NGN-401, A Novel Regulated Gene Therapy for Rett Syndrome: Preliminary Results from the First-in-Human Study

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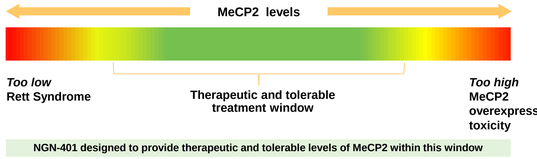
Rett Syndrome and Rationale for Gene Therapy

- Rett syndrome (RTT) is a severe X-linked neurodevelopmental disorder, occurring predominately in females.
- Most cases of RTT are caused by loss-of-function variants in the *MECP2* gene that lead to deficiency of methyl CpG binding protein 2 (MeCP2), a ubiquitously expressed nuclear protein critical for brain function[1,2].
- The cardinal clinical features of the disease phenotype include impairments in hand function/fine motor, ambulation/gross motor, language/communication and autonomic dysfunction (e.g., constipation, sleep, and dysphagia).
- In the natural history of RTT[3], simple developmental skills (e.g., raking grasp, pincer grasp, babbling) are generally acquired but majority are lost during regression phase (~1-4 years). More complex skills (e.g., using utensils to eat, climbing up/down stairs without help, and pointing for wants) are generally not acquired. If gross motor skills are acquired (e.g., sitting and walking), they are not generally lost; however, approximately 50% of girls with RTT are non-ambulatory.
- Gene therapy has potential to address the root cause of RTT by delivering functional copies of the *MECP2* gene to the brain and nervous system, thereby potentially restoring MeCP2 protein.

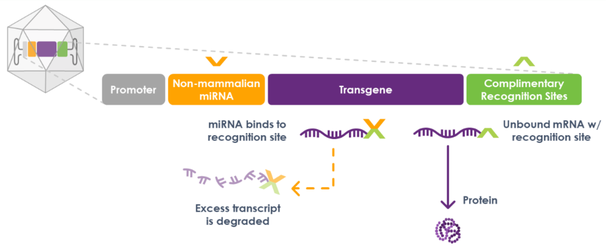
Fig. 1. RTT requires tight transgene regulation



NGN-401 designed to provide therapeutic and tolerable levels of MeCP2 within this window

NGN-401 is Designed to Be a Best-In-Class Gene Therapy for the Treatment of Rett Syndrome

Fig. 2. NGN-401 Construct Design

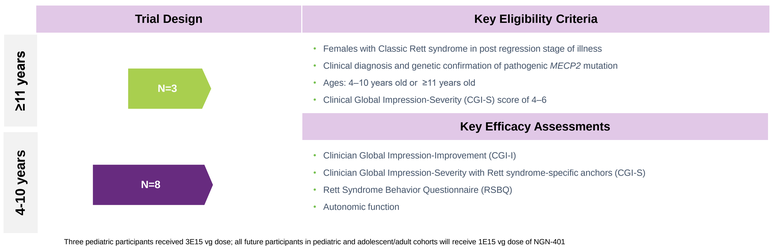


- EXACT™ is designed to fine-tune transgene expression to deliver consistent MeCP2 levels across wild type and deficient cells without overexpression toxicity.
- Full-length human *MECP2* gene maximizes potential for efficacy.
- Intracerebroventricular (ICV) administration delivers *MECP2* to the brain and nervous system. In non-human primate studies, ICV dosing resulted in significantly better distribution than intrathecal-lumbar (IT-L) to key areas of the nervous system underlying RTT pathophysiology[4].
- Mammalian ubiquitous promoter is used broadly in approved gene therapy products.

Methods and Study Design

- The Phase 1/2 open-label trial is enrolling pediatric and adolescent/adult female participants with classic RTT (NCT05898620) to receive a one-time ICV administration of NGN-401 at a dose of 1E15 vg (total vector genomes). All participants receive prophylactic immunosuppression.
- Data cut-off for the interim safety and efficacy presented in this poster was 17 October 2024.

Fig. 3. RTT-200 Phase 1/2 Trial Overview



Three pediatric participants received 3E15 vg dose; all future participants in pediatric and adolescent/adult cohorts will receive 1E15 vg dose of NGN-401

Baseline Characteristics of Dosed Participants Range from Moderate to Severe Disease

Table 1

	1E15 vg (Low Dose)					3E15 vg (High Dose)*	
	Participant 1 (LD:1)	Participant 2 (LD:2)	Participant 3 (LD:3)	Participant 4 (LD:4)	Participant 5 (LD:5)	Participant 1 (HD:1)	Participant 2 (HD:2)
Age at Dosing in Years	7	4	6	7	6	5	7
***MECP2* Mutation Severity**	Mild	Severe	Severe	Severe	Severe	Severe	Unclassified
Baseline Disease Severity as Indicated by CGI-S Score	4 (moderately ill)	5 (markedly ill)	5 (markedly ill)	5 (markedly ill)	5 (markedly ill)	5 (markedly ill)	4 (moderately ill)
Time Post Treatment with NGN-401 in Months	~15	~12	~9	<6	~1	~5	~2

*As of November 11, 2024, Neurogene discontinued use of 3E15 vg dose and has updated the Phase 1/2 protocol to use 1E15 vg dose for all future participants

Despite Similar CGI-S Scores, Individual Baseline Presentations Vary Widely Across Core Clinical Domains

1E15 vg Dose of NGN-401 Has a Favorable Safety and Tolerability Profile

1E15 vg dose:

- No treatment-related serious adverse events (SAEs)
- Most AEs are known potential risks of AAV, have been responsive to corticosteroid treatment and have resolved or are resolving

Both doses:

- No signs or symptoms indicative of MeCP2 overexpression, consistent with preclinical data
- No intracerebroventricular (ICV) procedure-related AEs
- No seizures reported in any participant after treatment with NGN-401
- Post-data cut-off date of October 17, 2024, the third participant receiving the 3E15 vg dose of NGN-401 died following complications from a rare hyperinflammatory syndrome associated with systemic exposure to high doses of AAV; Phase 1/2 protocol has been updated to remove the 3E15 vg dose

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal
TEAE = Treatment-emergent adverse event; SAE = Serious adverse event

Table 2

	1E15 vg Number of Events [Number of Participants]	3E15 vg Number of Events [Number of Participants]
Related TEAE	21 [4]	22 [2]
Grade 1	21 [4]	16 [2]
Grade 2	0	4 [1]
Grade 3	0	2 [1]
Related SAE	0	0
Unrelated SAE	1 [1]	2 [1]

- Grade 3 AEs were AST (7X ULN) and ALT (5X ULN) that resolved with corticosteroid treatment
- Grade 2 AEs were elevated ALT (1), AST (1), and decreased platelets (1) that all resolved with corticosteroid treatment and anorexia (1) that also resolved
- Two Grade 1 AEs of abnormal sural (sensory) nerve conduction study
  - 1 LD participant & 1 HD participant, both participants are asymptomatic
- Unrelated SAEs were urinary tract infection (2) and sepsis (1)

Consistent Improvement Across Key Rett Syndrome Scales, Bolstered by Functional Improvements in Core Clinical Domains

Table 3

	CGI-I		CGI-S Total Score		RSBQ		Gain of Skills, Developmental Milestones and Symptom Improvement in RTT Clinical Domains				
	Improved?	How many points?*	Improved?	How many points?	Improved?	How many points? (% Change)	Hand Function	Gross Motor	Communi-cation	Autonomic	Attentive-ness
LD:1 15 mos. post-NGN-401	✓	2 pts.			✓	10 pts. (-28%)	✓	✓	✓	✓	✓
LD:2 12 mos. post-NGN-401	✓	2 pts.	✓	1 pt.	✓	32 pts. (-52%)	✓	✓	✓	✓	✓
LD:3 9 mos. post-NGN-401	✓	2 pts.			✓	5 pts. (-29%)	✓	✓		✓	✓
LD:4 3 mos. post-NGN-401	✓	2 pts.			✓	8 pts. (-28%)	✓			✓	✓

*Each participant achieved a 2-point improvement from "no change," or a score of 4

All Treated Participants Achieved CGI-I Rating of "Much Improved"

Clinically Meaningful Improvement Observed Early After Treatment, with Deepening Response and Durability Over Time

Table 4

	CGI-I Score ≤ 3 = Clinically Meaningful Improvement				
LD:1	3 – Minimally Improved	2 – Much Improved	2 – Much Improved	2 – Much Improved	2 – Much Improved
LD:2	2 – Much Improved	2 – Much Improved	2 – Much Improved	2 – Much Improved	
LD:3	3 – Minimally Improved	3 – Minimally Improved	2 – Much Improved		
LD:4	2 – Much Improved				
	3 mos.	6 mos.	9 mos.	12 mos.	15 mos.

Post Treatment with NGN-401

Baseline Functional Characteristics of Low Dose 1-4 in Core Clinical Domains

Table 5

	LD:1 Baseline - 7 Years Old	LD:2 Baseline - 4 Years Old	LD:3 Baseline - 6 Years Old	LD:4 Baseline - 7 Years Old
Hand Function / Fine Motor	• Raking grasp • Limited ability to feed herself • Dropped items quickly	• No functional hand use; right hand fixed in clenched position • Could not reach for, grasp, or hold items	• Raking grasp • Could not self-feed, on pureed diet due to aspiration; all meals required spoon-feeding by caregiver	• Raking grasp, some thumb use • Used adaptive utensils because of inability to grasp and hold onto a regular fork or spoon
Ambulation / Gross Motor	• Impaired, ataxic, unstable gait: often froze and walked on tiptoes • Could not go up/down stairs on own • Could not get on/off bed on own	• Impaired, ataxic, unstable gait: frequent falls and walked on tiptoes • Required caregiver support to stand from seated position • Could not bend at waist & touch floor	• Could not sit, stand, or walk independently due to poor core strength and lower extremity weakness	• Could not stand or walk independently
Language / Communication	• Vocalized, could not babble • Could not communicate needs, wants, emotions, or choices • Unable to follow commands	• Rarely vocalized, could not babble • Unable to follow commands • Rarely made choices	• Vocalized, could not babble • Rarely made choices • Unable to follow commands	• Rarely vocalized, could not babble • Made choices with eye gaze device • Unable to follow commands

Multi-Domain Improvements Deepened Over Time, and Not Expected Based on Rett Syndrome Natural History

Table 6

	Select LD:1 Developmental Skills Post-NGN-401	Months Post-NGN-401				
		3	6	9	12	15
Fine Motor	Uses a pincer grasp		✓	✓	✓	✓
	Holds bottle or cup unpropped		✓	✓	✓	✓
	Uses spoon/fork to self-feed					✓
	Transfers objects between hands					✓
Gross Motor	Heel-to-toe walking			✓	✓	✓
	Climbs up stairs without help		✓	✓	✓	✓
	Climbs down stairs without help				✓	✓
Communication	Follows a command without gesture		✓	✓	✓	✓
	Waves hello*				✓	✓
	Taps for wants				✓	✓

Additional Improvements Post NGN-401 for LD:1
Hand Function / Fine Motor:
- Uses both hands to drink on her own

Ambulation / Gross Motor:
- More fluid gait; climbs out of high rimmed bathtub; gets on/off furniture; climbs out of car seat to exit car

Language / Communication:
- Navigates her house to the car to go to school; waves hello to her grandfather on daily video calls; frowns/shouts to show displeasure; follows > 10 commands such as "give a kiss," "sit down," "give it to me", "put item in trash," "open/close door," "flush toilet."

	Select LD:2 Developmental Skills Post-NGN-401	Months Post-NGN-401			
		3	6	9	12
Fine Motor	Reaches for an object	✓	✓	✓	✓
	Uses raking grasp to retrieve an object			✓	✓
	Self-feeds			✓	✓
Gross Motor	Stands independently from seated position	✓	✓	✓	✓
	Bends down, touches floor, and recovers			✓	✓
	Steps off curb with help				✓
Communication	Follows a command without a gesture	✓	✓	✓	✓
	Uses words with meaning	✓	✓	✓	✓

Additional Improvements Post NGN-401 for LD:2
Hand Function / Fine Motor:
- Holds juice box and drinks; frequently grabs and holds her security blanket; places pacifier in her mouth to self-soothe, turns on videos by tapping tablet

Ambulation / Gross Motor:
- Faster, steadier gait with infrequent falls; bends over to pick up her blanket from the floor; steps off a curb with one hand held

Language / Communication:
- Says "mama", "dada," and "nana" clearly and in context; follows commands such as "come here" and "give a kiss" and more regularly choosing preferred foods

	Select LD:3 Developmental Skills Post-NGN-401	Months Post-NGN-401		
		3	6	9
Fine Motor	Uses a pincer grasp		✓	✓
	Able to self-feed			✓
Gross Motor	Sits independently	✓	✓	✓

Additional Improvements Post NGN-401 for LD:3
Hand Function / Fine Motor:
- Able to self-feed solid foods, swallow liquids

Ambulation / Gross Motor:
- Improved posture; able to stand with less support; able to advance feet forward better with support

Language / Communication:
- Laughs at jokes made by caregiver; makes some choices

Select LD:4 Developmental Skills Post-NGN-401	Months Post-NGN-401
	3
Uses a pincer grasp	✓
Can use utensils to self-feed (without assistance)	✓

Additional Improvements Post NGN-401 for LD:4
Hand Function / Fine Motor:
- Uses regular utensils to self-feed; reaches with more precision

Language / Communication:
- Laughs at appropriate moments while watching favorite movie or listening to audio program; vocalizes to express discomfort or show emotion

In Participants with Constipation at Baseline, Symptoms Improved within 6 Months as Reported by Caregiver Observation on Modified Bristol Stool Form Scale

Conclusions

- The 1E15 vg dose of NGN-401 has been well-tolerated and has a favorable safety profile
- Rapid response post-treatment, with deepening of response over time; all participants "much improved" on CGI-I
- Consistent gains observed across core clinical domains of hand function, gross motor function, and communication, despite heterogeneous baseline presentation
- Clinically meaningful gain of skills and developmental milestones, which are not expected based on natural history data
- Many of the milestones achieved involve integration across multiple domains, which is atypical for apraxic RTT patients
- Improvements in autonomic domains of constipation, dysphagia, and sleep (not shown)
- Improvements have led to increased independence, including the ability to follow daily routines for participant with longest follow up

References: (1) www.orpha.net. (2) Neul JL, et al. *Ann Neurol* 2010;68:944-50. (3) Neul J, et al. *Journal of Neurodevelopmental Disorders* (2014) 6:20. (4) American Society of Gene & Cell Therapy 24th Annual Meeting. May 2021.

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