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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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Disclosures

Dr. Elizabeth Berry-Kravis

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Rett Syndrome: Rare, Debilitating, Progressive, Neurodevelopmental Disorder



Cause: Variants in the *MECP2* gene on the X chromosome lead to deficiency of functional MeCP2 protein¹

- MeCP2 is a DNA-binding protein essential for normal brain and nervous system function²

Onset: Developmental delay occurs at 6–18 months, followed by loss of previously acquired milestones during regression and subsequent developmental plateau at ~3 years³

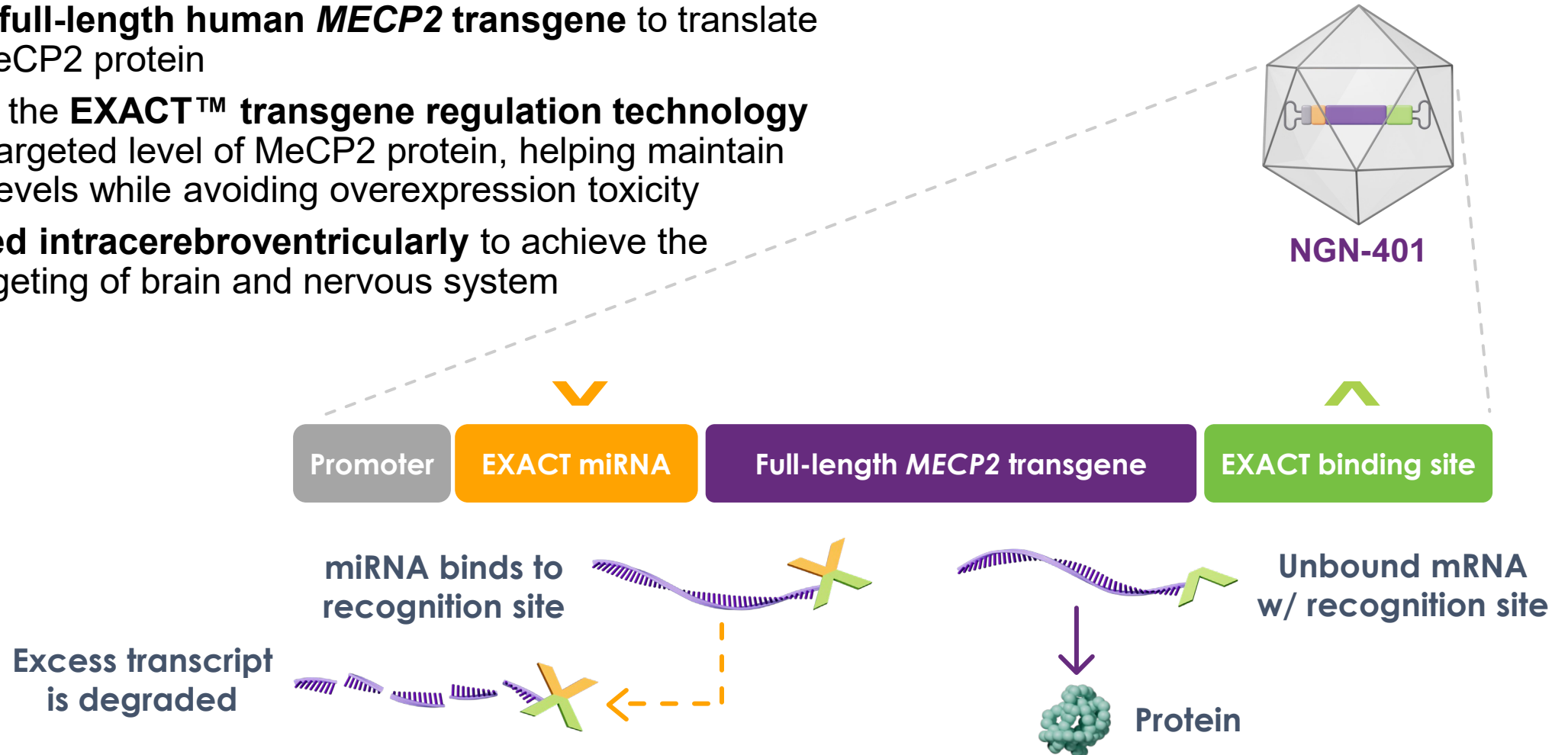
Hallmark features^{4,5}:

- Loss of expressive and receptive communication
- Loss of purposeful hand function with repetitive movements
- Gait abnormalities and mobility challenges
- Seizures, breathing irregularities, severe constipation

1. Amir RE *et al.* *Nat Genet* 1999; 23 (2): 185–188. 2. Gold WA *et al.* *Nat Rev Dis Primers* 2024; 10 (1): 84. 3. Amoako AN *et al.* *J Appl Res Intellect Disabil* 2020; 33 (5): 808–827. 4. Neul JL *et al.* *Ann Neurol* 2010; 68 (6): 944–950. 5. Smeets EE *et al.* *Mol Syndromol* 2012; 2 (3–5): 113–127.
MECP2, methyl-CpG binding protein 2.

NGN-401 is an Investigational AAV9 Gene Therapy in Development for Rett Syndrome

- Delivers the **full-length human *MECP2* transgene** to translate functional MeCP2 protein
- Incorporates the **EXACT™ transgene regulation technology** to deliver a targeted level of MeCP2 protein, helping maintain therapeutic levels while avoiding overexpression toxicity
- **Administered intracerebroventricularly** to achieve the broadest targeting of brain and nervous system



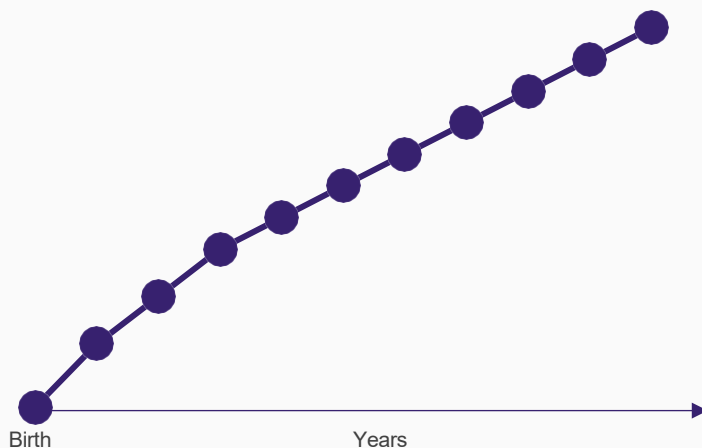
NGN-401 is investigational and has not been approved by any regulatory authority.

Restarting Developmental Progression Is the Goal for a One-time Gene Therapy



Typical Development

Organized, cumulative acquisition of developmental milestones

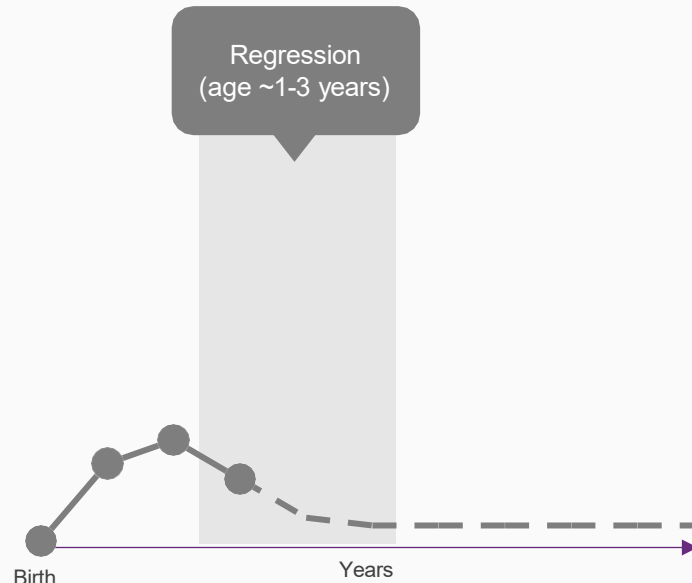


Developmental milestones build over time across domains in a coordinated and integrated manner¹



Rett Syndrome

Milestones lost in regression, exceedingly rare to gain milestones post-regression

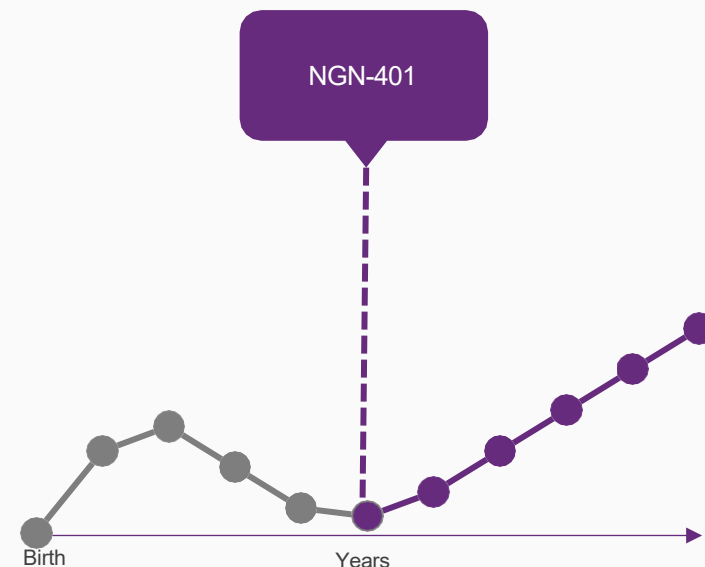


Simple developmental milestones are gained and then lost during regression, leading to 24/7, lifelong care²



Restarted Developmental Progression

NGN-401 has potential to restart the typical developmental progression



Restart of developmental trajectory across multiple domains can lead to increased independence and reduced caregiver burden

Graphs for illustrative purposes only.

1. Frankenburg WK *et al.* Denver II. Denver Developmental Materials, Inc.; 1992. 2. May D *et al.* *J Neurodev Disord* 2024; 16 (1): 42.

NGN-401 Clinical Study Design for Treatment of Rett Syndrome

Phase 1/2 converted into a single registrational study

Study Design

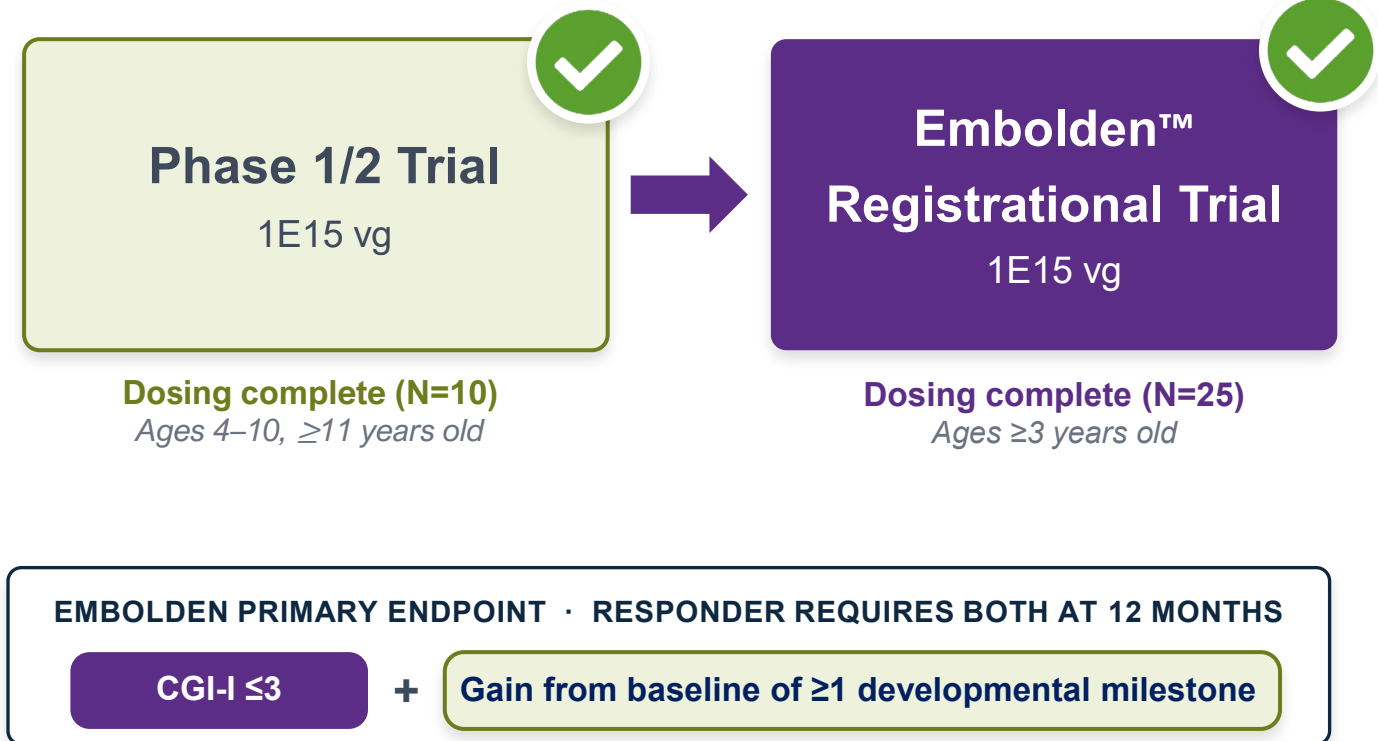
- Baseline-controlled, open-label, multicenter, single-arm pivotal trial (13 US sites)
- Evaluates efficacy, safety & tolerability of one-time ICV-delivered NGN-401

Population Eligibility Criteria

- Females with genetically confirmed classic Rett syndrome
- Post-regression (≥ 6 months since last skill loss); CGI-S 4–6 at screening

Key Clinical Assessments

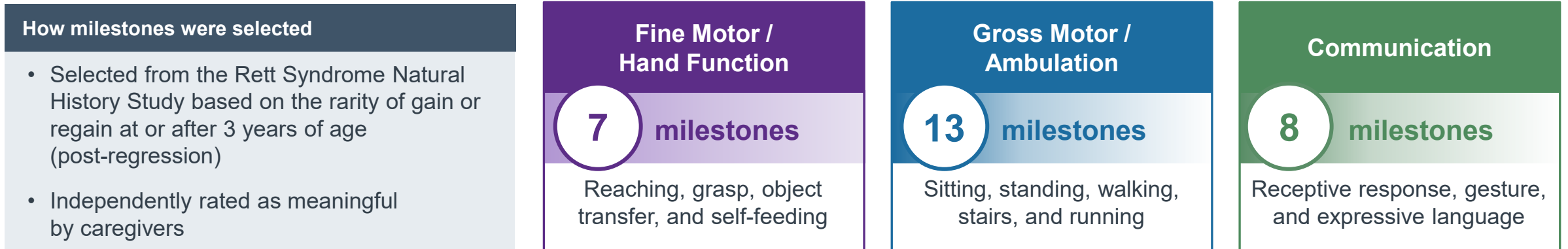
- CGI-I and CGI-S with Rett-specific anchors
- Developmental milestones
- RSGMS and RSHFS



Participants enrolled in the Phase 1/2 study spanned pediatric, adolescent, and adult age groups (4–18 years) and represented a broad range of clinical (CGI-S 4–6, moderate to severe) and genetic variant (mild to severe) severity

Rigorous Embolden Milestone Criteria Evaluation Applied to Phase 1/2 Data

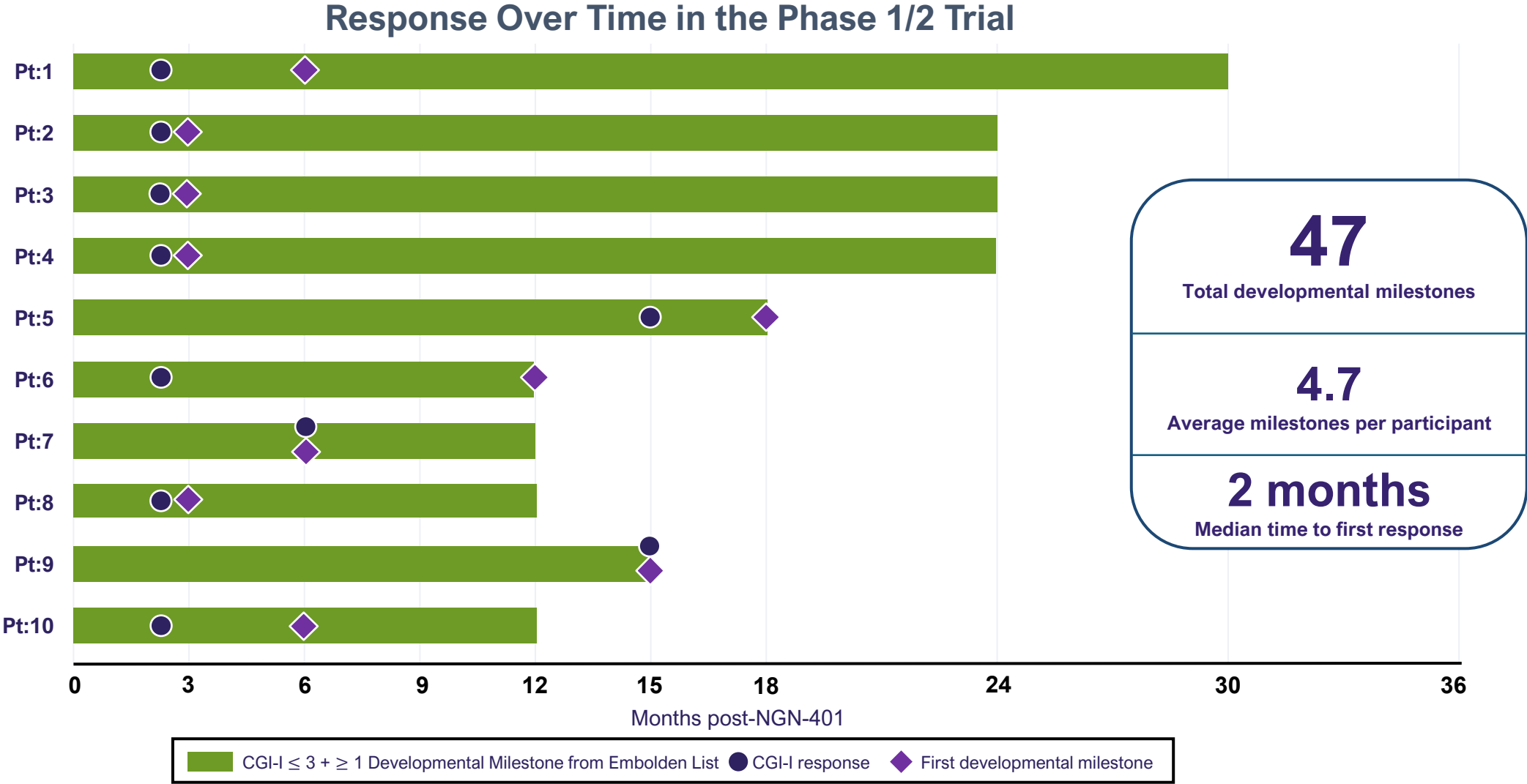
Total of 28 developmental milestones in 3 core domains of Rett syndrome



Utilizing the same standardized assessment criteria enables the Phase 1/2 developmental milestone data to be comparable to the Embolden definition



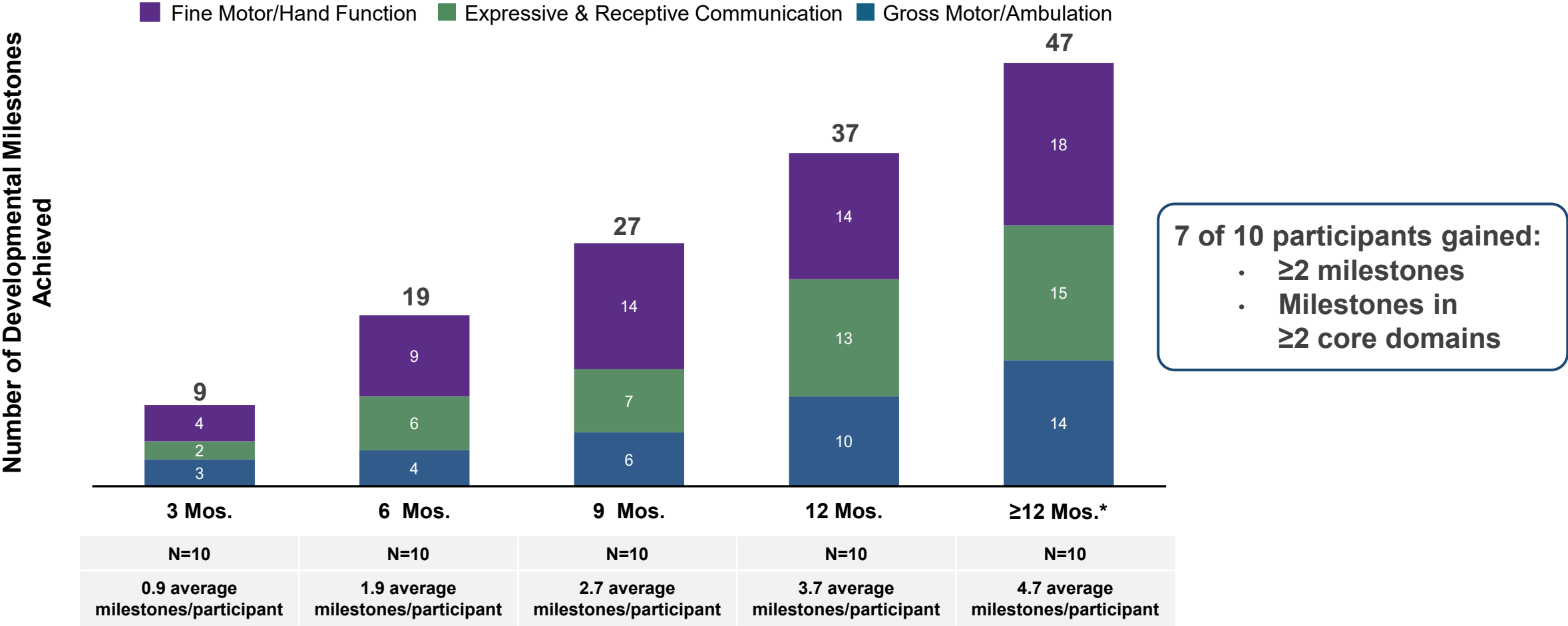
Rapid Response Observed Post NGN-401 that Deepened Over Time



CGI-I, Clinical Global Impression – Improvement; mos., months; Pt, participant. As of data cutoff date of June 16, 2026.
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.

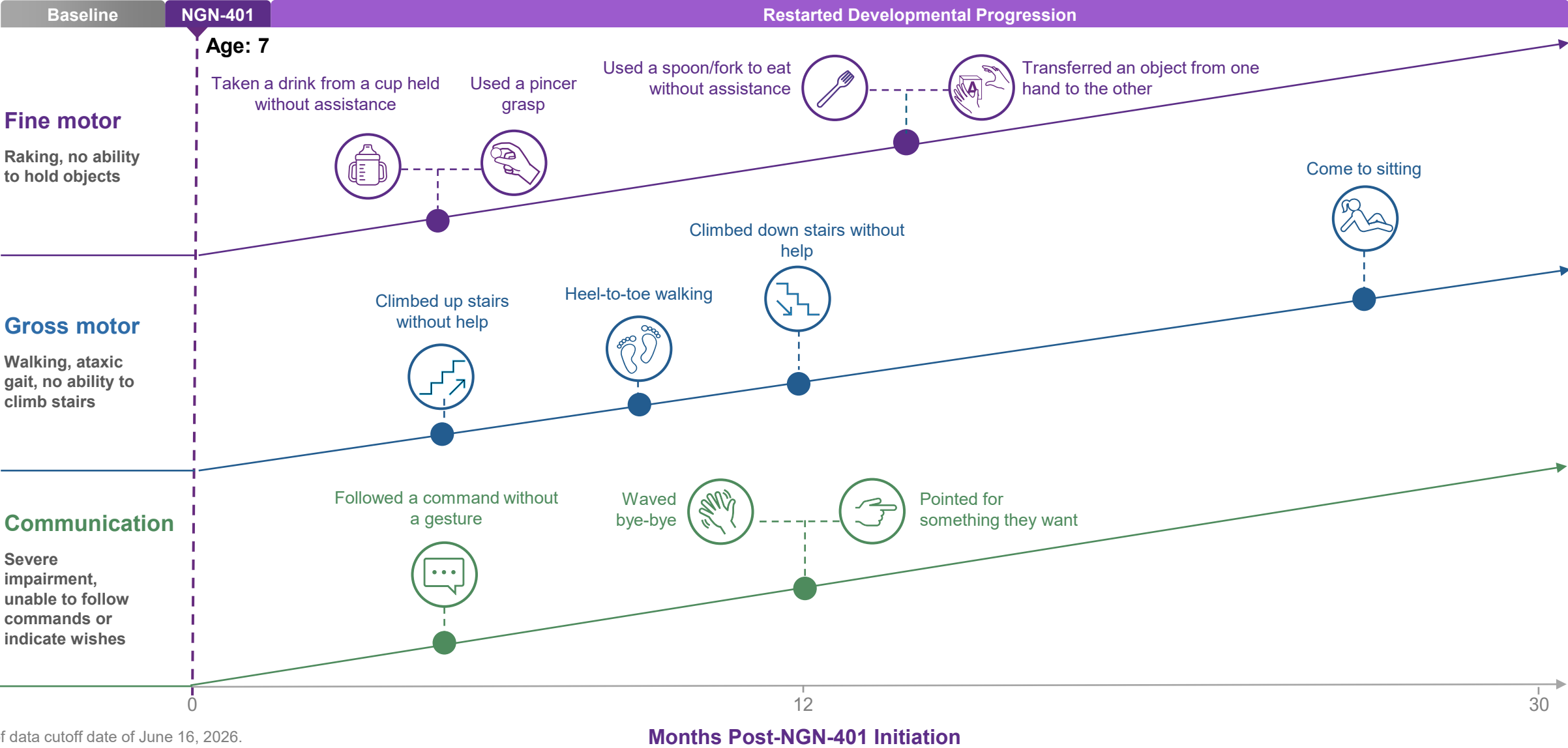
NGN-401 Drove Durable Accumulation of Multidomain Milestones Across Core Domains that Matter Most to Caregivers

Developmental Milestones Increased by Domain Over Time Post-NGN-401 Treatment



CGI-I, Clinical Global Impression – Improvement; mos., months; Pt, participant. As of data cutoff date of June 16, 2026.
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

Pt:1 Developmental Milestones Gained in Ordered, Developmental Progression



As of data cutoff date of June 16, 2026.
Pt, participant.

Pt:1 Multidomain Improvements Led to New Abilities Beyond 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

**Moves more
independently
at home**



Gets in/out of
bathtub, on/off
furniture &
up/down stairs
without help

**Joins family
outings**



Shops with Mom,
carrying the
basket with both
hands

**Navigates
the world
independently**



Climbs in & out of
the car & shuts
the door herself

**Follows
multi-step
directions**



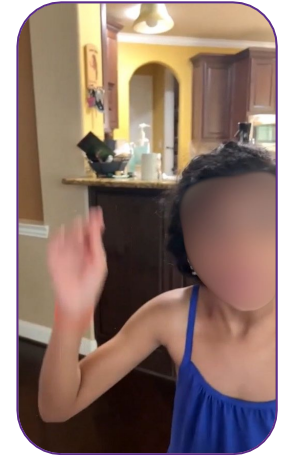
Carries her backpack,
takes the stairs & closes
the door – following
directions in 2 languages

**Follows
instructions to pick
the right colors**



Uses hands to select
correct colors when
asked

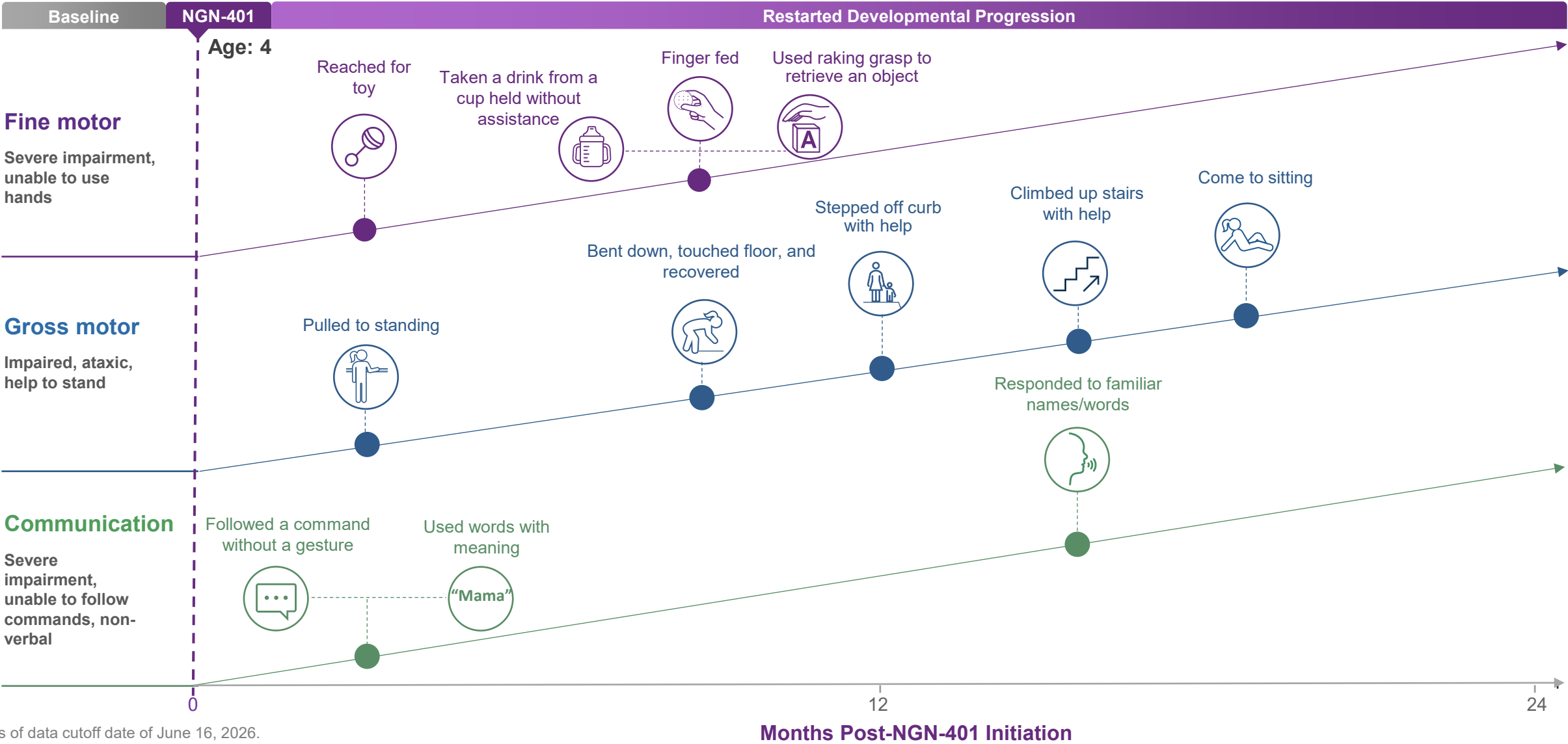
**Greets family
in context**



Waves hello to greet
people on video calls

Enhanced Independence and Reduced Caregiver Burden Post-NGN-401

Pt:2 Developmental Milestones Gained in Ordered, Developmental Progression



As of data cutoff date of June 16, 2026.
Pt, participant.

Pt:2 Multidomain Improvements Led to New Abilities Beyond Developmental Milestones

**At baseline
(Age 4):**

Severe impairment:
Unable to use hands

Gross motor impairment:
Ataxic, needs help to stand

Severe communication impairment:
Unable to follow commands

**Less caregiver
assistance at mealtime**



Self-feeds and
holds own drinks

**Moves more independently
with less supervision**



Bends down to pick up toys &
blankets without help

Connects with family



Turns when called, says words with
meaning & follows instructions

Enhanced Independence and Reduced Caregiver Burden Post-NGN-401

NGN-401 Remains Generally Well-Tolerated at the 1E15 vg Dose Level in the Phase 1/2 Trial

Phase 1/2 Trial	1E15 vg Dose Total 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

- 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

As of data cutoff date of June 16, 2026.
AAV, adeno-associated virus; AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; HLH, hemophagocytic lymphohistiocytosis; ICV, intracerebroventricular; MeCP2, methyl-CpG binding protein 2; Pt, participant; SAE, serious adverse event; TEAE, treatment-emergent adverse event; vg, vector genome.

Thank you to all participants and their families and caregivers!





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Milestones Gained from Embolden List Across 10 Phase 1/2 Participants Treated with NGN-401

21 of 28 Total Milestones Gained from Embolden Milestone List



7/7

Fine Motor/Hand Function

- ✓ Reached for toy
- ✓ Taken a drink from a cup held without assistance
- ✓ Used a pincer grasp (either refined or modified)
- ✓ Used raking grasp to retrieve an object
- ✓ Finger fed
- ✓ Transferred an object from one hand to the other
- ✓ Used a spoon/fork without assistance

Participating in self care and increasing independence — playing games with family, feeding themselves, drinking from a cup



7/13

Gross Motor/Ambulation

- ✓ Sat without support when placed
- ✓ Come to sitting
- ✓ Pulled to standing
- ✓ Cruised/walk with support
- ✓ Climbed up stairs with help
- ✓ Climbed up stairs without help
- ✓ Climbed down stairs without help

Moving more independently — sitting up, standing, and walking — easing everyday care for families



7/8

Communication

- ✓ Responded to familiar names/words
- ✓ Followed a command with a gesture
- ✓ Followed a command without a gesture
- ✓ Pointed for something they want
- ✓ Waved bye-bye
- ✓ Used words with meaning
- ✓ Spoken in phrases

Connecting with the people around them — understanding others, and making their wants and feelings known

28 Clearly Defined Developmental Milestones: Derived from Natural History Study & Key Component of Primary Endpoint



Fine Motor/ Hand Function

- ◆ Reached for toy
- ◆ Taken a drink from a cup held without assistance
- ◆ Used raking grasp to retrieve an object
- ◆ Used a pincer grasp (either refined or modified)
- ◆ Finger fed
- ◆ Transferred an object from one hand to the other
- ◆ Used a spoon/fork to eat without assistance



Gross Motor/Ambulation

- ◆ Sat with support when placed
- ◆ Sat without support when placed
- ◆ Come to sitting
- ◆ Pulled to standing
- ◆ Stood while holding on
- ◆ Stood independently
- ◆ Cruised around furniture or holding on to someone (i.e., walk with support)
- ◆ Walked independently
- ◆ Climbed up stairs with help
- ◆ Climbed up stairs without help
- ◆ Climbed down stairs with help
- ◆ Climbed down stairs without help
- ◆ Ran 10 feet without falling



Communication

- ◆ Responded to familiar names/words
- ◆ Followed a command with a gesture
- ◆ Followed a command without a gesture
- ◆ Pointed for something they want
- ◆ Waved bye-bye
- ◆ Babbled
- ◆ Used words with meaning
- ◆ Spoken in phrases (2 words or more with meaning)