Daily Living Skills on the Vineland Adaptive Behavioral Scale Version 2 (VABS-II) Following Investigational RGX-121 Treatment in Neuronopathic Mucopolysaccharidosis Type II (MPS II)

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Introduction

Neuronopathic MPS II

- MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) enzyme leading to accumulation of glycosaminoglycans (GAGs). In neuronopathic MPS II, GAGs accumulate in neuronal tissue producing progressive cognitive deterioration, severe behavioral disturbances and global developmental delay.
- Neuronopathic MPS II results in irreversible neurodevelopmental decline that is not addressed by intravenously administered enzyme replacement therapy.
- Patients with neuronopathic MPS II experience significantly lower functioning in daily living and socialization skills compared to normative data and compared to patients with attenuated MPS II.[1] Expressive Language, Personal Daily Living Skills and Interpersonal Relationships had the lowest mean values in natural history at > 3SD from normative mean.[1]
- The body system impairments typical to neuronopathic MPS II impact the child's ability to perform activities of daily living and children often require assistance or accommodations to complete tasks.[2] Children with neuronopathic MPS II who are <5 years of age have more challenges with dressing, toileting, eating, bathing, conversation and understanding compared to typically developing peers.[2]

VABS-II

- The VABS-II is an individually administered measure of adaptive behavior for ages birth through 90 years.[3] Adaptive behavior is defined as the personal and social skills for everyday living. [3]
- The VABS-II has excellent test-retest reliability coefficients and good to excellent internal consistency. [3]

The VABS-II Expanded Interview Format

- The interviewer asks open ended questions to prompt the respondent to talk about the examinees behaviors in the areas assessed. The interviewer does not read the items to the respondent or ask him/her to provide the scores. The interviewer uses the elicited information to score the items him or herself.
  - Technique is designed to reduce inaccuracies that may result from the respondent not comprehending item content or misreporting (deliberate or unintentional).
  - Provides more consistent scoring because the scoring is the responsibility of the interviewer, who is a trained professional with a thorough understanding of the criteria for scoring each item and who can probe in depth as necessary, to obtain sufficient information to score each item correctly.
- Includes Communication, Daily Living Skills, Socialization and Motor Skills. Each item is scored on a 5-point rating system based on frequency that behaviors are completed such as almost always, often, sometimes, rarely and never.
- The domains and subdomains are listed in Table 1. From each subdomain a V score (mean 15, SD of 3) and age equivalent score (AEq) can be derived. The highlighted subdomains of Daily Living Skills/Personal, Socialization/Play and Leisure Time and Socialization/Interpersonal represent daily activity content that is relevant to children less than 5 years old with neuronopathic MPS II.

Table 1. VABS-II Domains and Subdomains

Domains	Subdomains
Communication	• Receptive: Understanding and responding to information from others • Expressive: Using words and sentences to express oneself • Written: Using reading and writing skills
Daily Living Skills	• Personal: Feeding, bathing, dressing, toilet training, brushing teeth
	• Domestic: Housecleaning/chores, food preparation, safety in home
	• Community: Telephone, safety outside home, calendar, time, money, using TV/radio/computer, restaurant skills etc.
Socialization	• Interpersonal Relationships: Social behaviors, emotions, helping, friendships, caring
	• Play and Leisure Time: playing with others, make believe, sharing, rules in games, social cues
	• Coping Skills: transitions, following rules, manners, controlling anger, physical and social safety, making decisions
Motor Skills	• Fine: One and two hand play, puzzles, coloring, doors and locks, drawing and writing, scissors/tape and glue, complex coordination skills, keyboarding
	• Gross: sitting, crawling, walking, climbing, stairs, jumping and hopping, ball skills, bicycle, carrying items, stamina
Maladaptive Behaviors	• Internalizing: caregiver dependence, withdrawal, sleeping and eating disturbances, anxiety, unsociable
	• Externalizing: impulsive, temper tantrums, disobeys rules, interrupts, stubborn, irritable, inappropriate behavior

Methodology

- In this phase I/II multi-center, open label study (NCT 03566043), participants with neuronopathic MPS II ages 4 months to 5 years receive one image-guided investigational RGX-121 injection to the central nervous system (CNS). RGX-121 is a recombinant adeno-associated virus serotype 9 capsid containing a human I2S expression cassette (AAV9.CB7.hIDS) that may provide a permanent source of secreted I2S.
- The VABS-II expanded interview format is used to assess the RGX-121 efficacy response related to the behavior, language, personal and social skills required for everyday living.
- The VABS-II AEq change from baseline is presented as the proportion of patients with skill acquisition, stability or decline in each subdomain. Change indices were developed from caregiver interviews to identify what would constitute a meaningful change. Change from baseline was defined by the following criterium:
  - Improvement defined as increase of ≥3 months on AEq
  - Stability defined as change from-3 < to <+3 AEq
  - Deterioration defined as decline ≥-3 AEq
- Additional analyses were completed on areas highlighted in Table 1; the Daily Living Skills/Personal, Socialization/Play and Leisure Time and Socialization/Interpersonal subdomains. Individual item scores for each content area in the listed subdomains have been summed to identify primary areas of functional change. Data is presented as the proportion of participants with any increase in total raw score.
- VABS-II language and motor analyses are not included within the scope of this poster.
- The Maladaptive Behavior Index is presented for each individual patient by baseline function. Average performance on the VABS-II Maladaptive Behavior domain is defined as a V scale score from 1-17. In children 3-5 years the maximum Maladaptive Behavior Index value that corresponds to a V scale of 17 is 11. A Maladaptive Behavior Index of <12 is defined as average performance for the population of participants in this study.

Interim Results

- Data is presented from 14 caregivers of participants who received investigational RGX-121 and have available longitudinal data of at least 6 months*. All patients in the study were male and have a confirmed diagnosis of neuronopathic MPS II.
- Study participants came from various geographic areas throughout the United States and Brazil. The age range at dosing ranged from 5 to 59 months.
- The majority of participants demonstrated stabilization or ongoing skill acquisition for the Receptive and Expressive Communication, Personal, Domestic, Community, Interpersonal Relationships, Play and Leisure Time and Coping Skills (Figure 1). The Written Subdomain includes reading and writing skills and is generally not applicable to a population of children < 5 years old.

Subdomain Content

- **Personal Subdomain**: 42.9 % of participants had an improved AEq of ≥3 months and 57.1% of participants stabilized. The activity areas with the greatest proportion of participants showing improvement were dressing, feeding and toilet training (Figure 2.).
- **Interpersonal Relationships Subdomain**: 42.9% of participants had an improved AEq of ≥3 months and 42.9% of participants stabilized. The activity areas with the greatest proportion of participants showing improvement were responding to familiar people, expressing and recognizing emotions, identifying self and others, imitating and beginning social behavior (Figure 3.)
- **Play and Leisure Time Subdomain**: 42.9% of participants had an improved AEq of ≥3 months and 50% of participants stabilized. The activity areas with the greatest proportion of participants showing improvement were beginning play, playing with others, make believe and sharing (Figure 4.).
- **Maladaptive Behavior:** 7 of 9 participants with elevated maladaptive behavior at baseline achieved a reduction in the maladaptive behavior index (Figure 5.). 4 of 5 participants with average maladaptive behavior for age at baseline maintained expected behavior for age (Figure 6.).

Figure 1. Change from Baseline in Age Equivalent VABS-II Scores by Subdomain

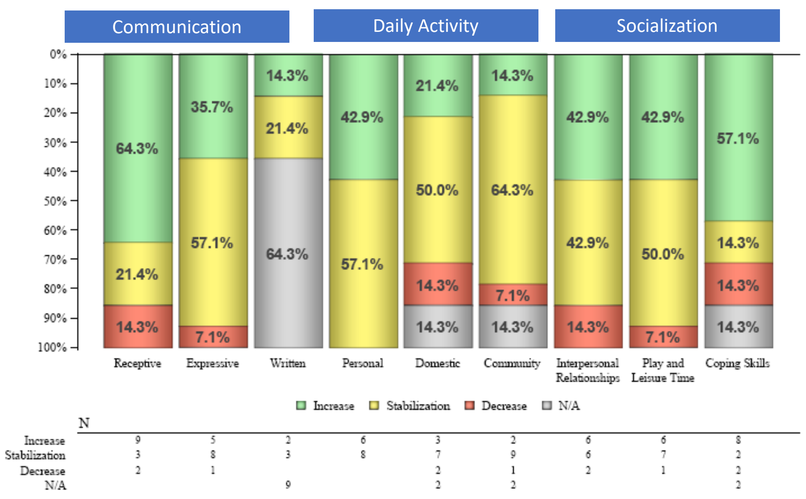


Figure 2. Proportion of Participants with Improvement from Baseline in VABS-II Daily Activity Personal Raw Scores

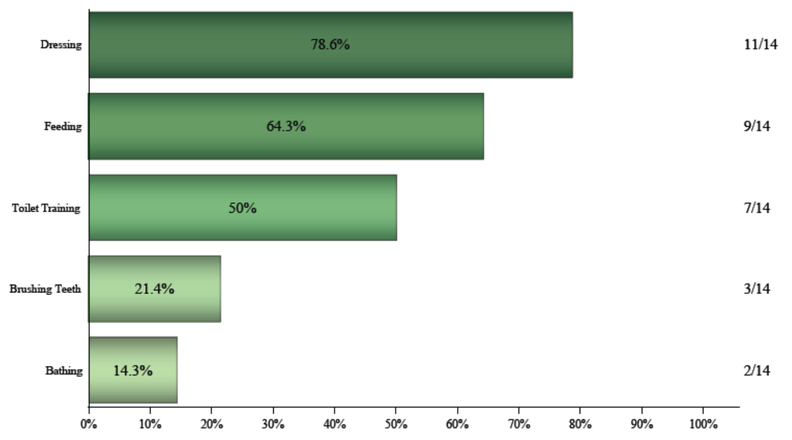


Figure 3. Proportion of Participants with Improvement from Baseline in VABS-II Socialization Interpersonal Relationship Raw Scores

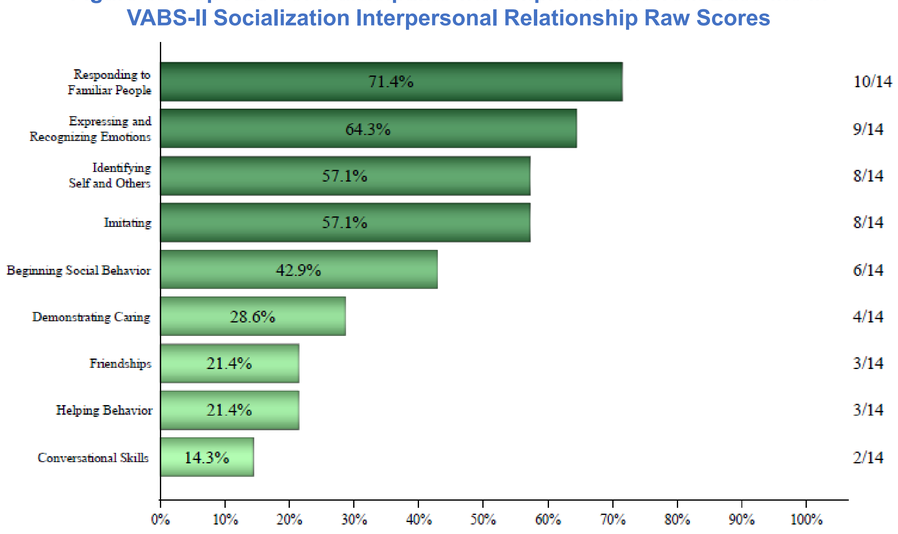


Figure 4. Proportion of Participants with Improvement from Baseline in VABS-II Socialization Play and Leisure Raw Scores

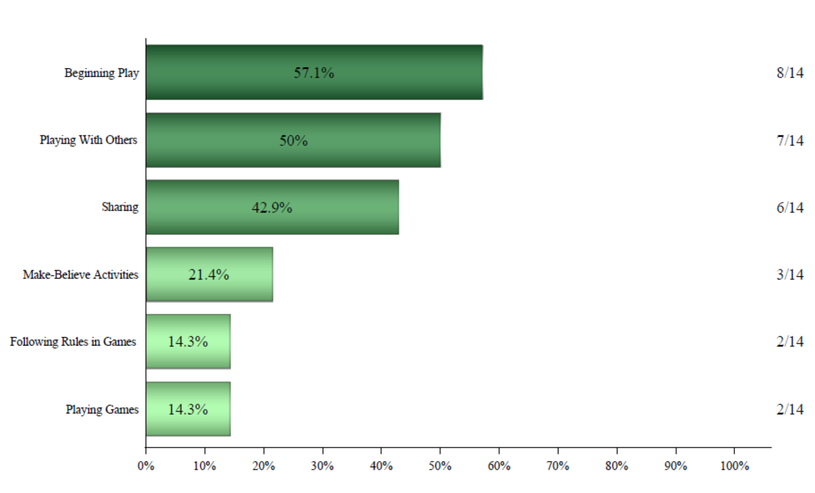


Figure 5. Change in Maladaptive Behavior in Participants with Elevated Scores at Baseline (≥ 12)

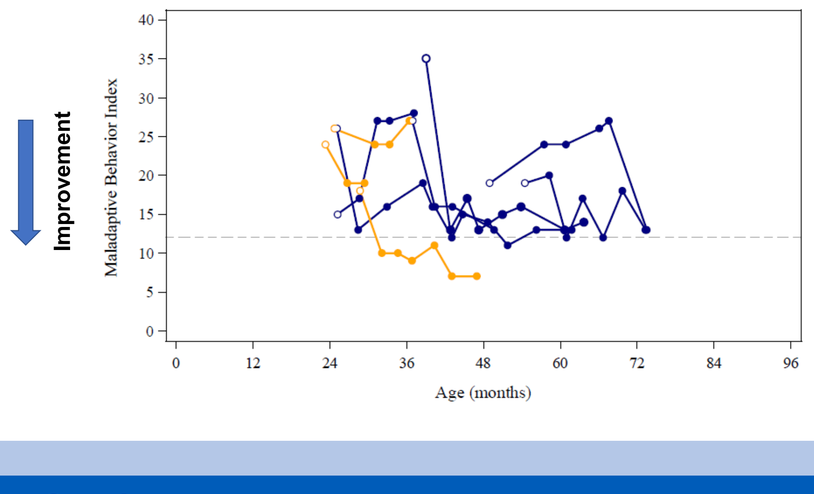
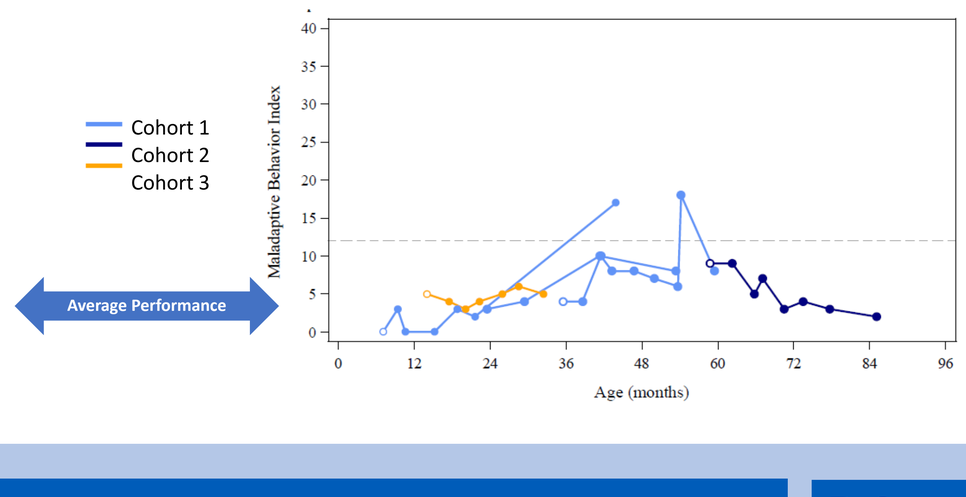


Figure 6. Change in Maladaptive Behavior in Participants with Average Performance at Baseline (<12)



Discussion and Interim Conclusions

- Body system impairments typical to neuronopathic MPS II impact the child's ability to perform activities of daily living and children often require assistance or accommodations to complete tasks.[2]
- Patient experience data from the caregiver perspective can help to quantify the disease impact on age-appropriate daily functioning and how the symptoms may change following RGX-121 administration.
- The expanded interview format of the VABS-II provides the caregiver perspective on their child's daily function and behavior. The interview format reduces potential recall inaccuracies and bias.
- The poster highlights areas of functional change in activities of daily living following investigational RGX-121 treatment in a phase I/II clinical trial for children < 5 years at baseline with neuronopathic MPS II.
  - The majority of participants demonstrated stabilization or ongoing skill acquisition on age-appropriate subdomains following RGX-121 administration. The subdomains include Receptive and Expressive Communication, Personal, Domestic, Community, Interpersonal Relationships, Play and Leisure Time and Coping Skills.
  - Key areas of improvement include dressing, feeding and toilet training and socialization behaviors that support the development of interpersonal relationships and collaborative play.
- Maladaptive behavior is a key disease impairment that impacts daily activity for children with neuronopathic MPS II. The majority of participants with an elevated maladaptive behavior index at baseline demonstrated improved behavior.
- The data presented includes all participants and did not separate by disease severity at baseline. Additional analyses will be conducted related to magnitude of change by baseline function.

* Interim analysis with data cut January 3, 2023

References

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3. Sparrow, S. S., Cicchetti, D., & Balla, D. A. (2005). *Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)* [Database record]. APA PsycTests. https://doi.org/10.1037/t15164-000

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