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

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INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disorder defined by a period of early childhood development, then regression of developmental milestones and severe impairment of communication, hand function, and gross motor function.[1–3]
- NGN-401 is an AAV9-based gene therapy in development for RTT using EXACT™ transgene regulation technology to deliver controlled MeCP2 expression on a cell-by-cell basis, delivered via ICV administration.[4]
- 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),[5] 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 post 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

Embolden Registrational Trial Design

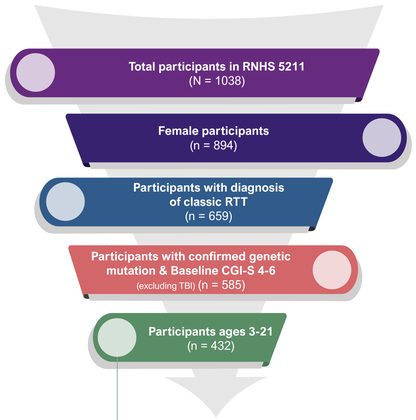
Single Arm, Baseline-Controlled, Open-Label Trial Evaluating 1E15 vg NGN-401

Target Population / Key Inclusion Criteria:
- Females ages 3 and above with genetically confirmed classic RTT
- CGI-S 4-6
- Post-regression stage: ≥6 months since last loss of key milestones in 3 core domains:
  - Hand function
  - Gross motor function
  - Communication

Primary Endpoint (Week 52)

Responder-based Composite Endpoint: Responder = CGI-I ≤3 AND ≥1 new developmental milestone not present at Baseline

RNHS 5211 Population of Participants



Population used to evaluate cumulative incidence rate of ever gaining/regaining a milestone

CGI-I, Clinical Global Impression – Improvement scale; CGI-S, Clinical Global Impression – Severity scale; RNHS, Rett Syndrome Natural History Study; RTT, Rett syndrome.

RESULTS

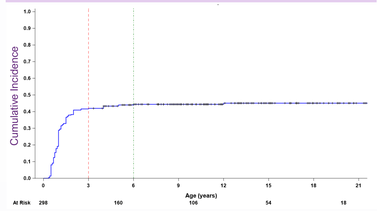
- Participants in the RNHS show that milestone gains concentrate in early childhood. The likelihood of gaining a milestone at ≥3 years of age is extremely low (**Figure 2**).
- 28 low-incidence milestones rated meaningful by caregivers were chosen for the Embolden Milestone List (**Figure 3**).
- Participants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

Fine Motor

Example Milestone: Taken a drink from a cup held without assistance

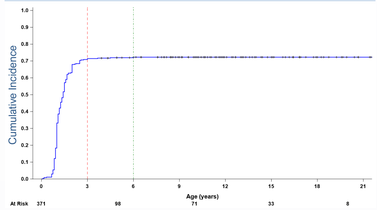
% ever gained/regained: **46%**
At age ≥3 years: **4.2%**
At age ≥6 years: **1.3%**



Gross Motor

Example Milestone: Cruised around furniture or holding on to someone (i.e., walk with support)

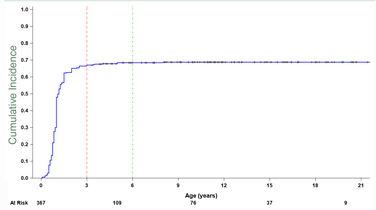
% ever gained/regained : **72%**
At age ≥3 years: **1.5%**
At age ≥6 years: **0.3%**



Communication

Example Milestone: Used words with meaning

% ever gained/regained: **69%**
At age ≥3 years: **2.5%**
At age ≥6 years: **0.4%**



Age at which caregiver reports milestone was first gained; if age gained is unknown, age at which caregiver reports milestone was regained

Scan for additional developmental milestone examples

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

Caregivers indicating milestone is meaningful (%)

100% 95% 90% 85% 80% 75%

Fine Motor

97%	Reached for toy
97%	Taken drink from cup held without assistance
93%	Used raking grasp to retrieve object
93%	Transferred object from one hand to other
93%	Finger fed
90%	Used a pincer grasp
90%	Used spoon/fork to eat without assistance

Gross Motor

100%	Sat without support when placed
97%	Come to sitting
97%	Pulled to standing
97%	Stood independently
97%	Walked independently
97%	Climbed up stairs without help
93%	Stood while holding on
93%	Cruised around furniture or holding on to someone (i.e., walk with support)
93%	Sat with support when placed
90%	Climbed up stairs with help
90%	Climbed down stairs without help
83%	Climbed down stairs with help
77%	Ran 10 feet without falling

Communication

100%	Followed command with gesture
100%	Followed command without gesture
97%	Used words with meaning
97%	Spoken in phrases
97%	Pointed for something they want
93%	Responded to familiar names/words
90%	Babbled
87%	Waved bye-bye

KEY CONCLUSIONS

1. 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.
2. 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.

Figure 4. In the Phase 1/2 study, observed multiple developmental milestone gains from Embolden Milestone List; 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.

Figure 4A. Pt:1 >6 years old gained 10 developmental milestones on the Embolden Milestone List (7 years old at Baseline)

	RNHS Study Sample % Gained/Regained At Age: ≥ 3 years	≥ 7 years
Fine Motor Baseline: Raking grasp, no ability to hold objects		
Taken drink from cup held without assistance	3.8%	0.7%
Transferred object from one hand to other	4.2%	0.7%
Used a pincer grasp	5.3%	2.0%
Used spoon/fork to eat without assistance	3.1%	1.6%
Gross Motor Baseline: Impaired, ataxic gait, no ability to climb stairs		
Climbed up stairs without help	4.5%	0.4%
Climbed down stairs without help	3.5%	0.4%
Come to sitting	2.2%	0.5%
Communication Baseline: Severe impairment, unable to follow commands, indicate wishes		
Followed a command with a gesture	7.6%	1.8%
Waved bye-bye	2.1%	0.0%
Pointed for something they want	2.7%	0.0%

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

	RNHS Study Sample % Gained/Regained At Age: ≥ 3 years	≥ 4 years
Fine Motor Baseline: Severe impairment, unable to use hands		
Reached for toy	1.9%	0.3%
Used raking grasp to retrieve an object	1.2%	1.2%
Finger fed	2.2%	1.6%
Taken a drink from a cup held without assistance	3.8%	3.1%
Gross Motor Baseline: Impaired, ataxic, help to stand		
Pulled to standing	1.4%	0.6%
Climbed up stairs with help	13.2%	7.9%
Come to sitting	2.2%	1.6%
Communication Baseline: Severe impairment, unable to follow commands, non-verbal		
Followed a command without a gesture	6.1%	4.5%
Used words with meaning	2.3%	1.2%
Responded to familiar names/words	3.2%	1.3%

Figure 4C. Pt:10 Adolescent 14 years old gained 2 developmental milestones on the Embolden Milestone List

	RNHS Study Sample % Gained/Regained At Age: ≥ 3 years	≥ 14 years
Fine Motor Baseline: Markedly impaired, unable to use hands		
Reached for toy	2.1%	0%
Communication Baseline: Markedly impaired; unable to follow commands, non-verbal		
Followed a command without a gesture	6.1%	0%

References

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