 2C) was assessed in eligible participants—those without full independence in that skill at baseline.
- 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 and 2C).

Figure 2. RSGMS score improvements.

