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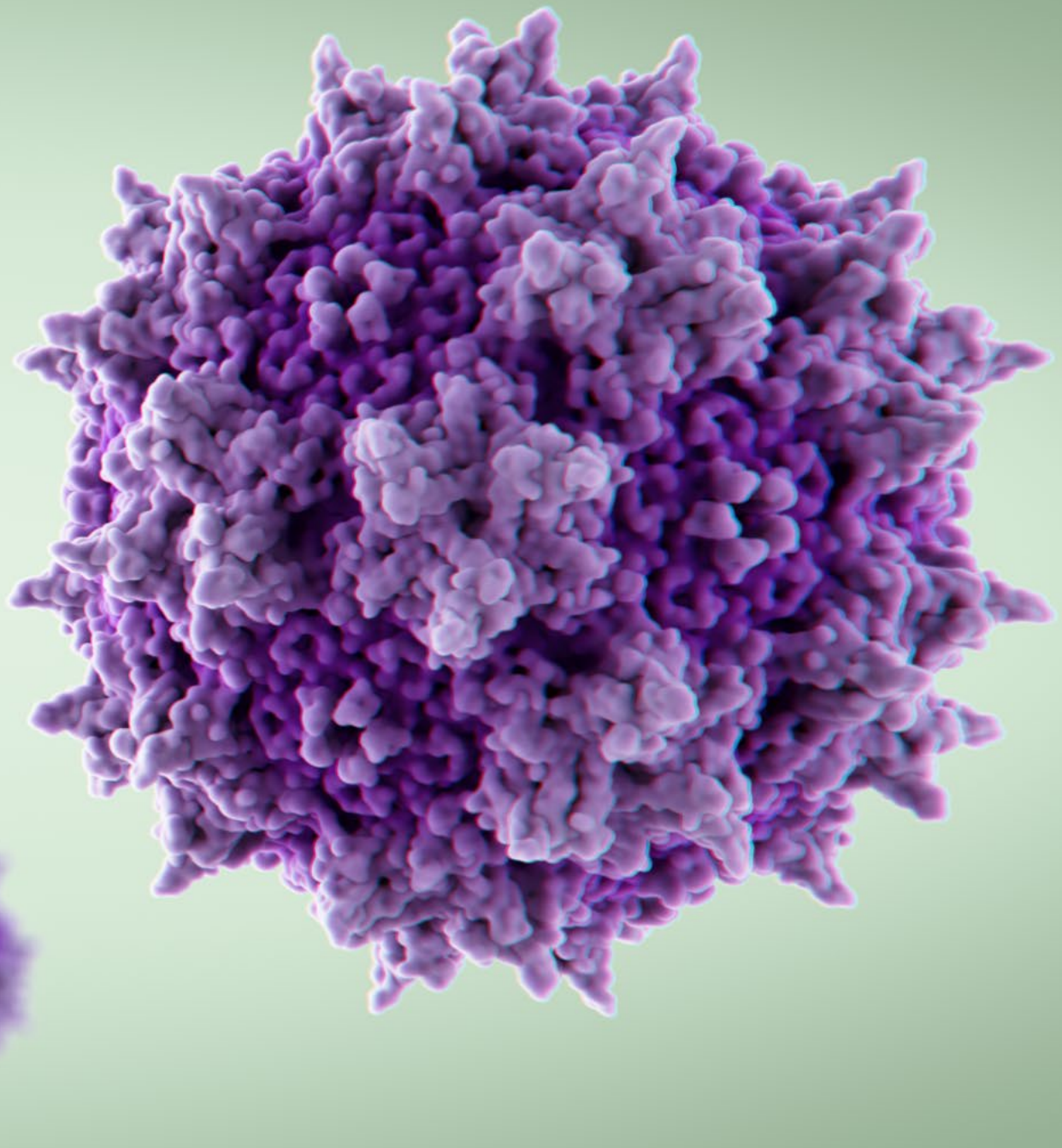
# Interim Clinical Data from Phase 1/2 Trial Evaluating NGN-401 Gene Therapy for the Treatment of Rett Syndrome

November 11, 2024



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# Agenda

**Introduction and NGN-401 Program Overview**

**Rett Syndrome Overview and Natural History**

**NGN-401 Phase 1/2 Clinical Trial Design**

**Baseline Characteristics and Safety Data**

**Interim Low-Dose Cohort Efficacy Data**

**NGN-401 Next Steps**

**Q&A**

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# Compelling Interim Clinical Data in Low-Dose Cohort Shows Gains of Function Across Core Domains and Improvements in Autonomic Function


**Durable improvements observed across multiple scales, incl. two-point improvement in CGI-I in all participants, with concordance of benefit across scales**

**Consistent gains observed across core clinical domains** of hand function, gross motor and communication, despite heterogeneous presentation

**Clinically meaningful gain of skills and developmental milestones** beyond those observed in natural history data

**Objective improvements in autonomic domains** of sleep and constipation

**Rapid response** post-treatment, with **deepening of response over time**

**Favorable safety profile** with low-dose NGN-401

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As of data cut-off date of 17 October 2024

# Leveraging START and RMAT to Accelerate Program to Registration; New Adult Cohort Underway

## Multiple Touch Points with FDA to Accelerate Registration

- START Program participation provides clear channel of communication with FDA to accelerate registrational planning
- RMAT designation provides eligibility for an Accelerated Approval pathway and rolling BLA and potential for Priority Review
- **FDA alignment on potency assay strategy to support future registrational trial and manufacturing scale-up plans at Neurogene Houston facility to support commercial launch plans**
- **Initiated adolescent/adult cohort at high dose to support potential for a broad label to capture higher portion of prevalent population**

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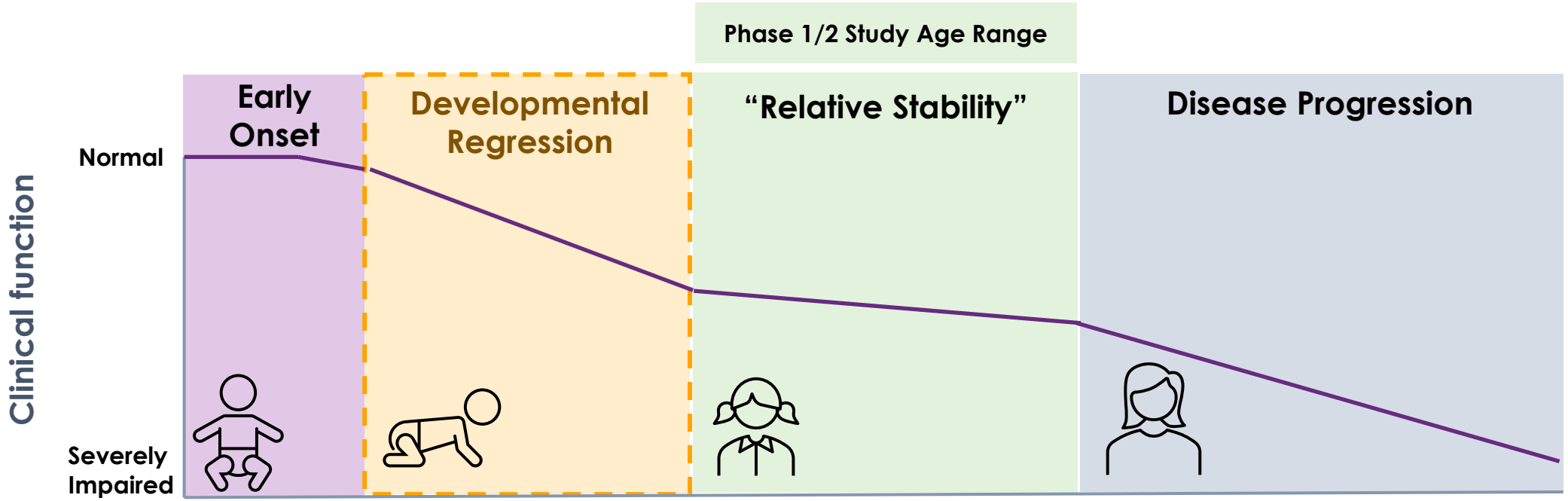
**Bold** = New update

# Rett Syndrome Overview and Natural History

# Rett Syndrome is Defined By Regression Period in Early Development




Delayed early development

- Arrested development; can be misdiagnosed as "developmental delay"
- Loss of acquired skills, including fine motor and communication


Pini G, et al. *Orphanet Journal of Rare Diseases* (2016) 11:132.
Neul J, et al. *Journal of Neurodevelopmental Disorders* (2014) 6:20
U.S. Natural History Study of Rett Syndrome (RNHS) Clinicaltrials.gov identifier: NCT02738281. Accessed 2022 from International Rett Syndrome Foundation (IRSF).

# Simple Skills Are Generally Acquired but Majority Are Lost During Regression; More Complex Skills are Generally Not Acquired

## Natural History of Rett Syndrome

| | Early Onset | Developmental Regression + | |
|---|---|---|---|
| | **Simple Skills Generally Acquired** | **Simple Skills Generally Lost*** | **Complex Skills Not Generally Acquired** |
| | **% Learned** | **% Lost** | **% Never Learned** |
| **Hand Function**<br>Fine motor more likely to be lost than gross motor | Raking Grasp (~85%)<br>Transferred Objects (~80%)<br>Hold Bottle (~80%)<br>Pincer Grasp (70%) | Loss → Raking grasp (~50%)<br>Transferred Objects (~60%)<br>Hold Bottle (~60%)<br>Pincer Grasp (~50%) | Spoon/Fork Without Assist - (~80%) |
| **Gross Motor**<br>Advanced skills less likely ever acquired | Sitting (>~90%)<br>Walking (~60%) | *If gross motor skills acquired, not generally lost<br>Sitting - ~80% retain<br>Walking - ~50% retain | Run (~75%)<br>Climb Up Stairs Without Help (82%)<br>Climb Down Stairs Without Help (86%) |
| **Communication**<br>Expressive more likely to be lost/never learned than receptive | Babbling (~90%)<br>Single Words (66%) | Loss → Babbling (~45%)<br>Single Words (~60%) | Waved Bye (~50%)<br>Points When Wants (~80%)<br>Spoken Phrases (~80%) |

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U.S. Natural History Study of Rett Syndrome (RNHS) Clinicaltrials.gov identifier: NCT02738281. Accessed 2022 from International Rett Syndrome Foundation (IRSF).
Data from the RNHS; N=200 female subjects with classic RTT, age 4-10 years, CGI-S score of 4 to 6 at baseline, confirmed genetic mutation
Neul J, et al. *Journal of Neurodevelopmental Disorders* (2014) 6:20

# NGN-401 Phase 1/2 Trial Design and Interim Results

# NGN-401 Phase 1/2 Clinical Trial Design in Females with Rett Syndrome

## Trial Design

**Adolescent/ Adult**

**Cohort 3**
**3E15 vg**
**N=3**

**Pediatric**

**Cohort 2**
**3E15 vg**
**N=8**

**Cohort 1**
**1E15 vg**
**N=8**

## Key Eligibility Criteria

- Females with Classic Rett syndrome in post regression stage of illness
- Clinical diagnosis and genetic confirmation of pathogenic *MECP2* mutation
- Pediatric: 4–10 years old; Adolescent/Adult: 16+ years old
- Clinical Global Impression-Severity (CGI-S) score of 4–6

## Key Efficacy Assessments

- Clinician Global Impression-Improvement (CGI-I)
- Clinician Global Impression-Severity with Rett syndrome-specific anchors (CGI-S)
- Rett Syndrome Behavior Questionnaire (RSBQ)
- Autonomic function

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Cohort 1 prophylactic immunosuppression regimen includes corticosteroids
Cohorts 2 and 3 prophylactic immunosuppression regimen includes a targeted regimen of rituximab, sirolimus and shorter course of corticosteroids

# Baseline Characteristics of Dosed Participants Range from Moderate to Severe Disease

| | Low-Dose Cohort 1 (1E15 vg) | | | | | High-Dose Cohort 2 (3E15 vg) | |
|---|---|---|---|---|---|---|---|
| | **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 |

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

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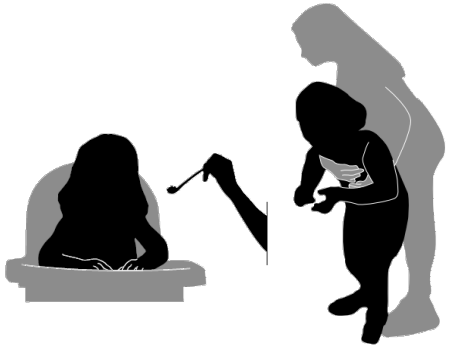
# Functional Characteristics of LD:1 – 4 in Core Clinical Domains



| | 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<br>• Limited ability to feed herself<br>• Dropped items quickly | • No functional hand use; right hand fixed in clenched position<br>• Could not reach for, grasp, or hold items | • Raking grasp<br>• Could not self-feed, on pureed diet due to aspiration; all meals required spoon-feeding by caregiver | • Raking grasp, some thumb use<br>• 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<br>• Could not go up/down stairs on own<br>• Could not get on/off bed on own | • Impaired, ataxic, unstable gait; frequent falls<br>• Required caregiver support to stand from seated position<br>• Could not bend at waist and 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<br>• Could not communicate needs, wants, emotions, or choices<br>• Unable to follow commands | • Rarely vocalized, could not babble<br>• Unable to follow commands<br>• Rarely made choices | • Vocalized, could not babble<br>• Rarely made choices<br>• Unable to follow commands | • Rarely vocalized, could not babble<br>• Made choices with eye gaze device<br>• Unable to follow commands |

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Images are representative of skills and are not photos of participants in the NGN-401 clinical trial

# NGN-401 Has a Favorable Safety and Tolerability Profile in 7 Participants Dosed (5 Low Dose and 2 High Dose)

- No treatment-related serious adverse events (SAEs)
- No signs or symptoms indicative of MeCP2 overexpression, consistent with preclinical data
- Most AEs are known potential risks of AAV, have been responsive to corticosteroid treatment and have resolved or are resolving
- No intracerebroventricular (ICV) procedure-related AEs
- No seizures reported in any participant after treatment with NGN-401

| | Low-Dose Number of Events [Number of Participants] | High-Dose 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)

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As of data cut-off date of 17 October 2024
TEAE = Treatment-emergent adverse event; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN= Upper limit of norma

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

| | 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%) | ✓ | | | ✓ | ✓ |

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

# Understanding the CGI-I with Rett Syndrome Specific Anchors

- Clinician-rated scale assessing improvement from baseline
- 1-point improvement considered clinically meaningful (score ≤ 3)*
- Factors considered to determine change included duration, onset, durability of change, and the context of sign/symptom change across the Rett syndrome specific domains of the CGI
- CGI-I is more sensitive to change than CGI-S

| Score | CGI-I |
|---|---|
| 1 | Very much improved |
| 2 | Much improved |
| 3 | Minimally improved |
| 4 | No change |
| 5 | Minimally worse |
| 6 | Much worse |
| 7 | Very much worse |

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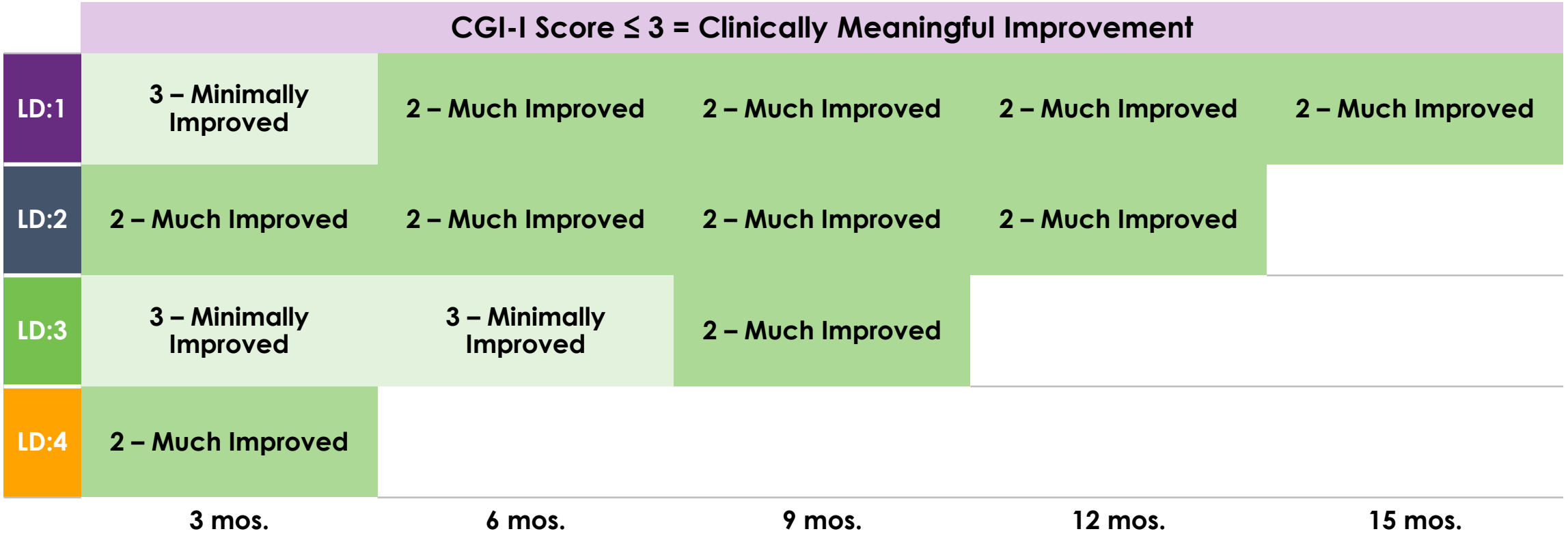
*Clinical Review Report: Brexpiprazole (Rexulti), 2017.
Neul J, et al. *J Child Neurol* (2015) 30(13):1743–1748

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

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




**Post Treatment with NGN-401**

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# Understanding the CGI-S with Rett Syndrome Specific Anchors

- Clinician-rated scale of disease severity across 7 clinical domains
- Communication, ambulation, and hand function, have the greatest weighting on total score
- The majority of patients with Classic Rett Syndrome have a CGI-S of 4-6
- Scale not designed to be sensitive to change; substantial gains across core domains required to improve scale by 1 point

| Score | CGI-S | |
|---|---|---|
| 1 | Normal, not at all ill | |
| 2 | Borderline ill | |
| 3 | Mildly ill | |
| 4 | Moderately ill | NGN-401 Clinical Trial Inclusion Criteria |
| 5 | Markedly ill | |
| 6 | Severely ill | |
| 7 | Extremely ill | |

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Neul J, et al. *J Child Neurol* (2015) 30(13):1743–1748

# CGI-S Clinical Domains Provide Insights Into Core Functional Areas; Scale Was Not Designed as Clinical Outcome Measure

Core functional domains

Key clinical focus is breathing abnormalities

Following commands clinically meaningful

| Clinical Domains | CGI-S 3 | CGI-S 4 | CGI-S 5 | CGI-S 6 |
|---|---|---|---|---|
| **Language/ Communication** | Phrases-sentences. May have conversations or echolalia | <5 words<br>Babbles<br>Makes choices 25%-50% | No words<br>Babbles<br>Makes choices ≤25% | Vocalizations<br>Occasionally screams<br>Rarely or makes no choices |
| **Ambulation** | Walks, able to use stairs/run<br>May ride tricycle or climb | Walks independently<br>Unable to use stairs or run | Walks with assistance | Stands with support or independently<br>May walk with support<br>Sits independently or with support |
| **Hand use** | Bilateral pincer grasp. May use pen to write but has fine motor issues like tremor | Reaches for objects, raking grasp or unilateral pincer<br>May use utensils/cup | Reaches<br>No grasps | Rarely-occasionally reaches out<br>No grasp |
| **Social (eye contact)** | Appropriate eye contact, >30s | Eye contact <20s | Eye contact <10s | Eye contact, inconsistent 5s |
| **Autonomic** | No or minimal breathing abnormalities (<5%) warm, pink extremities | Breathing dysrhythmia <50%<br>No cynanosis<br>Cool UE, Pink LE | Breathing dysrhythmia 50%<br>No cynanosis<br>Cold UE, Pink LE | Breathing dysrhythmia 50-100%<br>May have cynanosis<br>Cool UE or LE, may be blue |
| **Seizures*** | None, with or without meds | Monthly-weekly | Weekly | Weekly-daily |
| **Attentiveness** | Attentive to conversation, follows commands | 50-100% | 50% | <50% |

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*Treated participants to date have been stable with no seizures on study
Neul J, et al. *J Child Neurol* (2015) 30(13):1743–1748

# **Hand Function:** All Participants Gained Meaningful Improvements and Gained Skills that Deepened Over Time

## All Participants Gained Higher-level Grasping and Improvements in Self-feeding

| | | Baseline | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. |
|---|---|---|---|---|---|---|---|
| **LD:1** 7 yrs. at dosing | CGI-S Domain Score | 4 | 4 | 4 | 4 | 4 | 4 |
| | | Raking grasp; Limited self-feeding | • More consistent self-feeding, able to take multiple bites of foods without dropping | • Modified pincer grasp to self-feed | • Drinks with two hands<br>• Able to place ball in basket on command | • Pincer grasp | • Uses fork to self-feed<br>• Transfers objects between hands |
| **LD:2** 4 yrs. at dosing | CGI-S Domain Score | 6 | 4 | 4 | 4 | 4 | |
| | | No functional hand use | • Palmer grasp | • Engages both hands | • Beginning to self-feed<br>• Picks up and grasps blanket with both hands<br>• Raking grasp | • Can place pacifier in own mouth | |
| **LD:3** 6 yrs. at dosing | CGI-S Domain Score | 4 | 4 | 4 | 4 | | |
| | | Raking grasp | • Modified pincer grasp | • Modified pincer grasp | • Beginning to self-feed | | |
| **LD:4** 7 yrs. at dosing | CGI-S Domain Score | 4 | 4 | | | | |
| | | Raking grasp; Self-feeds with adaptive utensils | • Modified pincer grasp;<br>• Uses utensils to self-feed | | | | |

**Time Post Treatment with NGN-401**

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# **Gross Motor Function:** Gains are Faster in Participants Who Walked Independently at Baseline

**First Three Participants Experienced Improvements in Gross Motor Function that Led to Greater Physical Independence From Caregivers**

| | | Baseline | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. |
|---|---|---|---|---|---|---|---|
| LD:1<br>7 yrs. at dosing | CGI-S Domain Score | 4 | 4 | 3 | 3 | 4 | 3 |
| | | Impaired, ataxic, unstable gait;<br>Freezes often and walks on tip-toes;<br>Unable to ascend or descend stairs independently | • More fluid gait, more heel-to toe | • Able to ascend stairs independently | • Can get on and off bed independently<br>• Ascends stairs independently<br>• Consistent heel-to-toe walking | • Able to ascend and descend stairs independently | • Able to climb out of bathtub independently<br>• Gets down from carseat and exits car independently |
| LD:2<br>4 yrs. at dosing | CGI-S Domain Score | 4 | 4 | 4 | 4 | 4 | |
| | | Impaired, ataxic unstable gait ;<br>Frequent falls;<br>Needs assistance to stand up from seated position | • Able to get up from seated position independently<br>• More fluid, faster gait | • Able to get off of couch independently<br>• Steps over objects more easily | • More stable, fluid gait<br>• Falls reduced by ~75%<br>• Bends over at hip to pick up blanket from floor, returns to standing | • Can step off a curb with one hand held | |
| LD:3<br>6yrs. at dosing | CGI-S Domain Score | 6 | 6 | 6 | 6 | | |
| | | Cannot sit, stand or walk independently | • Sits independently | • Sits independently | • Needs less support to get up from seated position and stand | | |
| LD:4<br>7 yrs. at dosing | CGI-S Domain Score | 5 | 5 | | | | |
| | | Cannot sit, stand or walk independently | • Cannot sit, stand or walk independently | | | | |

**Time Post Treatment with NGN-401**

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# **Communication:** All Participants Demonstrated Improvement in Ability to Convey Choices (Slide 1 of 2)

**Ability to Follow Caregiver Commands Demonstrated in Patients With Longest Follow Up**

| | | Baseline | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. |
|---|---|---|---|---|---|---|---|
| **LD:1** 7 yrs. at dosing | CGI-S Domain Score | 6 | 6 | 5 | 5 | 4 | 4 |
| | | Makes choices 50% of time; Unable to follow commands | • Some choice-making | • Makes choices most of time; food 80–90% of time<br>• Intermittently follows commands | • Makes choices nearly 100% of time for food<br>• Follows multiple commands | • Makes choices 100% of time for food<br>• Taps food items she wants<br>• Follows >10 commands, many without gesture | • Consistently makes choices for food<br>• Follows >10 commands, many without gesture<br>• Actively seeks attention from others |
| **LD:2** 4 yrs. at dosing | CGI-S Domain Score | 6 | 5 | 4 | 4 | 4 | |
| | | Rarely makes choices; Unable to follow commands | • Makes choices 25–50% of time | • Makes choices 25–50% of time | • Makes food choices 50–75% of time<br>• Follows simple commands | • Makes choices 50% of time<br>• Follows simple commands | |
| **LD:3** 6yrs. at dosing | CGI-S Domain Score | 6 | 6 | 6 | 6 | | |
| | | Rarely makes choices; Unable to follow commands | • Makes choices 50% of time | • Makes choices 25% of time | • Makes choices <25% of the time | | |
| **LD:4** 7 yrs. at dosing | CGI-S Domain Score | 4 | 5 | | | | |
| | | Makes choices with eye gaze device; Unable to follow commands | • Makes choices ~25% of time | | | | |

**Time Post Treatment with NGN-401**

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# **Communication:** All Participants Experiencing Improvements in Ability to Express Themselves (Slide 2 of 2)

| | | Baseline | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. |
|---|---|---|---|---|---|---|---|
| LD:1 7 yrs. at dosing | CGI-S Domain Score | 6 | 6 | 5 | 5 | 4 | 4 |
| | Vocalizations | | • Vocalizations | • Vocalizations | • Vocalizations | • Babbles<br>• Consistently waves "hello" on command | • Shouts or yells to express emotions when unhappy or uncomfortable |
| LD:2 4 yrs. at dosing | CGI-S Domain Score | 6 | 5 | 4 | 4 | 4 | |
| | Vocalizations | | • Occasional babbling, "dada" for Daddy | • Says "mama" and "dada" clearly | • Says "mama," "dada" and "nana" purposefully and in context | • Says "mama," "dada" and "nana" purposefully and in context | |
| LD:3 6yrs. at dosing | CGI-S Domain Score | 6 | 6 | 6 | 6 | | |
| | Vocalizations | | • Increased Vocalizations | • Increased Vocalizations | • Laughs when caregiver makes jokes playing with toys | | |
| LD:4 7 yrs. at dosing | CGI-S Domain Score | 4 | 5 | | | | |
| | Vocalizations | | • Laughs at jokes when watching a movie<br>• Vocalizations to express discomfort or protest | | | | |

**Time Post Treatment with NGN-401**

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As of data cut-off date of 17 October 2024

# **Autonomic Function:** Breathing Dysrhythmias Are Variable, Difficult to Assess Clinically Meaningful Improvements at Clinic Visits

| | | Baseline | 3 mos. | 6 mos. | 9 mos. | 12 mos. | 15 mos. |
|---|---|---|---|---|---|---|---|
| LD:1 7 yrs. at dosing | CGI-S Domain Score | 5 | 5 | 3 | 4 | 4 | 5 |
| | Breathing dysrhythmias 50% of the time | | • Breathing dysrhythmias 50% of the time | • No or minimal breathing abnormalities, <5% of time | • Breathing dysrhythmias <50% of the time | • Much less breath holding but still hyperventilating 50% of the time | • Much less breath holding but still hyperventilating 50% of the time |
| LD:2 4 yrs. at dosing | CGI-S Domain Score | 6 | 4 | 4 | 3 | 5 | |
| | Significant dysrhythmias, breath holding and hyperventilation episodes >50% of the time | | • Reduced breath holding and hyperventilation | • Breathing dysrhythmias are much less than 50% of the day | • Breathing dysrhythmias < 5% of the day | • 50% huffing and puffing, more with anxiety | |
| LD:3 6yrs. at dosing | CGI-S Domain Score | 3 | 3 | 3 | 3 | | |
| | No or minimal breathing abnormalities | | • No breath holding, hyperventilation | • No breath holding, hyperventilation | • No breath holding, hyperventilation | | |
| LD:4 7 yrs. at dosing | CGI-S Domain Score | 4 | 4 | | | | |
| | No breathing dysrhythmias | | • Breath holding 25% of the time | | | | |

**Time Post Treatment with NGN-401**

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As of data cut-off date of 17 October 2024

# Understanding the Rett Syndrome Behavior Questionnaire (RSBQ)

- Caregiver-completed scale consisting of 45 items measuring behavior in females with RTT
- Developed as a diagnostic tool to differentiate females with Rett syndrome from those with severe intellectual disability
- Scale is limited due to no questions on communication and very limited number of questions on gross motor function
- Higher score indicates greater behavioral symptoms; scale does not correlate with disease severity

| Subscales | Total Possible Points (90) |
|---|---|
| **General mood** | 16 |
| **Breathing problems** | 10 |
| **Hand behaviors** | 12 |
| **Repetitive face movements** | 8 |
| **Body rocking and expressionless face** | 12 |
| **Nighttime behaviors** | 6 |
| **Fear/anxiety** | 8 |
| **Walking/standing** | 4 |
| **Other** | 14 |

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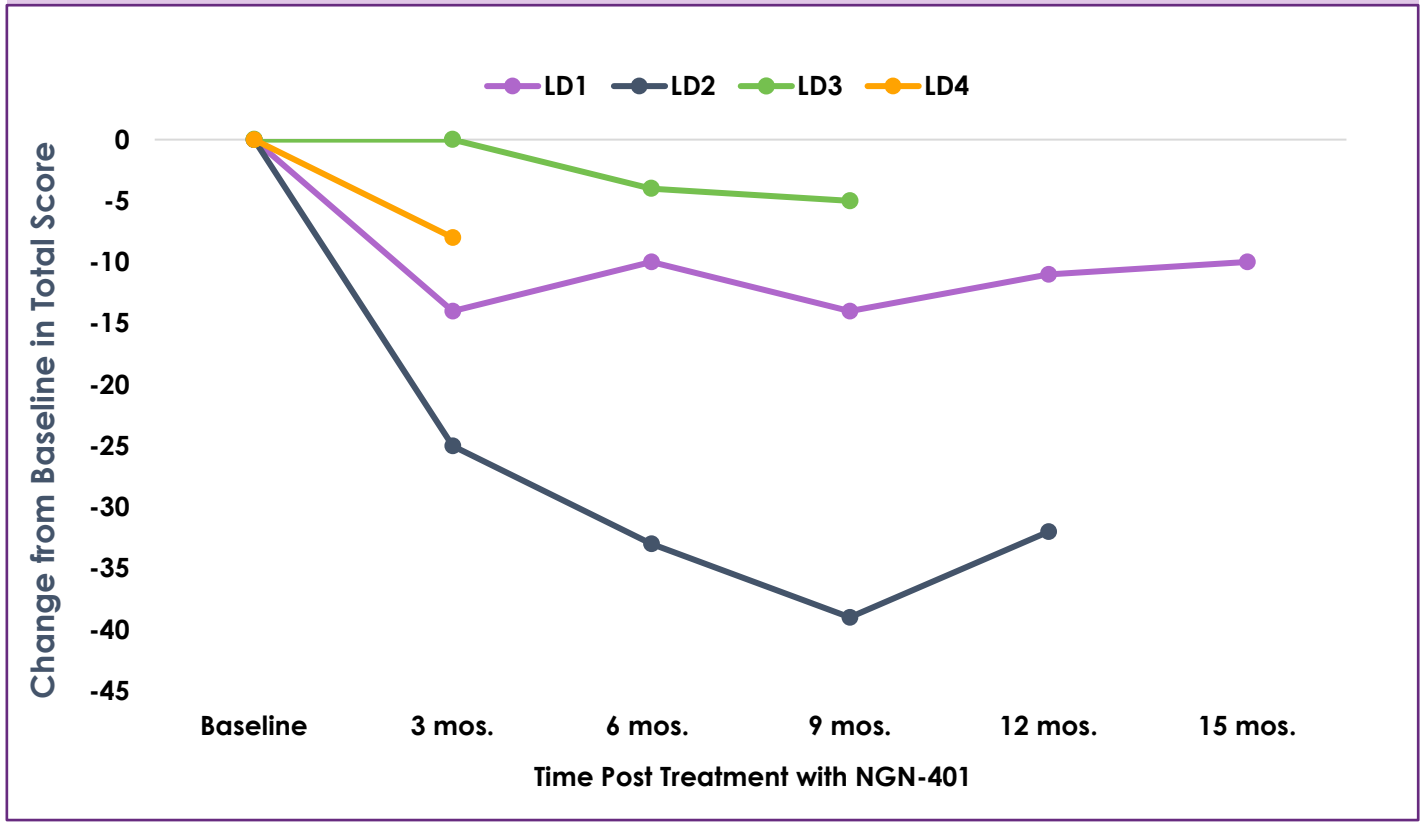
Percy A, et al. *Front Pediatr* (2023)

# All Participants Have Experienced Improvement in RSBQ Score

**RSBQ: Change from Baseline**
**Reduction in Score = Improvement**




| Participant | Baseline CGI-S Score | Baseline RSBQ Score | Change from Baseline | % Change |
|---|---|---|---|---|
| LD:1 | 4 | 39 | -10 | -28% |
| LD:2 | 5 | 62 | -32 | -52% |
| LD:3 | 5 | 17 | -5 | -29% |
| LD:4 | 5 | 29 | -8 | -28% |

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As of data cut-off date of 17 October 2024

# All Participants Experienced Improvements in Autonomic Function, as Measured by Objective Assessments

- **LD:1** and **LD:2**, who had sleep deficits at Baseline, experienced improvements in sleep parameters, as measured by a wearable device
  - LD:1 sleep efficiency increased from 83% to 90% at 6 months
  - LD:2 sleep efficiency increased from 90% to >95% at 6 months, considered ideal

- **LD:1**, **LD:2** and **LD:4** had constipation at Baseline, and experienced improvements over time as measured by the caregiver-reported modified Bristol Stool Form Scale

- **LD:3** had dysphagia, or difficulty swallowing, at Baseline, requiring a pureed diet and had to be spoon-fed by caregiver due to aspiration; she is now able to swallow liquids from a cup and chew and swallow food items

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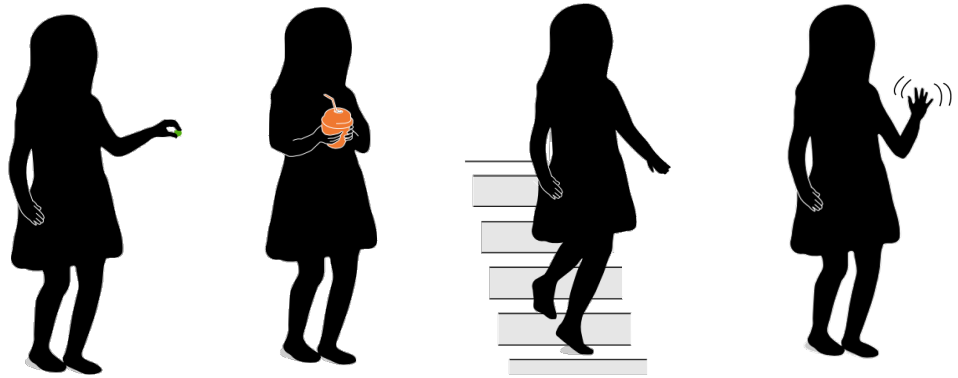
Detailed data provided in Appendix

# Participant Vignettes

# **LD:1** From Pre-Treatment to 15 Months Post NGN-401

| | | |
|---|---|---|
| **Hand Function / Fine Motor** | • Had a raking grasp, briefly held objects, dropping items quickly, with limited ability to self-feed | • Developed a pincer grasp, able to self-feed, has begun using a fork to eat; uses both hands to drink on her own |
| **Ambulation / Gross Motor** | • Walked independently, but would stay on her tip-toes, freeze often and required a parent to help her go up/down stairs or get on/off a bed | • More fluid gait with heel to toe walking, and does the following on her own: goes up/down the stairs, climbs out of high rimmed bathtub, gets on/off furniture, climbs out of her car seat to exit the car |
| **Language / Communication** | • Unable to indicate her wishes, follow simple commands from her parents, or express emotion | • Without being told, navigates her house to the car to go to school, waves hello to her grandfather on daily video calls, taps on food items to express choices, frowns/shouts to show displeasure<br>• Follows >10 commands such as "give a kiss," "sit down," "give it to me," "put item in trash," "open/close door," "flush toilet" |

**Baseline (7 years old)**



**Post Treatment with NGN-401**

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Images are representative of skills and are not photos of participants in the NGN-401 clinical trial
As of data cut-off date of 17 October 2024

# **LD:1** Multi-Domain Improvements Deepened Over Time, and Not Expected Based on Rett Syndrome Natural History

| | 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 | | | | ✓ | ✓ |

| LD:1 Complex Developmental Skills Learned/Re-Learned Well Outside RNHS | |
|---|---|
| LD:1 Newly Learned Complex Skills Post-NGN-401 | % Never Learned in RNHS |
| Climbs up stairs without help | 82% |
| Climbs down stairs without help | 86% |

| LD:1 Re-Learned Complex Skill Post-NGN-401 | % Re-Learned in RNHS |
|---|---|
| Waves hello* | 4% |

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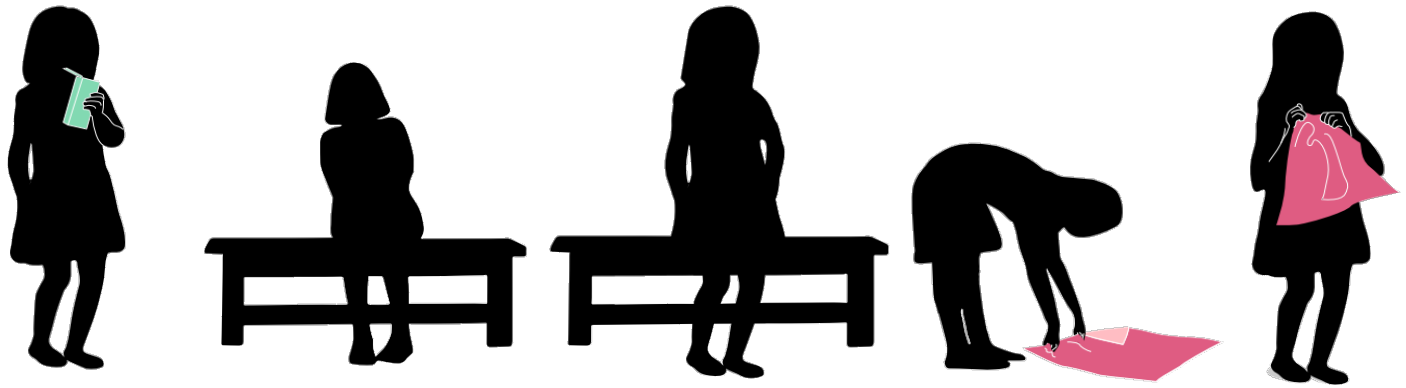
Data from the RNHS; N=200 female subjects with classic RTT, age 4-10 years, CGI-S score of 4 to 6 at baseline, confirmed genetic mutation
*Skill learned is "Wave hello;" however, RNHS tracked "Waves Bye Bye"
As of data cut-off of 17 October 2024

# **LD:2** From Pre-Treatment to 12 Months Post NGN-401

| | Baseline (4 years old) | Post Treatment with NGN-401 |
|---|---|---|
| **Hand Function / Fine Motor** | • Had no functional hand use, clenched hands, could not grab, reach, hold objects | • Holds juice box and drinks, starting to self feed, frequently grabs and holds her security blanket, places pacifier in her mouth to self-soothe, turns on videos by tapping tablet |
| **Ambulation / Gross Motor** | • Walked independently, but fell frequently, couldn't stand up from seated position without being pulled up, couldn't bend over | • Faster, steadier gait with infrequent falls; on her own she can: stand from seated position, bend over and pick up her blanket from the floor, step off a curb with one hand held |
| **Language / Communication** | • No babbling, no ability to make choices, not able to follow commands | • Says "mama," "dada," and "nana" clearly and in context<br>• Follows commands such as "come here" and "give a kiss" and more regularly choosing preferred foods |



Images are representative of skills and are not photos of participants in the NGN-401 clinical trial
As of data cut-off date of 17 October 2024

# **LD:2** Multi-Domain Improvements from Severe Impairments at Baseline Deepened Over Time, and Not Expected Based on Rett Syndrome Natural History

| | 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 | ✓ | ✓ | ✓ | ✓ |

| LD:2 Developmental Skills Learned/Re-Learned Well Outside RNHS | |
|---|---|
| LD:2 Newly Learned Complex Skills Post-NGN-401 | % Never Learned in RNHS |
| Follows a command without a gesture | 64% |
| **LD:2 Re-Learned Skills Post-NGN-401** | **% Re-Learned in RNHS** |
| Uses raking grasp to retrieve an object | 3% |
| Reaches for an object | 13% |
| Uses words with meaning | 8% |

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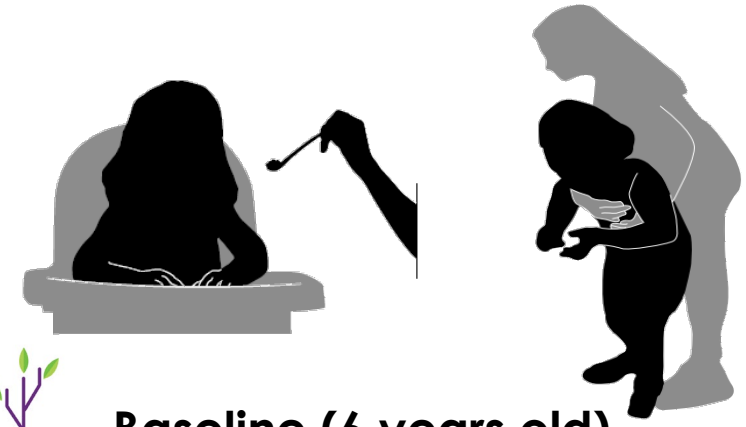
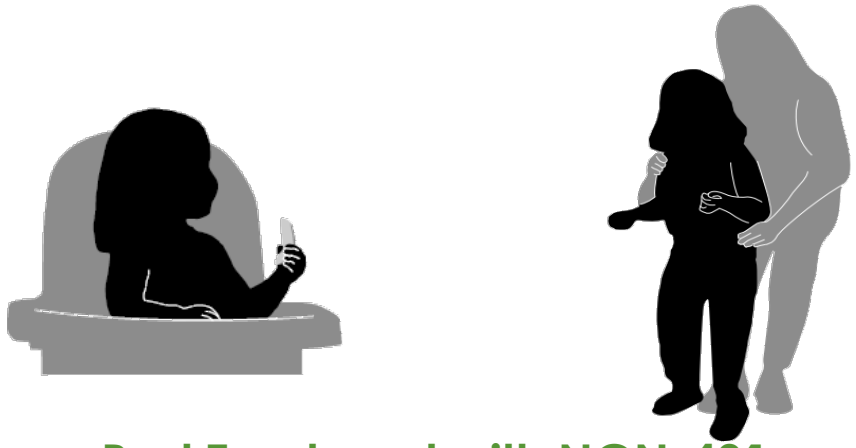
Data from the RNHS; N=200 female subjects with classic RTT, age 4-10 years, CGI-S score of 4 to 6 at baseline, confirmed genetic mutation
As of data cut-off date of 17 October 2024

# LD:3 From Pre-Treatment to 9 Months Post NGN-401

| | | |
|---|---|---|
| **Hand Function / Fine Motor** | • Raking grasp, required caregiver to spoon feed all meals due to inability to swallow anything safely other than pureed food | • Able to self-feed solid foods, swallow liquids |
| **Ambulation / Gross Motor** | • Could not sit, stand, or walk independently due to poor core strength and lower extremity weakness | • Sits independently, improved posture, able to stand with less support, able to advance feet forward better with support |
| **Language / Communication** | • No choice making, babbling; not able to follow commands | • Laughs at jokes made by caregiver<br>• Makes some choices |



**Baseline (6 years old)**



**Post Treatment with NGN-401**

Images are representative of skills and are not photos of participants in the NGN-401 clinical trial
As of data cut-off date of 17 October 2024

# LD:3 Multi-Domain Improvements Not Expected Based on Rett Syndrome Natural History

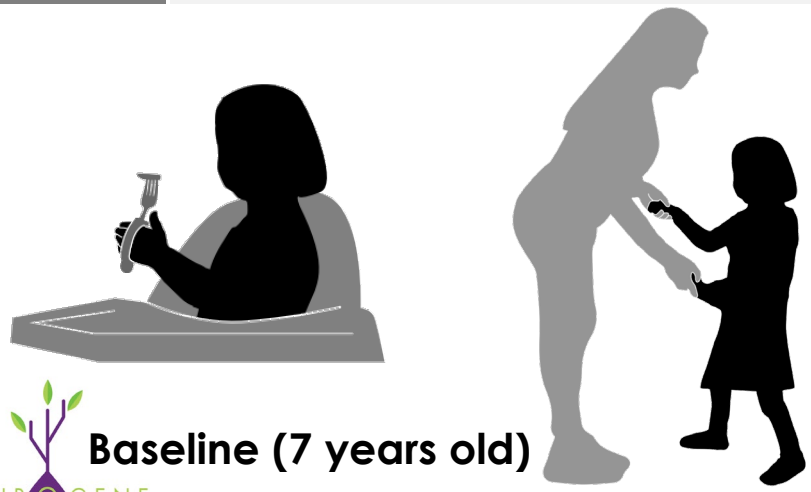
| | Select LD:3 Developmental Skills | Months Post-NGN-401 | | |
|---|---|---|---|---|
| | | 3 | 6 | 9 |
| Fine Motor | Uses a pincer grasp | | ✓ | ✓ |
| Fine Motor | Able to self-feed | | | ✓ |
| Gross Motor | Sits independently | ✓ | ✓ | ✓ |

| LD:3 Developmental Re-Learned Well Outside RNHS | |
|---|---|
| LD:3 Re-Learned Skills Post-NGN-401 | % Re-Learned in RNHS |
| Uses a pincer grasp | 6% |
| Able to self-feed | 8% |
| Sits independently | 7% |

Data from the RNHS; N=200 female subjects with classic RTT, age 4-10 years, CGI-S score of 4 to 6 at baseline, confirmed genetic mutation
As of data cut-off date of 17 October 2024

# LD:4 From Pre-Treatment to 3 Months Post NGN-401

| | | |
|---|---|---|
| **Hand Function / Fine Motor** | • Raking grasp, able to use adaptive utensils to self-feed, unable to hold or use regular utensils | • Able to use regular utensils to self-feed, reaches with more precision |
| **Ambulation / Gross Motor** | • Could not stand or walk independently | • No substantial improvement observed yet at 3 months post treatment with NGN-401 |
| **Language / Communication** | • No babbling, unable to follow commands, laughed out of context | • Laughs at appropriate moments while watching favorite movie or listening to an audio program<br>• Vocalizes to express discomfort or show emotion |



**Baseline (7 years old)**

**Post Treatment with NGN-401**

Images are representative of skills and are not photos of participants in the NGN-401 clinical trial
As of data cut-off date of 17 October 2024

# LD:4 Early Improvements in Hand Function Not Expected Based on Rett Syndrome Natural History

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

| LD:4 Developmental Skills Learned Well Outside RNHS | |
|---|---|
| LD:4 Newly Learned Complex Skill Post-NGN-401 | % Never Learned in RNHS |
| Can use utensils to self-feed (without assistance) | 80% |

Data from the RNHS; N=200 female subjects with classic RTT, age 4-10 years, CGI-S score of 4 to 6 at baseline, confirmed genetic mutation
As of data cut-off date of 17 October 2024

# Neurogene: Differentiated Clinical-Stage Company Utilizing EXACT Technology to Treat Complex Neurological Diseases

## NGN-401: Best-in-Class Potential w/ Compelling Interim Data

- Potential best-in-class efficacy: Durable and concordant improvements observed across multiple scales, incl. two-point improvement in CGI-I in all participants
- Consistent gains observed across core clinical domains incl. hand function, gross motor, communication and autonomic function
- Favorable safety profile with low-dose NGN-401

## Expedited Regulatory Path for NGN-401 via START and RMAT

- START Pilot Program: provides clear communication channel with FDA to accelerate registrational planning
- RMAT designation: eligibility for Accelerated Approval pathway and rolling BLA and potential for Priority Review

## Recent Accomplishments

- FDA alignment on CMC potency assay strategy and manufacturing scale-up planning
- Initiated adolescent/adult high-dose cohort
- Registrational study planning underway

**Wholly-owned and fully integrated in-house manufacturing capabilities designed for commercial scale**

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As of data cut-off date of 17 October 2024

# Next Steps

# Key Upcoming Anticipated Milestones and Pipeline Developments

## Rett syndrome (NGN-401)

- ☑ Expand ongoing Phase 1/2 clinical trial in 1H:24 to enroll a larger cohort of pediatric patients
- ☑ Interim Phase 1/2 clinical data in pediatrics in 4Q:24
- ☑ Complete low-dose enrollment in pediatrics in 4Q:24 (N=8)
- ❑ ***Provide regulatory update in 1H:25 regarding pivotal trial design***
- ❑ Announce additional Phase 1/2 clinical data in 2H:25

## Early-stage discovery

- ❑ Advance one program into the clinic (2025)

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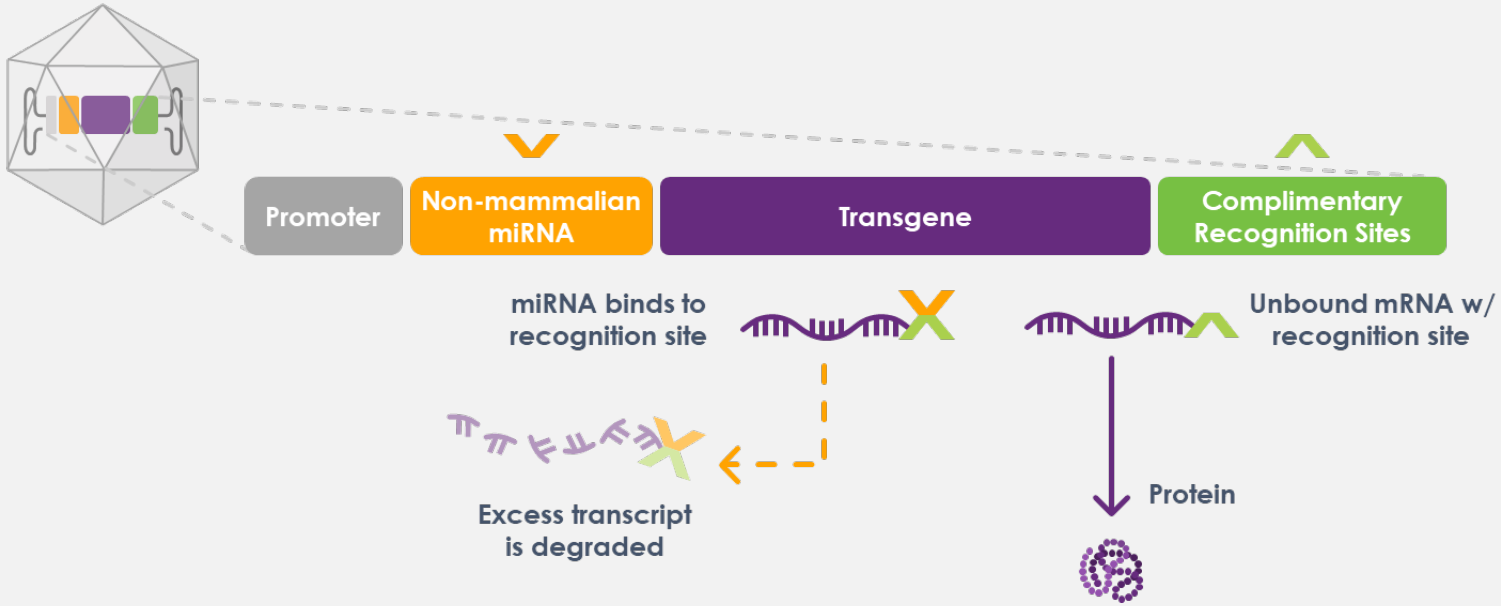
# Thank You

# Presentation Appendix

# NGN-401 Designed to be Best-in-Class Gene Therapy for Treatment of Rett Syndrome




**Intracerebroventricular (ICV) administration** delivers *MECP2* to regions of the brain involved in pathophysiology of Rett syndrome

**Mammalian ubiquitous promoter** used broadly in approved gene therapy products

**Full-length human *MECP2* gene** maximizes potential for efficacy

**EXACT™** designed to fine-tune transgene expression to deliver consistent levels across wild type and deficient cells without overexpression toxicity

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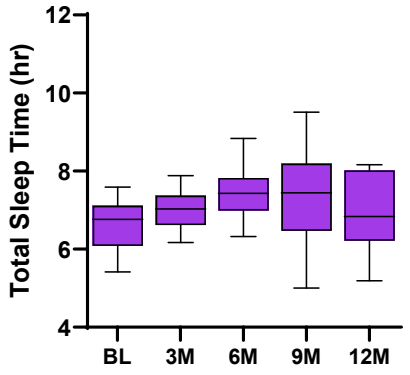
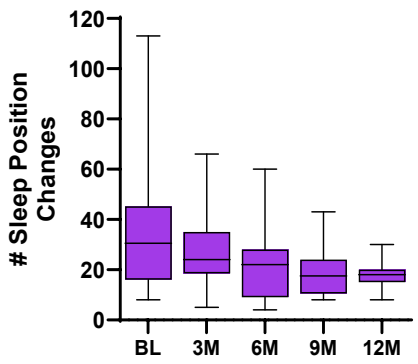
# **LD:1 Autonomic Function:** Objective Improvements Observed in Sleep Parameters and Constipation

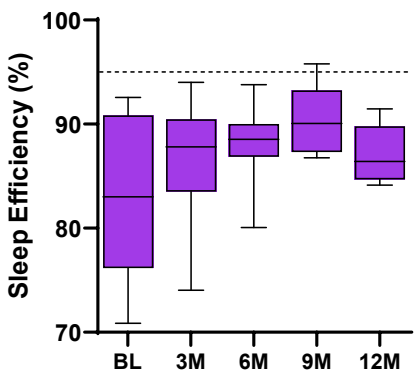
## Improvements in All Sleep Parameters, as Assessed by Wearable Device




Total sleep time **increased from 6.6 to 7 hrs./night**

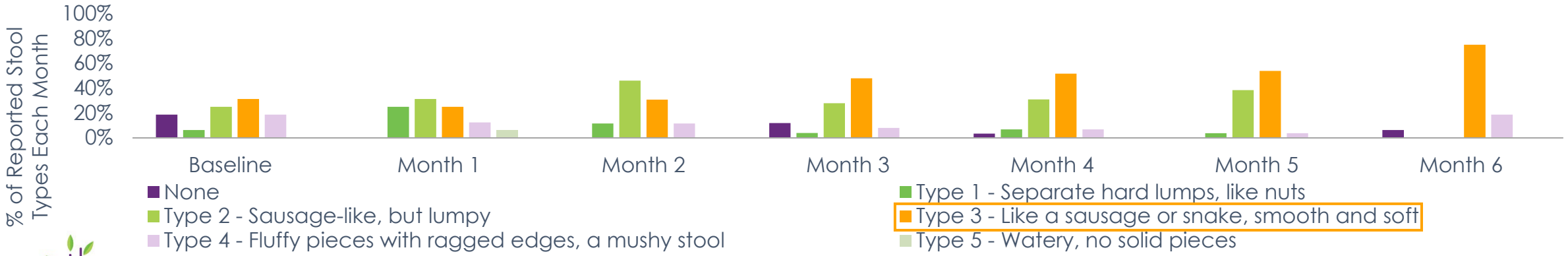



Number of position changes **decreased from 37 to 18** per night




Sleep efficiency* **increased from 83% to ~90%** (95% is ideal)

## Constipation Improved Over Time, as Measured by Stool Consistency and Frequency**

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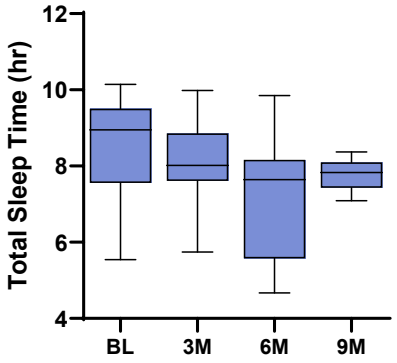
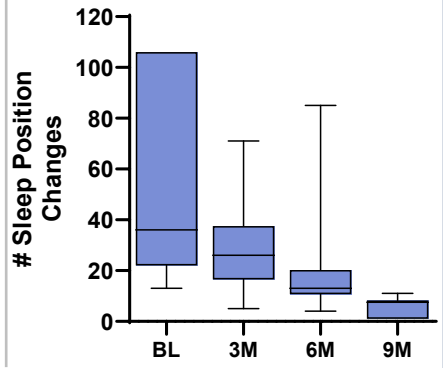
*Sleep efficiency defined as time spent asleep vs. total time spent in bed
**As measured by Caregiver on modified Bristol Stool Form Scale
As of data cut-off date of 17 October 2024

# **LD:2 Autonomic Function:** Objective Improvements Observed in Sleep Parameters and Constipation

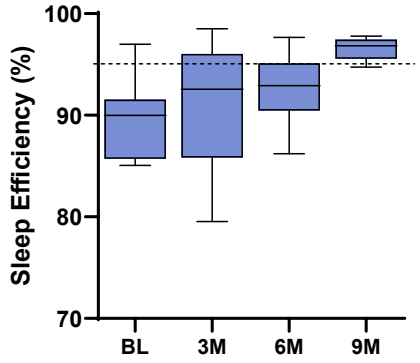
## Transition to More Restful Sleep, as Assessed by Wearable Device




Total sleep time decreased; however, **more restful sleep occurring**

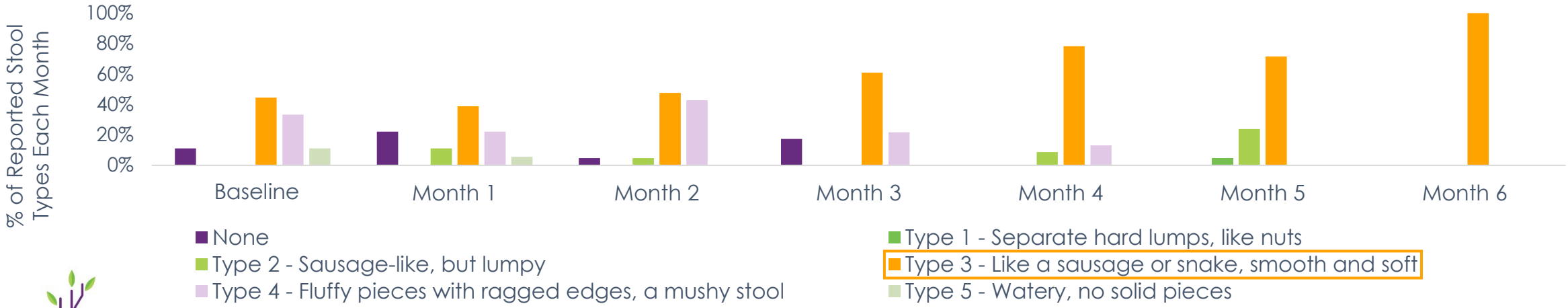



Number of position changes **decreased from 37 to 8** per night




Sleep efficiency* **increased to >95%**, which is ideal

## Constipation Improved Over Time, as Measured by Stool Consistency and Frequency**




*Sleep efficiency defined as time spent asleep vs. total time spent in bed
**As measured by Caregiver on modified Bristol Stool Form Scale
As of data cut-off date of 17 October 2024

# LD:3 Autonomic Function: Experienced Clinically Meaningful Improvement in Swallowing and Gained Ability to Self-feed

At Baseline, LD:3 had dysphagia requiring a pureed diet and had to be spoon-fed by caregiver due to aspiration

Beginning 3 months post-NGN-401, LD:3 could swallow liquids, such as clear soup and water from a sippy cup, and chew and swallow soft items, such as meatballs and cooked carrots, without choking

At 9 months post-NGN-401, she is now able to grasp food such as apple slices and self-feed

**LD:3 did not have Baseline deficits in autonomic categories of sleep or constipation**

- Sleep duration and quality maintained post-treatment
- No change in Modified Bristol Stool Form Scale scores post-treatment

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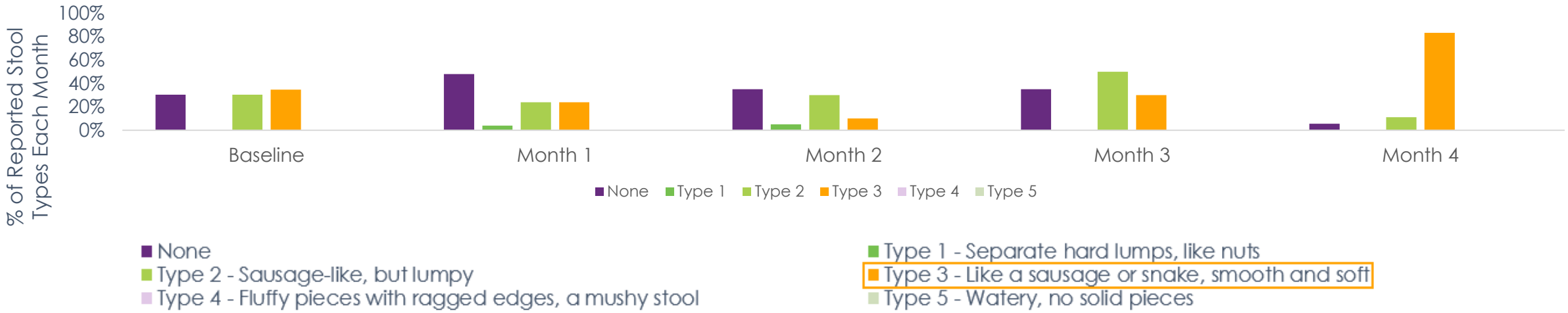
As of data cut-off date of 17 October 2024

# LD:4 Autonomic Function: Objective Improvement Observed in Constipation

**Constipation Improved in Month 4, as Measured by Stool Consistency and Frequency***




**LD:4 did not have Baseline deficits in autonomic category of sleep**

Sleep quality maintained post-treatment

*As measured by Caregiver on modified Bristol Stool Form Scale
As of data cut-off date of 17 October 2024