



# From Baseline Impairment to Progressive Developmental Gains Across Motor and Communication Domains After Treatment With NGN-401 in Phase 1/2 Trial for Rett Syndrome



Poster #288

Bernhard Suter<sup>1</sup>, Timothy A. Benke<sup>2</sup>, David Lieberman<sup>3</sup>, Elizabeth Berry-Kravis<sup>4</sup>, Jeffrey L. Neul<sup>5</sup>, Jenny Downs<sup>6</sup>, Melissa Licari<sup>6</sup>, Alana Salvucci<sup>7</sup>, Julie Jordan<sup>7</sup>, Christine Mikail<sup>7</sup>

<sup>1</sup>Departments of Pediatrics & Neurology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA; <sup>2</sup>Department of Pediatrics-Neurology, Children's Hospital of Colorado, Anschutz Medical Campus, University of Colorado School of Medicine, Aurora, CO, USA; <sup>3</sup>Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; <sup>4</sup>Departments of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center, Chicago, IL, USA; <sup>5</sup>Department of Pediatrics-Neurology, Monroe Carell Jr. Children's Hospital at Vanderbilt, Vanderbilt University Medical Center, Nashville, TN, USA; <sup>6</sup>The Kids Research Institute Australia, Centre for Child Health Research, The University of Western Australia, Perth, WA, Australia; <sup>7</sup>Neurogene Inc., New York, NY, USA.

medicalinfo@neurogene.com

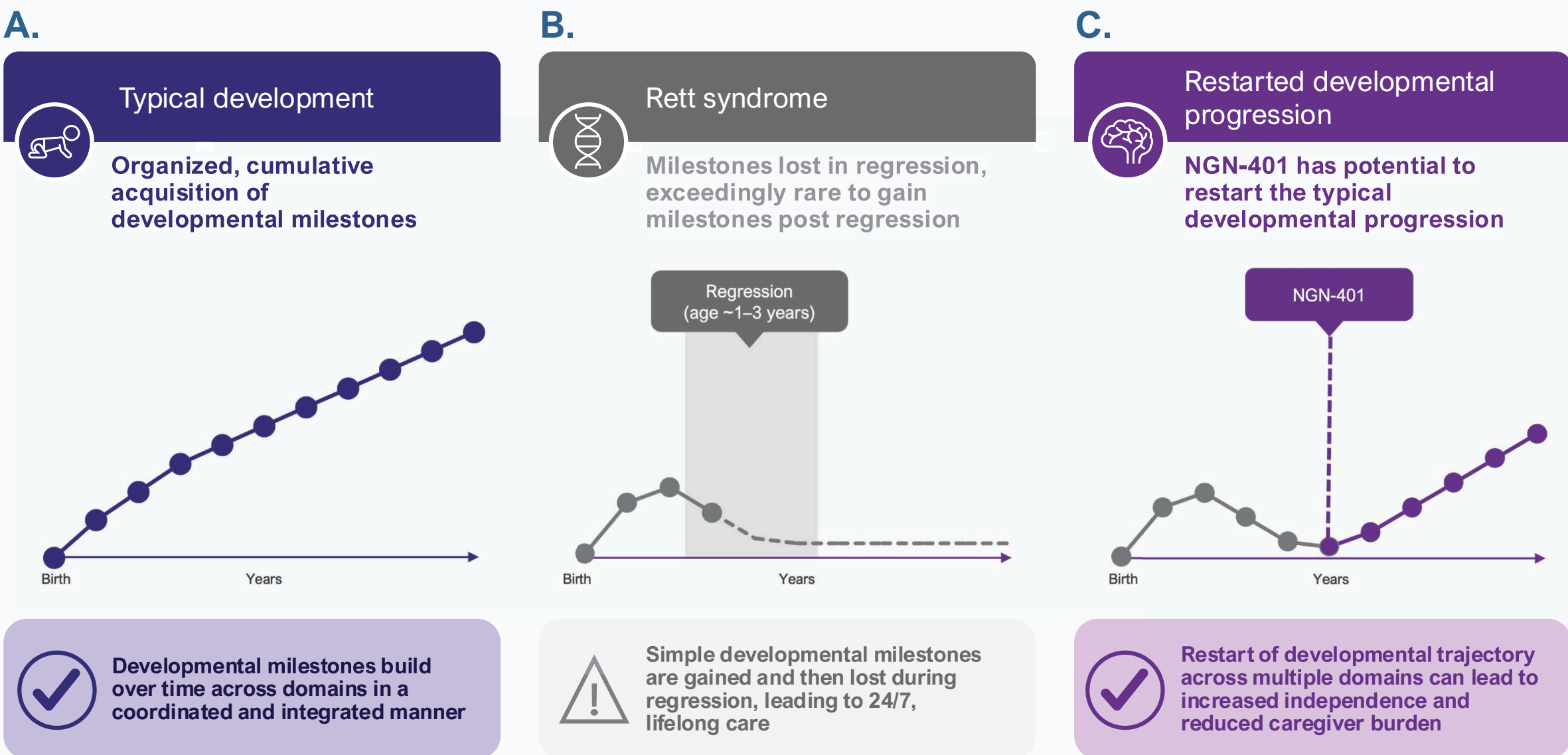
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## INTRODUCTION

- 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.<sup>1</sup>
- Typical development follows a predictable sequence in which milestones are acquired in a consistent order across fine motor, gross motor, and communication domains, and standardized developmental surveillance instruments are constructed on this ordered structure (**Figure 1A**).<sup>2,3</sup>
- Within each domain, skills build hierarchically, with earlier milestones serving as prerequisites for more advanced ones (e.g., raking grasp precedes pincer grasp; independent sitting precedes pulling to stand and independent ambulation).<sup>3,4</sup>
- RTT is characterized by regression of acquired developmental milestones and severe impairments in fine motor skills, gross motor abilities, and communication; following regression, spontaneous acquisition of new developmental milestones and reacquisition of lost milestones at  $\geq 3$  years of age are extremely rare (**Figure 1B**).<sup>5-7</sup>

- NGN-401 is an investigational adeno-associated virus 9 (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.<sup>1</sup>
- Here, we evaluated whether NGN-401-treated participants with the longest follow-up in the Phase 1/2 trial acquire milestones in a developmentally ordered, progressive manner, similar to typical developmental trajectory.

**Figure 1. Restarting developmental progression is the goal for a one-time gene therapy.**



Frankenburg WK et al. *Pediatrics*. 1992; 89 (1): 91-97 and May D et al. *J Neurodev Disord*. 2024; 16 (1): 42. Graphs for illustrative purposes only.

## RESULTS

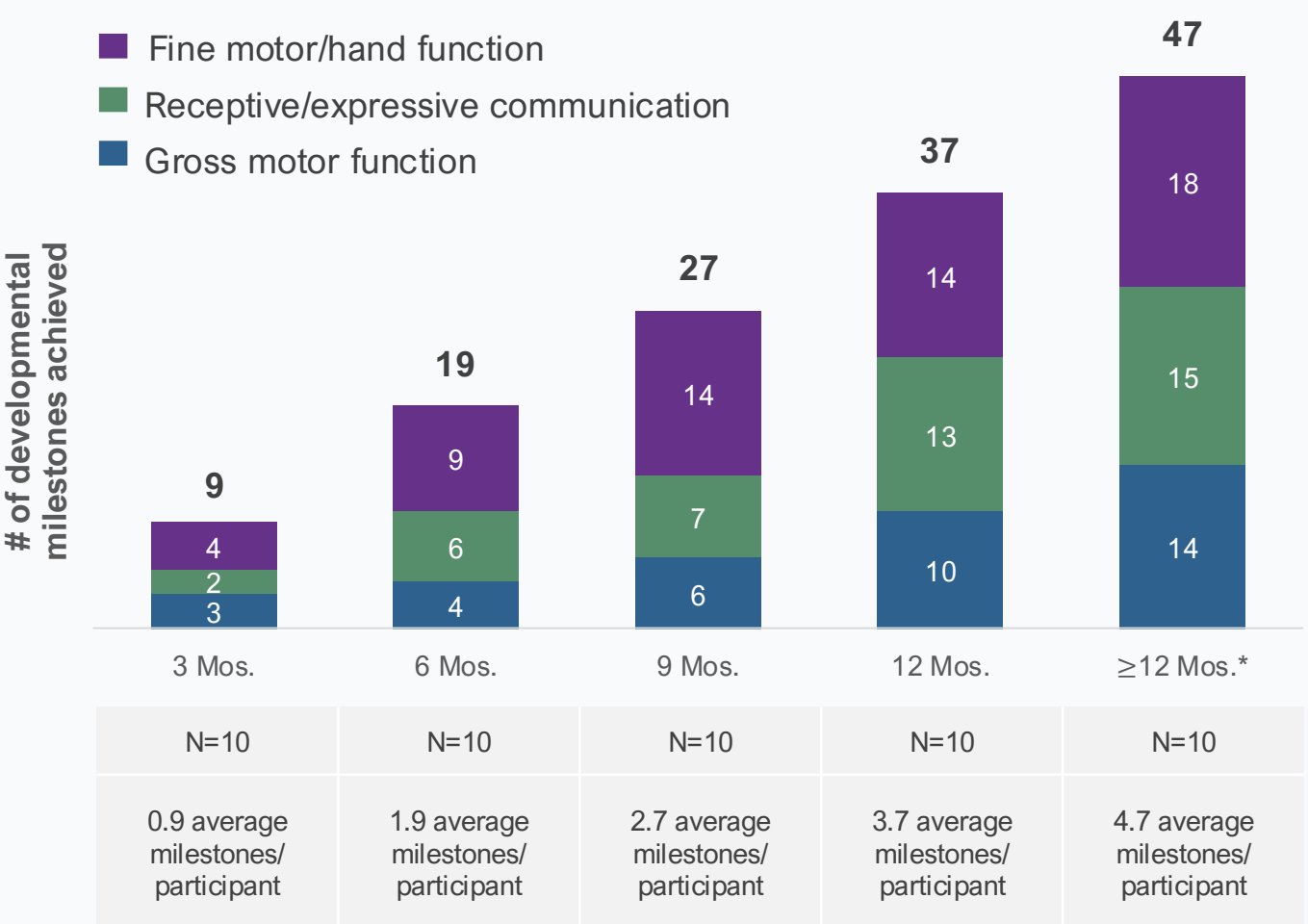
### Baseline characteristics

- 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.
  - Among these, the four participants with longest follow-up (Pt:1-4) were 4-7 years of age at dosing, with baseline CGI-S scores of 4-5 (moderately to markedly ill) and genetic variant severity ranging from mild to severe.

### Efficacy

- 100% of participants gained  $\geq 1$  developmental milestone and improved on CGI-H.
- NGN-401 achieved a rapid response post treatment with a median time to first response of 2 months that deepened over time.
- 47 total milestones gained; 4.7 avg milestones gained per participant.
  - NGN-401 drove durable accumulation of multi-domain milestones across core domains that matter most to caregivers (**Figure 3**).

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



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.  
Mos., months.

### Safety

- NGN-401 remains generally well tolerated at the 1E15 vg dose level in the Phase 1/2 trial.
- All treatment-emergent adverse events (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 (**Table 1**).
  - Most common related TEAEs: Mild ALT/AST elevation.

- No new treatment-related serious adverse events (SAEs) reported since last data cutoff date (October 2025).
  - Two previously disclosed Grade 2 SAEs in Pt:5 resolved.
- No cases of hemophagocytic lymphohistiocytosis (HLH).
- No intracerebroventricular (ICV) procedure-related adverse events.
- No signs or symptoms of MeCP2 overexpression.
- Seizures have remained well controlled following NGN-401.

**Table 1. Safety data.**

| Phase 1/2 trial                    | 1E15 vg dose<br>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      |

### Restarted developmental progression leads to real-world impact

- Evidence of developmental progression restarting was 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**).
- All four participants (age 4-7 years) demonstrated stepwise acquisition of developmentally higher skills relative to baseline with durability across follow-up.

**Figure 4a. Pt:1 developmental milestones.**

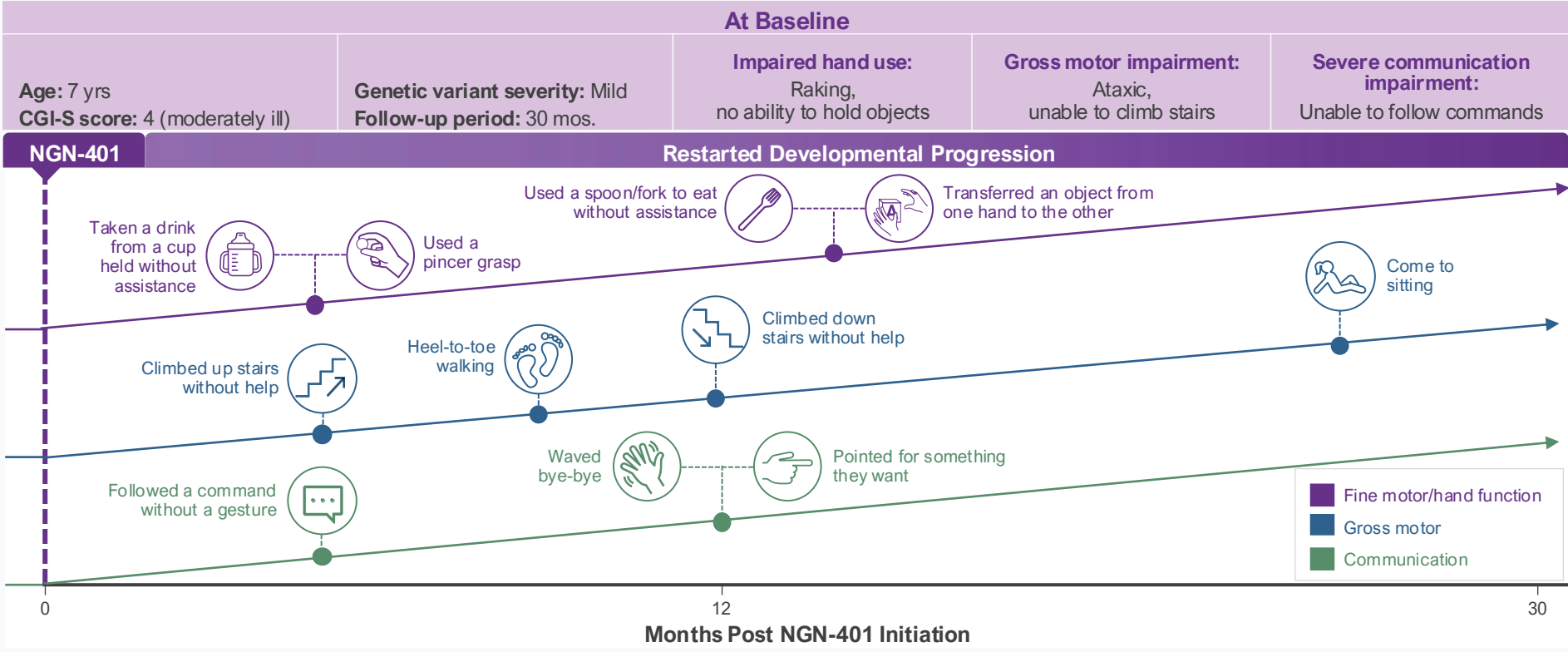
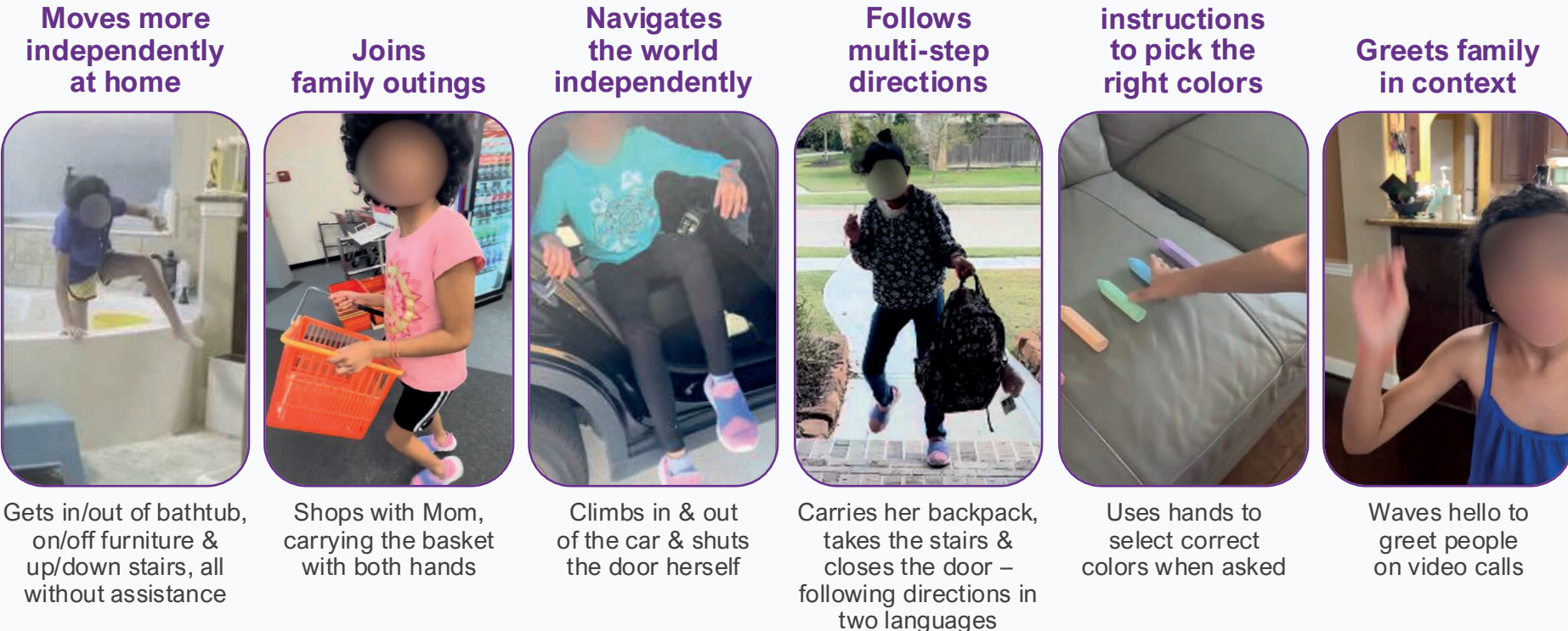


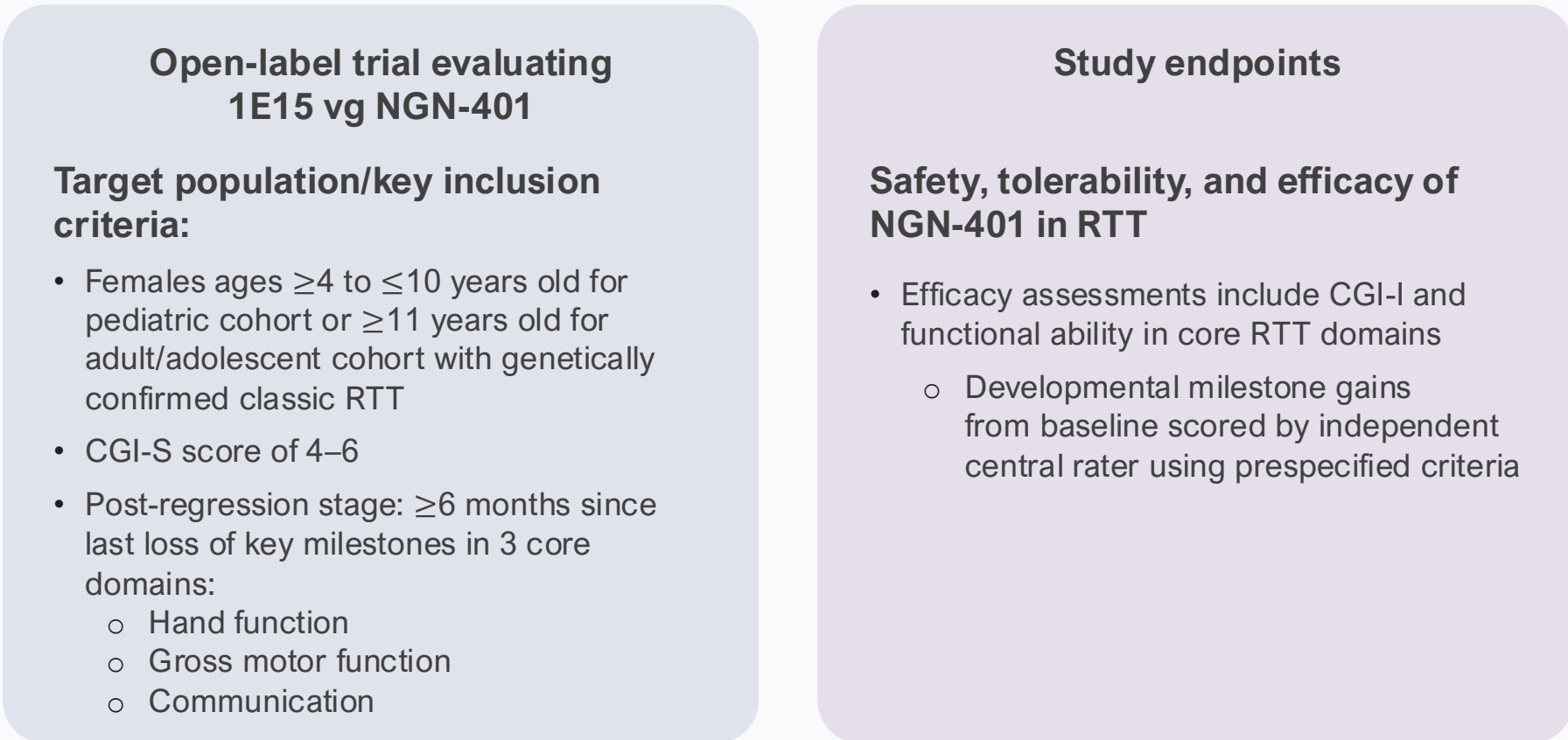
**Figure 4b. Pt:1 real-world impact.**



## 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 2**).<sup>9</sup>

**Figure 2. Phase 1/2 study design.**



CGI-I, Clinical Global Impression - Improvement; CGI-S, Clinical Global Impression - Severity.

- Milestone acquisition across fine motor, gross motor, and communication was assessed longitudinally in four participants treated with NGN-401 with longest follow-up (through 30 months) in the Phase 1/2 trial. Data cut as of June 16, 2026.
- Developmental milestones were confirmed to be absent at baseline (medical history, caregiver report, video) with gains from baseline documented in caregiver and CGI videos scored via independent central rating.
- Milestones were interpreted within a hierarchical developmental ladder.

**Figure 5a. Pt:2 developmental milestones.**

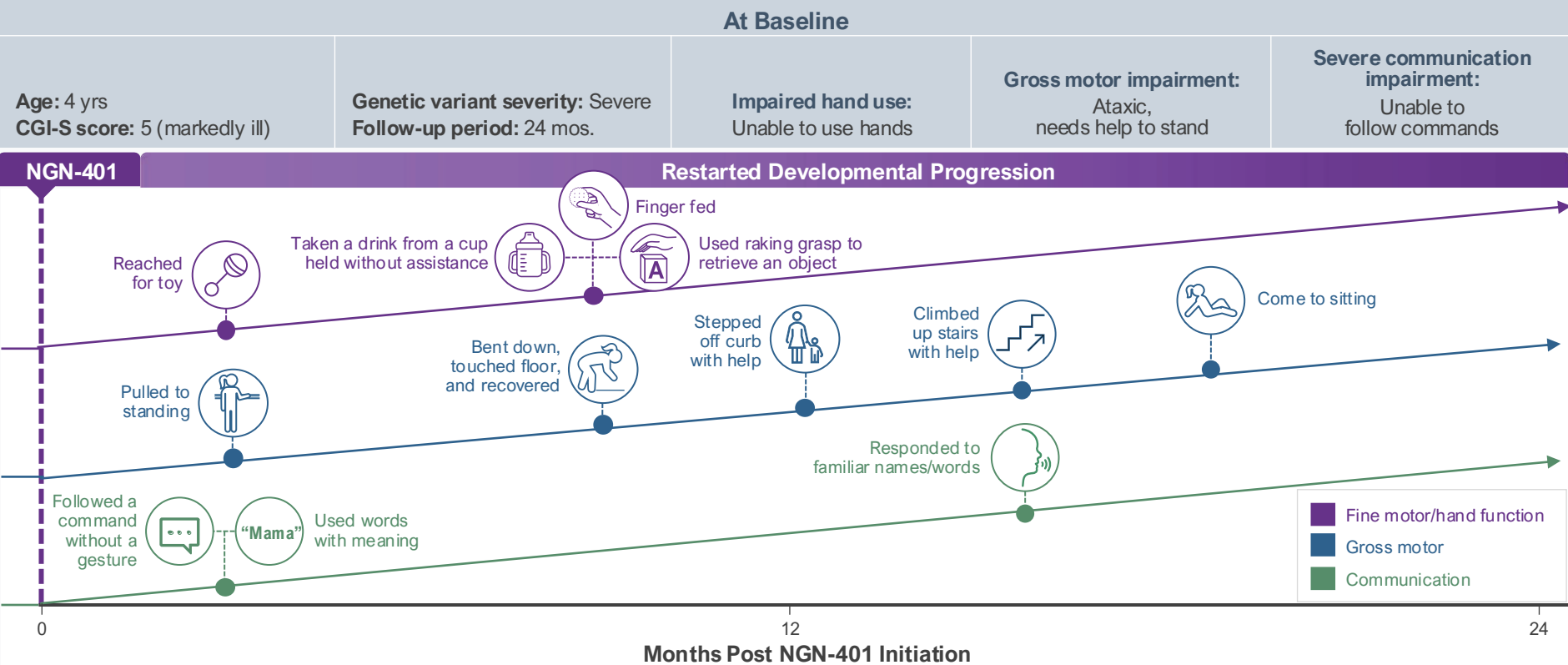


**Figure 5b. Pt:2 real-world impact.**

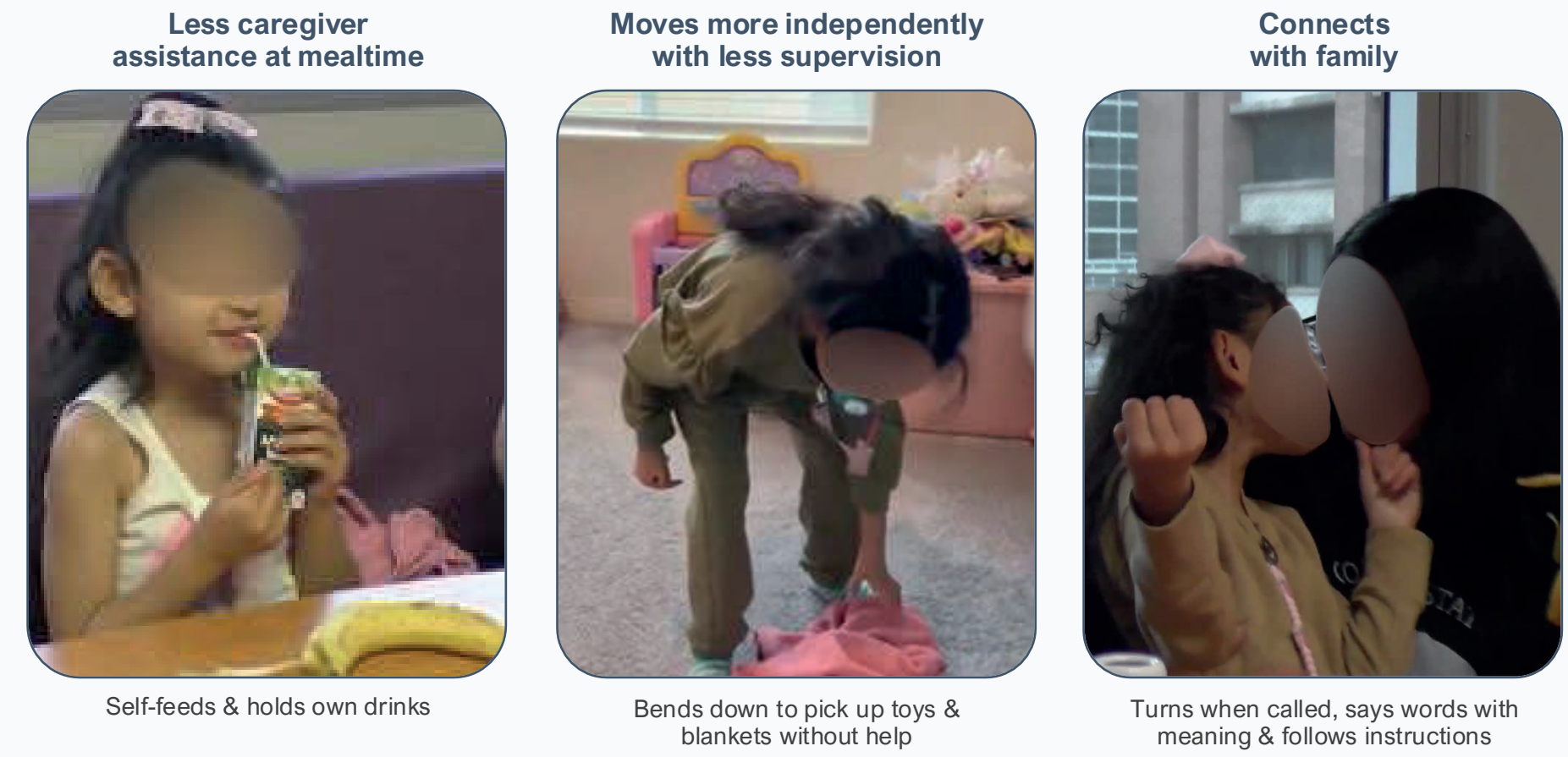


**Figure 6. Pt:3 real-world impact.**

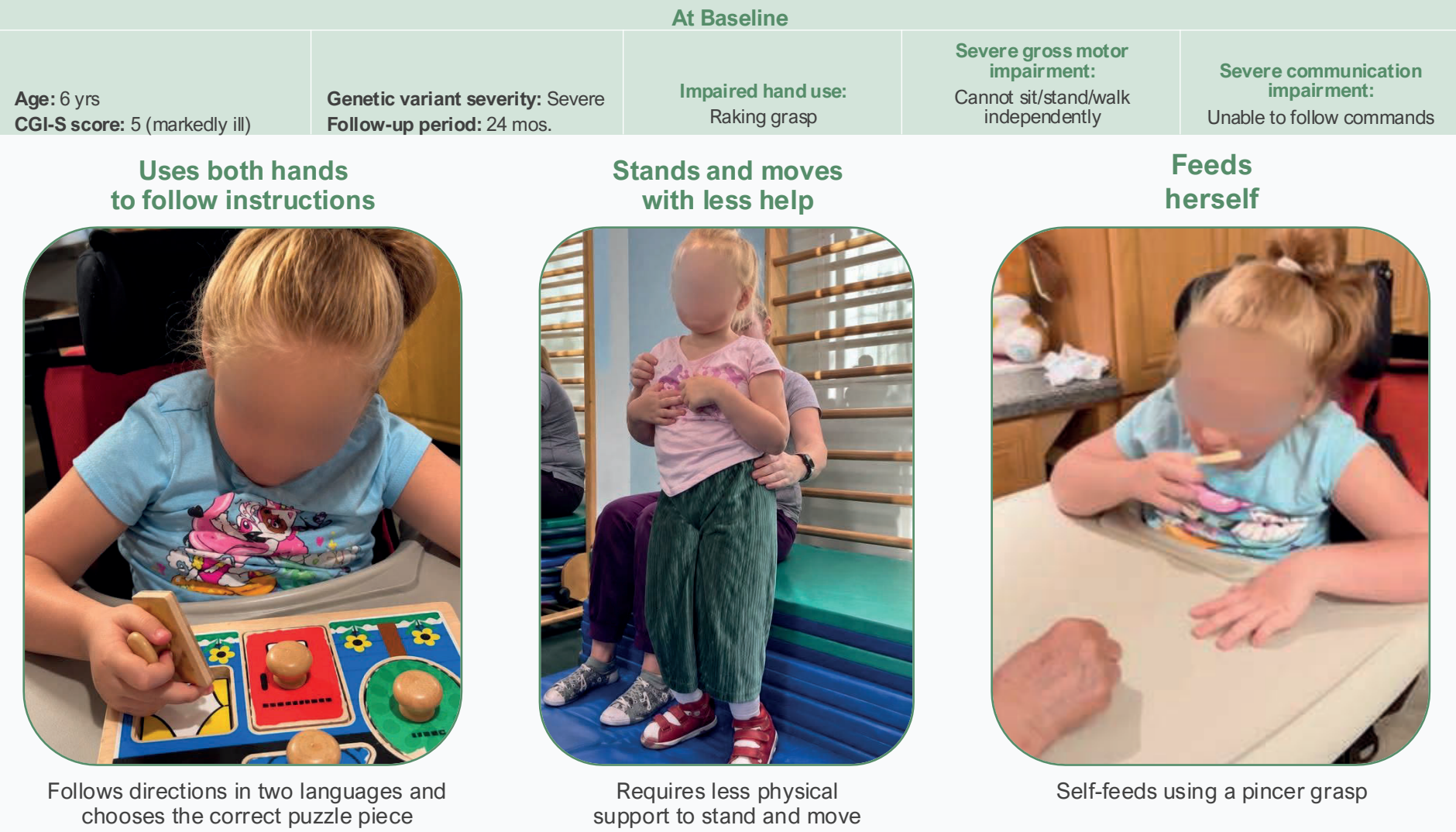


**Figure 7. Pt:4 real-world impact.**



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