



# Leveraging Rett Syndrome Natural History and Caregiver Input to Assess Treatment Effects in Embolden™ Pivotal Trial of NGN-401



Poster #254

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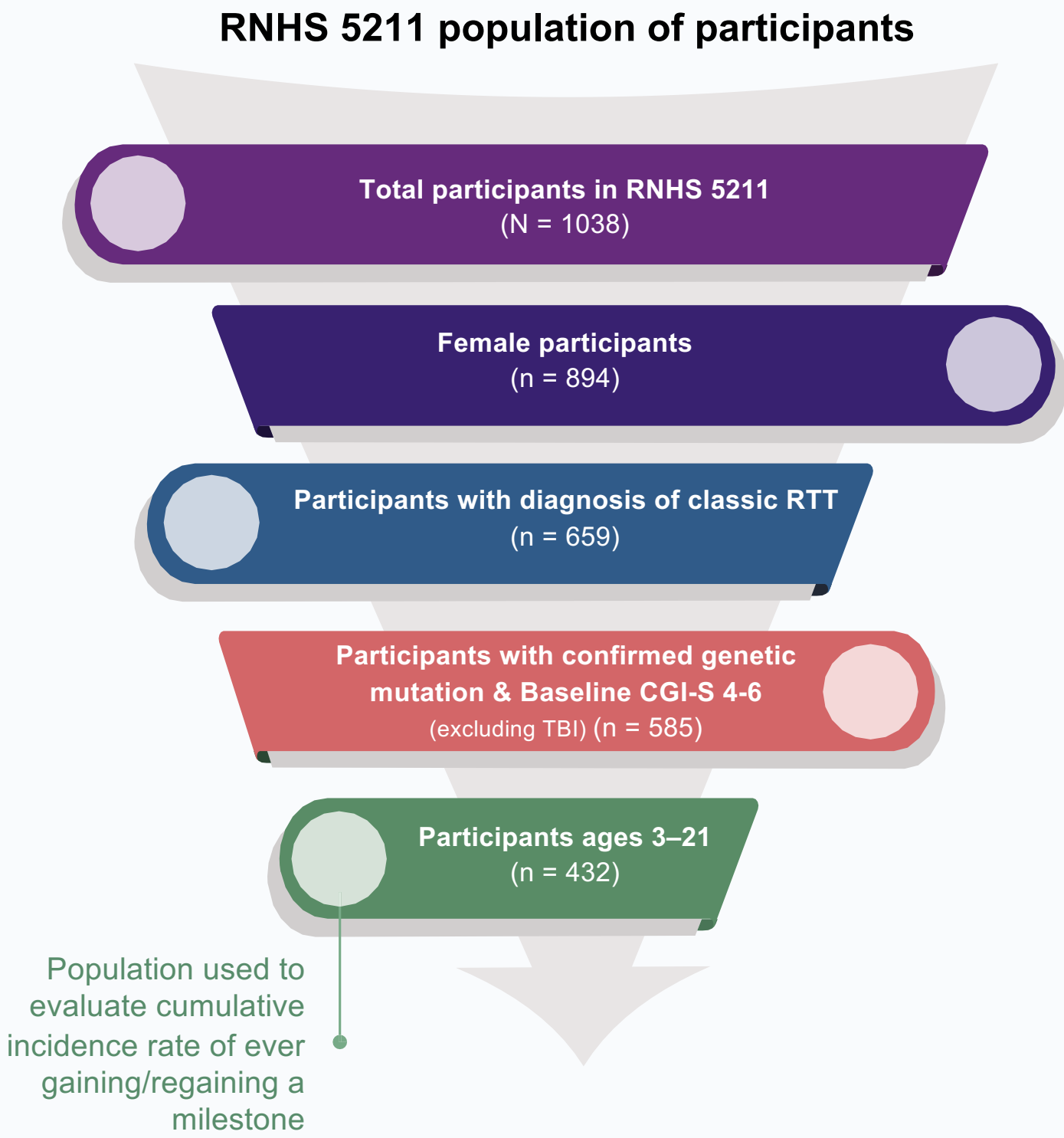
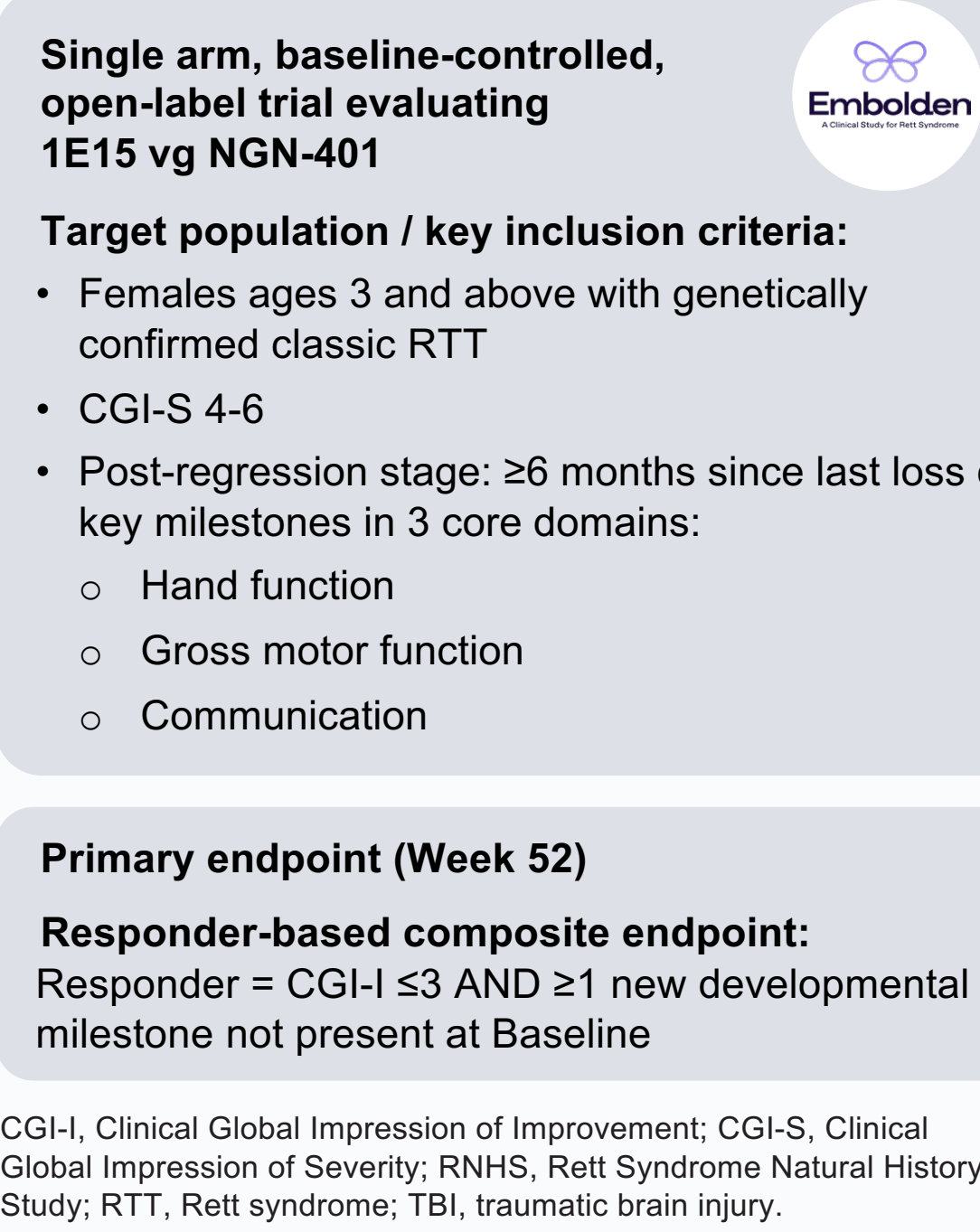
## INTRODUCTION

- 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.<sup>1,2</sup>
- RTT is defined by a period of early childhood development, then regression of developmental milestones and severe impairment of communication, hand function, and gross motor function.<sup>1-3</sup>
- 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.<sup>4</sup>
- To assess NGN-401 effects in the Embolden™ registrational trial, we identified developmental milestones that would be clinically meaningful if gained and that are not expected to be gained at age ≥3 years (regression typically complete),<sup>5</sup> the lower age of eligibility in the Embolden trial.

## METHODS

- In the NIH-sponsored 5211 Rett Syndrome Natural History Study (RNHS), matched to the Embolden inclusion criteria (Figure 1), we estimated cumulative incidence rates of gaining/regaining a developmental milestone.
- 30 caregivers of females with RTT rated the meaningfulness of developmental milestones in the Rett Caregiver Voice Survey.
- Caregivers completed an online quantitative survey to indicate the meaningfulness of acquiring different developmental milestones after treatment.
- Together these defined a pre-specified list of 28 clinically meaningful developmental milestones for the Embolden trial's primary endpoint.

**Figure 1.** RNHS subjects matched to Embolden registrational trial key inclusion/exclusion criteria.



## RESULTS

- Participants in the RNHS show that milestone gains concentrate in early childhood. The likelihood of gaining a milestone at ≥3 years of age is extremely low (Figure 2).
- 28 low-incidence milestones rated meaningful by caregivers were chosen for the Embolden Milestone List (Figure 3).
- Participants in the Phase 1/2 study (Figure 4) demonstrate the rarity of gains in developmental milestones on the Embolden Milestone List.

**Figure 2.** Clinically meaningful gains concentrate before age 3 years and stay low at age ≥3 years, with little difference at age ≥6 years.

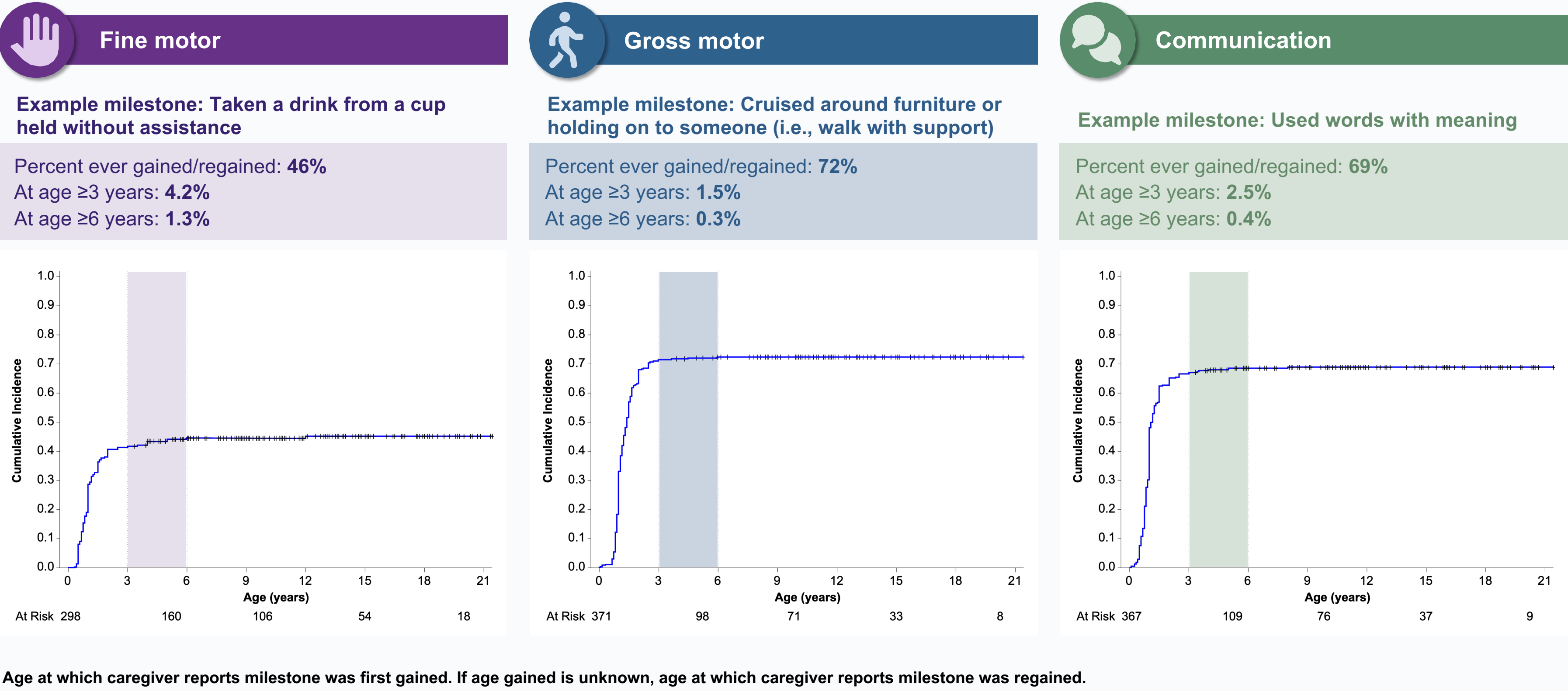
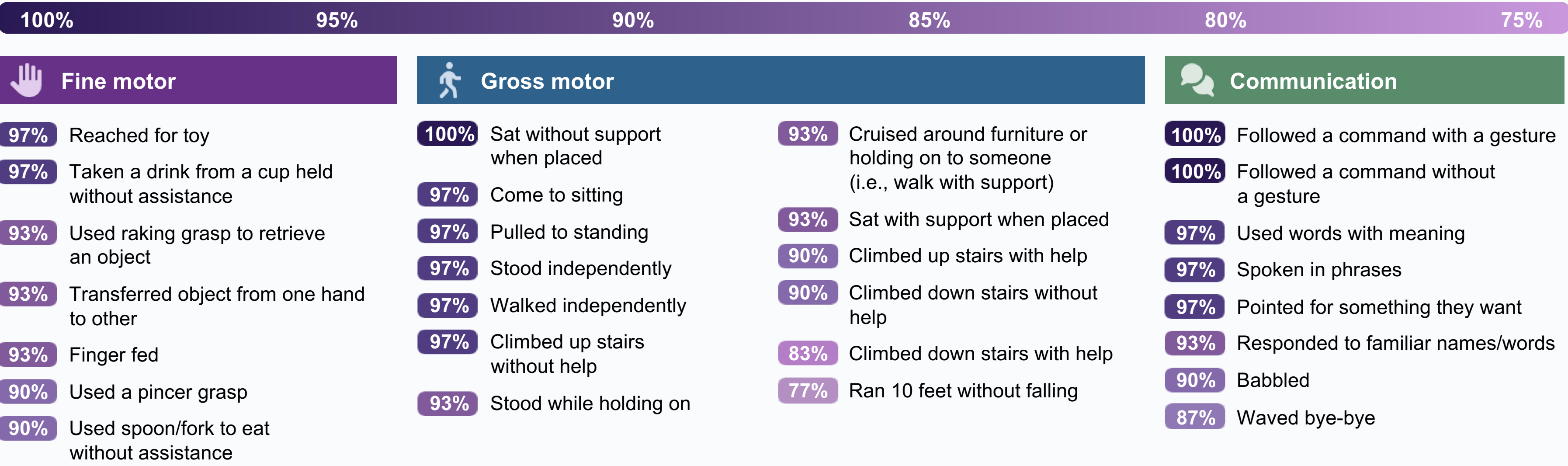


**Figure 3.** Caregivers rated the acquisition of 28 developmental milestones as clinically meaningful.

Caregivers indicating milestone is meaningful (%).



## KEY CONCLUSIONS

- In Rett syndrome, clinically meaningful developmental gains are rare at/after age 3. Across all 28 milestones, the rate of gaining or regaining a skill stays low from age 3 and beyond.
- NGN-401–treated participants gained multiple milestones – a pattern not seen in natural history.
  - Each milestone is rarely gained after age 3, and gaining several in one participant is exceedingly rare at any age.
  - The same was observed in older children and adolescents, where natural history gains are rarest – supporting a treatment effect.

### References

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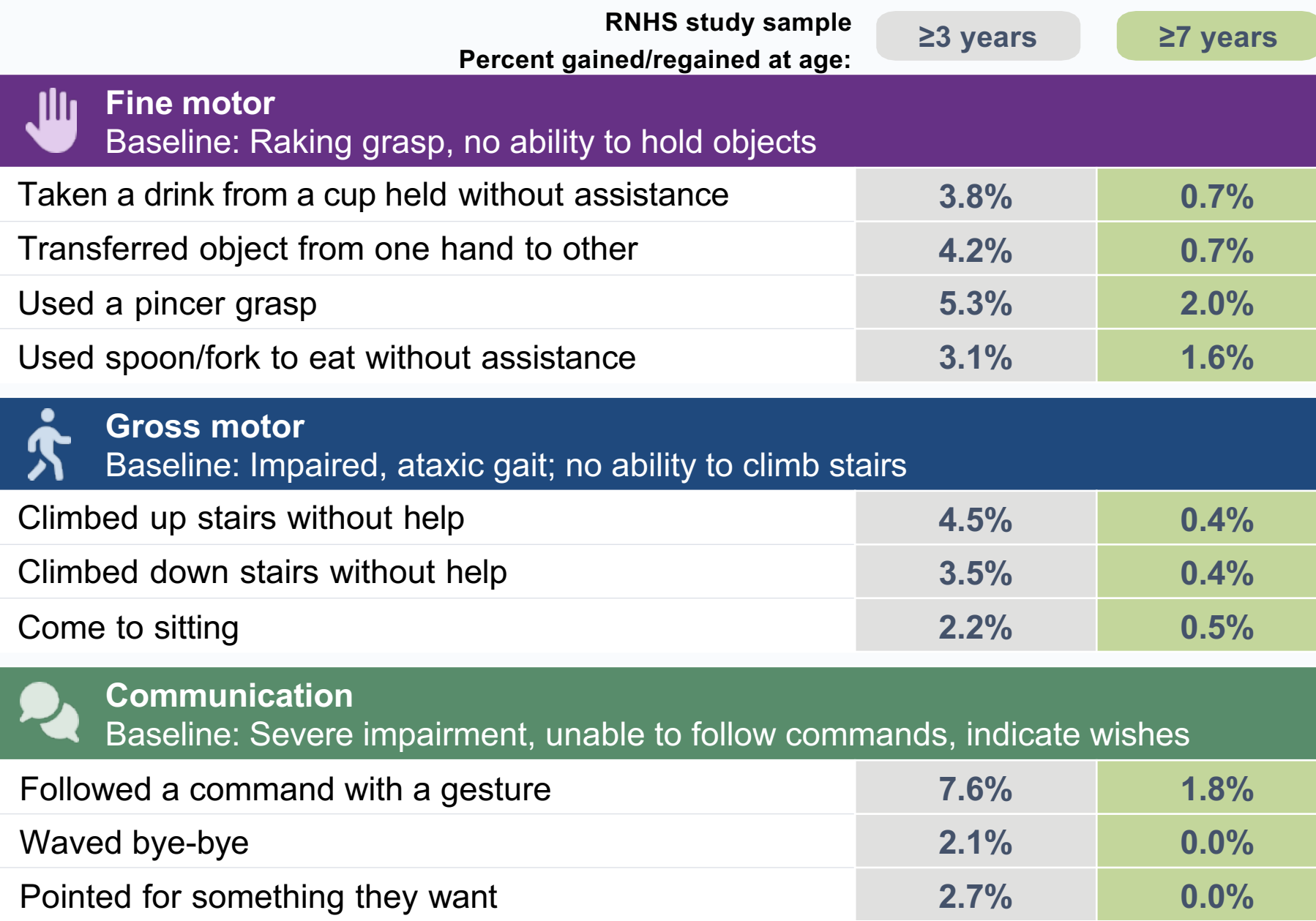
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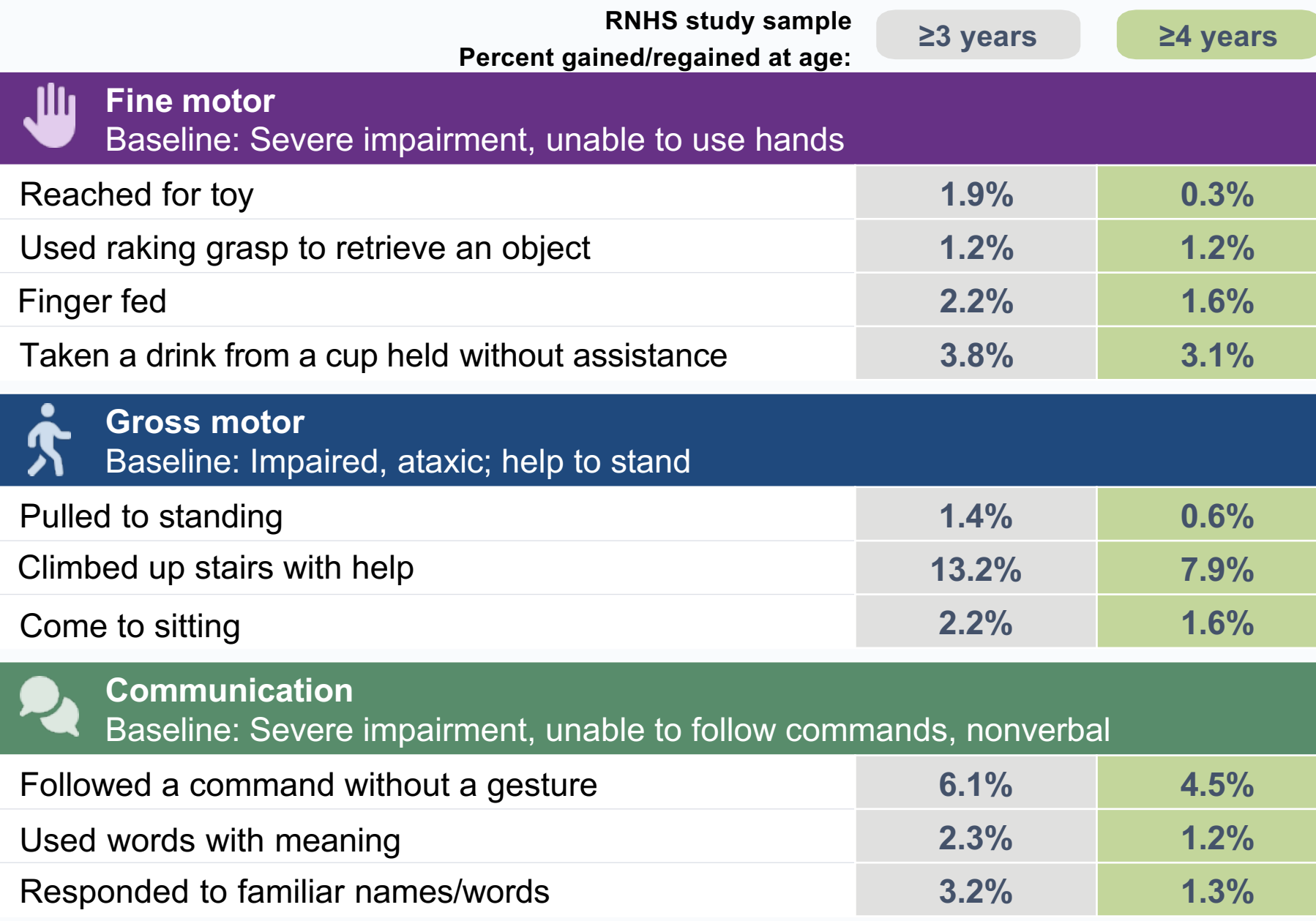
**Figure 4.** In the Phase 1/2 study, multiple developmental milestone gains from the Embolden Milestone List were observed; gains occurred across individually low-incidence milestones at the relevant age.

- Treated participants gained multiple milestones. Each gain is individually low-incidence in age-matched natural history, and multiple gains in any participant are exceedingly rare.

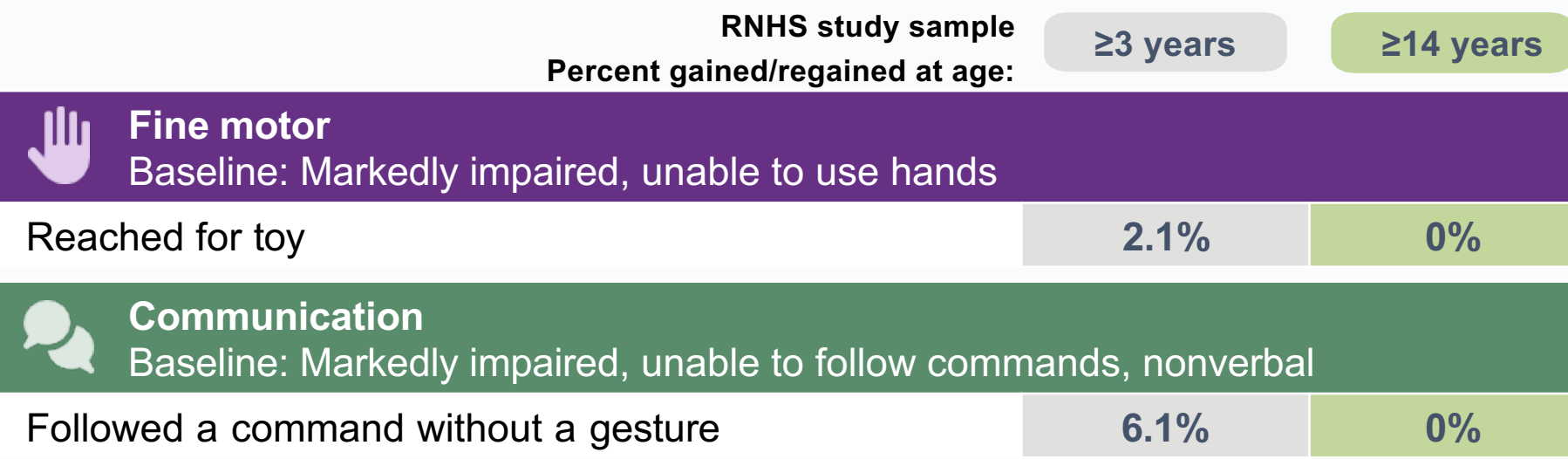
A. Pt:1 >6 years old gained 10 developmental milestones on the Embolden Milestone List (7 years old at Baseline).



B. Pt:2 <6 years old gained 10 developmental milestones on the Embolden Milestone List (4 years old at Baseline).



C. Pt:10 Adolescent 14 years old gained 2 developmental milestones on the Embolden Milestone List.



Pt, participant; RNHS, Rett Syndrome Natural History Study.