RGX-121 Gene Therapy for the Treatment of Severe Mucopolysaccharidosis Type II:

Interim Analysis of the First in Human Study

Presented by:

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Mucopolysaccharidosis Type II (MPS II)

MPS II is also known as Hunter syndrome

Rare X-linked recessive genetic disease (predominantly occurs in males)

Caused by a deficiency of iduronate-2-sulfatase (I2S), an enzyme required for the degradation of the glycosaminoglycans (GAGs)

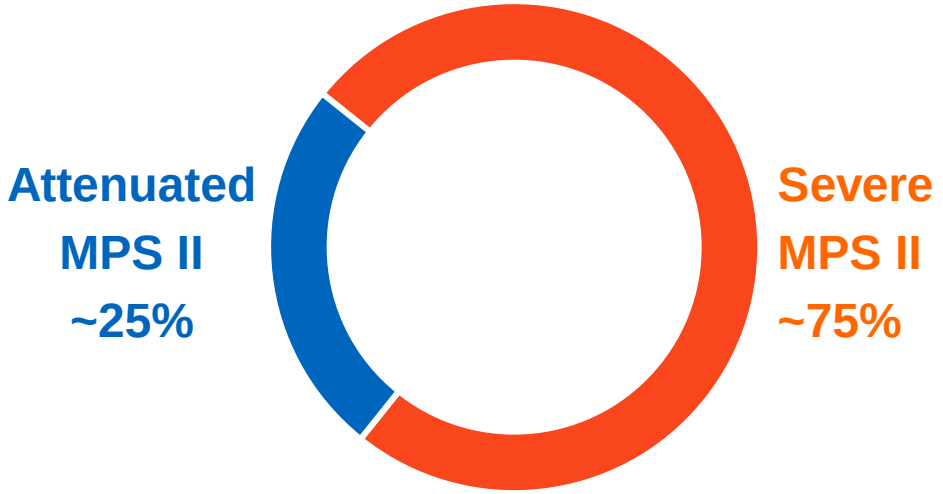
GAG build-up causes:

- Systemic Symptoms
- Frequent Neurodegeneration
- Early Death

Standard of care includes IV enzyme replacement therapy (ERT), which does not address CNS disease involvement

Incidence

Prevalence



1. Martin (2008) Pediatrics
2. Scarpa, https://www.ncbi.nlm.nih.gov/books/NBK1274) 2007; Updated 2018

RGX-121: MPS II Phase 1/2 Clinical Study Summary

NCT03566043 on ClinicalTrials.gov

Participants

Enrollment up to 18 severe MPS II patients
(≥ 4 months to < 5 years of age)

May be on Standard of Care IV ERT
or
ERT Naïve

Cohorts (dose levels)

Genome copies/g brain mass

RGX-121
AAV9 + *IDS*

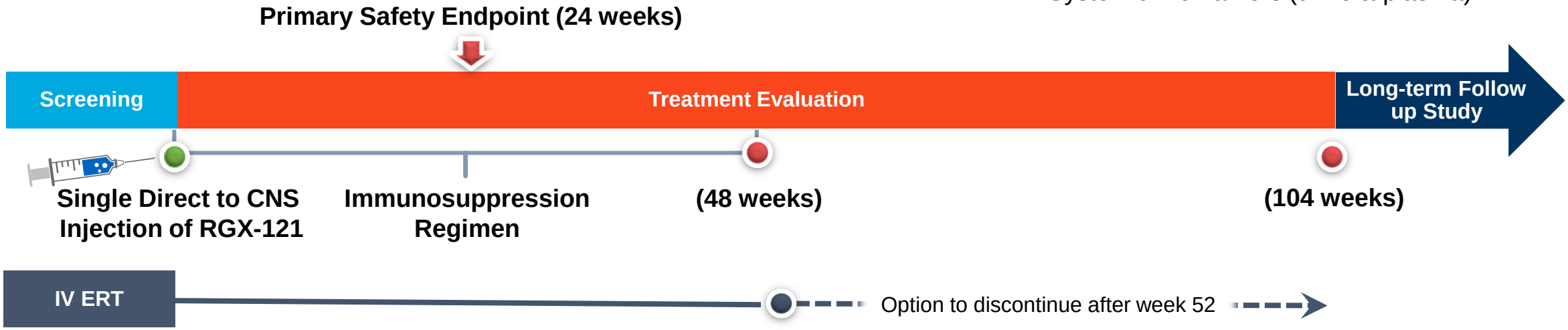
Cohort 1: 1.3 x 10^{10}
Cohort 2: 6.5 x 10^{10}
Cohort 3: 2.9 x 10^{11} *

Data

Primary Endpoint is Safety

Secondary & Exploratory Endpoints Include:

- CSF Biomarkers (Heparan Sulfate / D2S6)
- Neurodevelopmental Assessments (Bayley)
- Caregiver Reported Outcomes (VABC; SDSC)
- Systemic Biomarkers (urine & plasma)

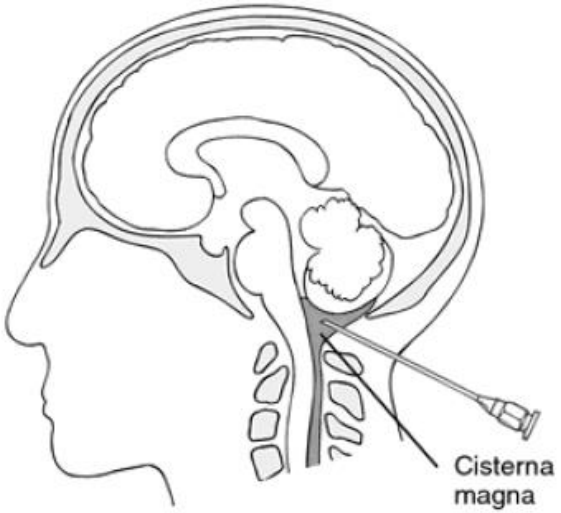


* Cohort 3 was previously reported as 2.0 x10^{11} GC/g of brain mass based on a Poly-A-specific PCR assay. This is equivalent to 2.9x10^{11} GC/g of brain mass using a transgene-specific PCR assay

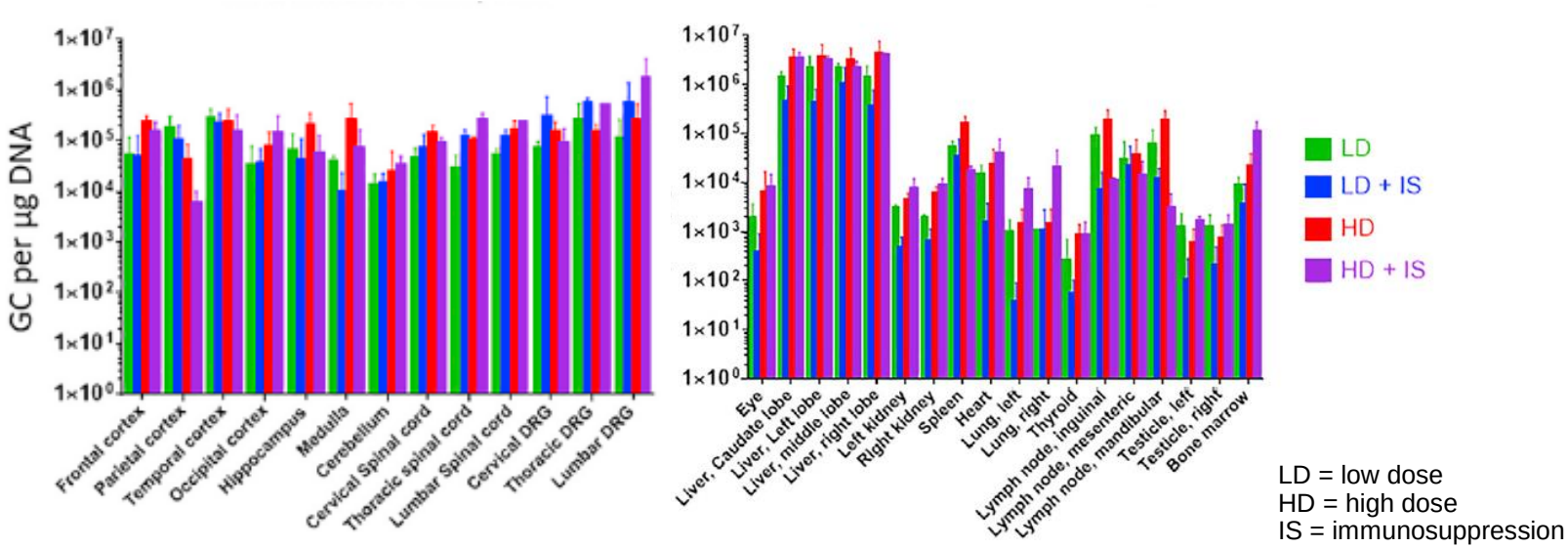
RGX-121 Central Nervous System Administration

Image-guided Intracisternal (IC) administration

- Modern imaging makes IC administration feasible[1]



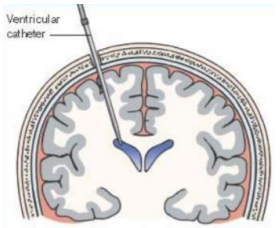
- Non-human primate studies indicate widespread CNS and systemic biodistribution after RGX-121 IC administration[2]



LD = low dose
HD = high dose
IS = immunosuppression

Image-guided Intracerebroventricular (ICV) administration

- For participants in whom IC administration may not be anatomically feasible, ICV administration will be considered



1. Ward (1989) Neurosurgery 2. Hordeaux (2018) Mol Ther Methods Clin Dev

RGX-121 Phase 1/2 Cohorts

- 13 participants dosed as of December 20, 2021
- Ages at dosing range from 5 months to 59 months
- *IDS* Mutations among severe MPS II trial participants include missense, gene inversion, and frameshift
- No SAEs related to study drug as of December 20, 2021
- Immunosuppression discontinued in all eligible participants (n = 8) per protocol

Cohort	N	Dose (GC/g Brain Mass)	Follow-Up (Weeks)	Immunosuppression Regimen Status	ERT (IV) Status†
Cohort 1	3	1.3×10^{10}	104	3 completed	1 weekly 2 discontinued
Cohort 2	7	6.5×10^{10}	8-104 wk	5 completed 2 active	4 weekly 1 discontinued 2 naïve
Cohort 3	3	2.9×10^{11}*	8-36 wk	3 active	3 weekly

* Cohort 3 was previously reported as 2.0 $\times 10^{11}$ GC/g of brain mass based on a Poly-A-specific PCR assay. This is equivalent to 2.9×10^{11} GC/g of brain mass using a transgene-specific PCR assay.

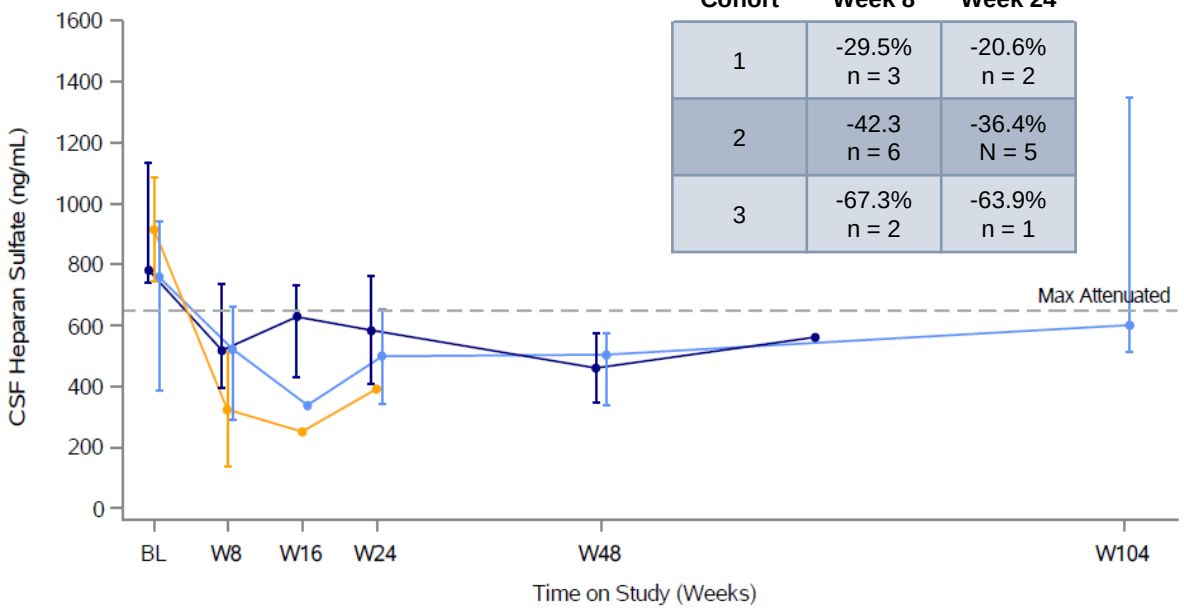
† Protocol allows ERT discontinuation after Week 52

Cerebrospinal Fluid (CSF) Biomarker: Heparan Sulfate (HS)

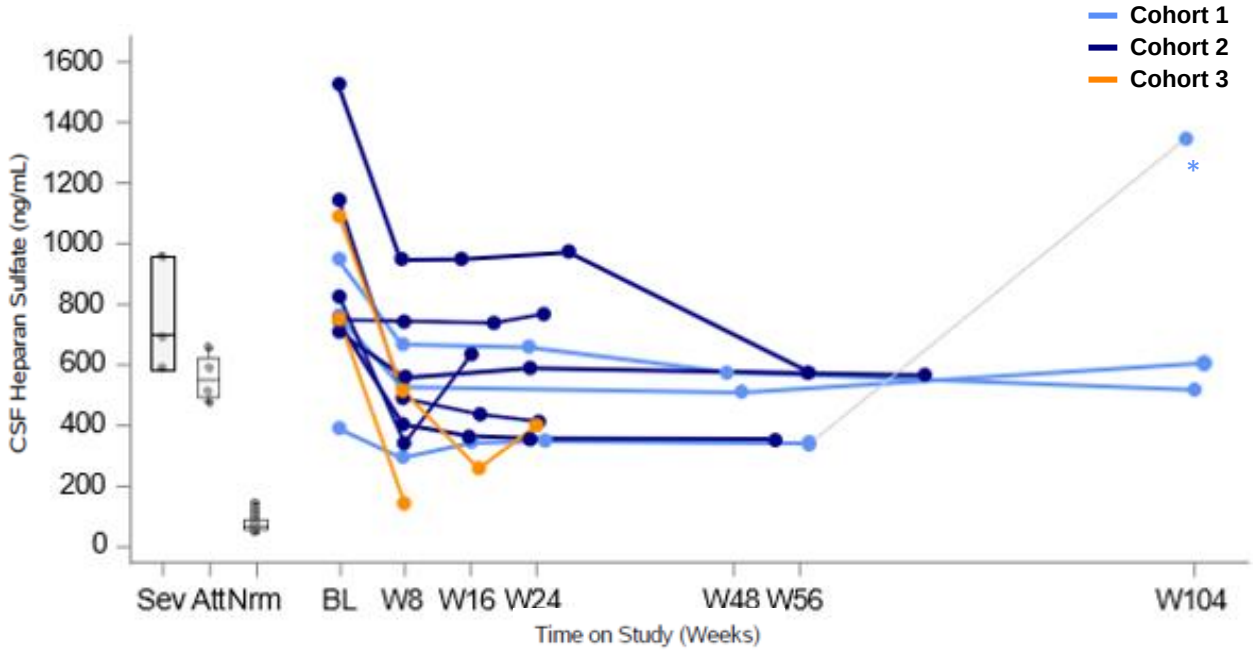
Cohorts (median†)

HS Reductions

Cohort	Week 8	Week 24
1	-29.5% n = 3	-20.6% n = 2
2	-42.3 n = 6	-36.4% N = 5
3	-67.3% n = 2	-63.9% n = 1



Individual Participants



- CSF HS measurements showed dose-dependent reductions in Cohorts 1-3 at Weeks 8 and 24
- Majority of participants in all three cohorts demonstrated decreased CSF HS at last time point available

Data cut December 20, 2021

* CNS related clinical event (ventriculoperitoneal shunt infection) took place on Day 522 post RGX-121 administration in this Cohort 1 patient that was deemed unrelated to study drug
† Median CSF HS concentration +/- Q1 and Q3 per cohort.
Normative data are based on 29 normal samples. The ages for 9 normative samples range from 1 month to 21 years old.
Severe defined as IQ < 70. The ages of 3 severe samples range from 4 years 8 months to 10 years old.
Attenuated defined as IQ ≥ 70. The ages of 4 attenuated samples range from 11 years to 29 years old.

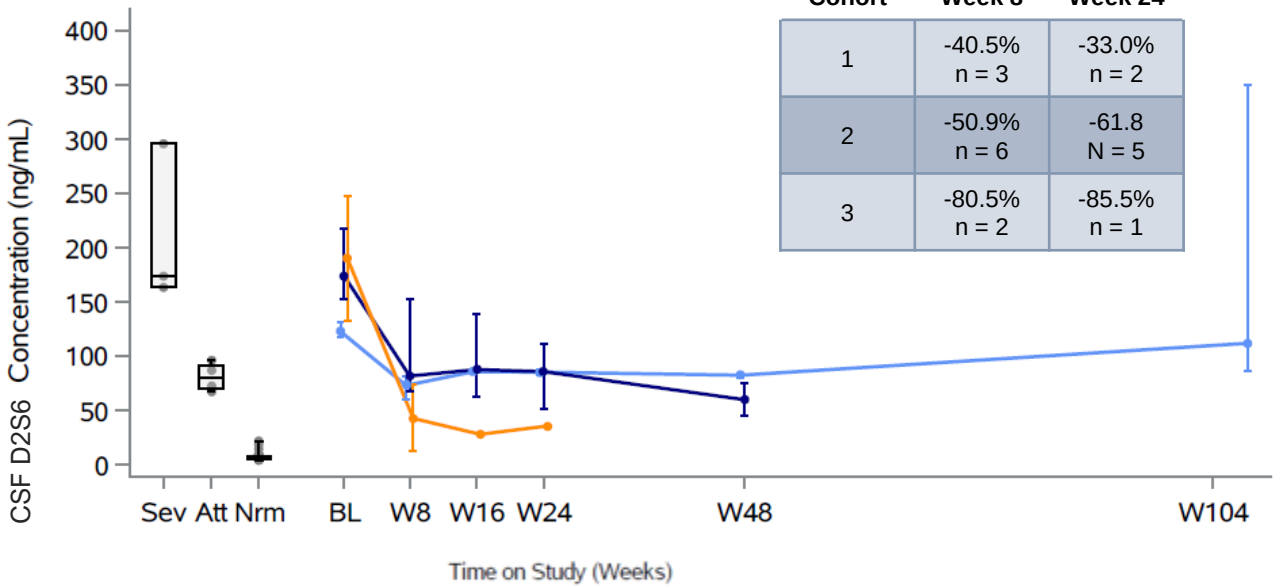
CSF Biomarker: HS D2S6 Disaccharide

D2S6 is a Correlate of Neuropathology Phenotype in severe MPS II[1-3]

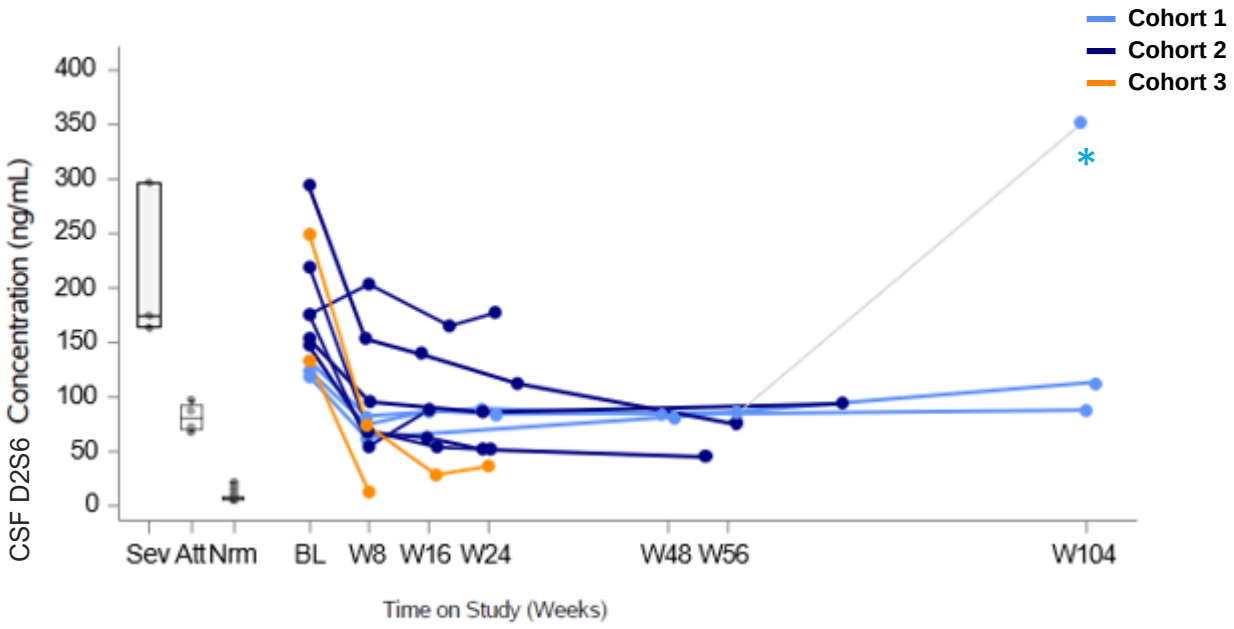
Cohorts (median†)

D2S6 Reductions

Cohort	Week 8	Week 24
1	-40.5% n = 3	-33.0% n = 2
2	-50.9% n = 6	-61.8 N = 5
3	-80.5% n = 2	-85.5% n = 1



Individual Participants



- CSF D2S6 measurement showed dose-dependent reductions in Cohorts 1-3 at Week 8 and 24, with Cohort 3 participants approaching normal levels
- Majority of participants in all three cohorts demonstrated decreased CSF D2S6 at last time point available
- Measurable CSF I2S protein concentration in Cohort 2 & 3 participants after RGX-121 administration (range 834 – 4830 pg/mL) **

1. Holley (2011) J Biol Chem 2. Wilkinson (2012) PLoS One 3. Gleiz (2018) EMBO Mol Med

Data cut December 20, 2021

* CNS related clinical event (ventriculoperitoneal shunt infection) took place on Day 522 post RGX-121 administration in this Cohort 1 patient that was deemed unrelated to study drug

† Median CSF D2S6 concentration +/- Q1 and Q3 per cohort. ** Data not presented

Normative data are based on 29 normal samples. The ages for 9 normative samples range from 1 month to 21 years old.

Severe defined as IQ < 70. The ages of 3 severe samples range from 4 years 8 months to 10 years old.

Attenuated defined as IQ ≥ 70. The ages of 4 attenuated samples range from 11 years to 29 years old.

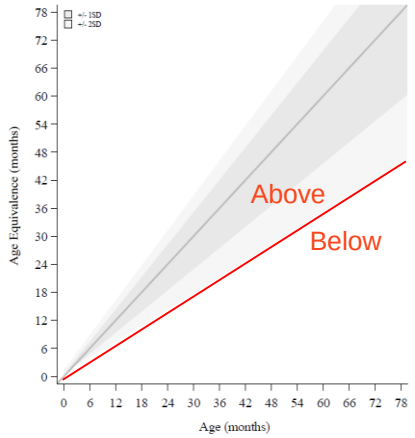
Neurodevelopment Assessments:
Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III)

- Participants were assessed using the BSID-III cognitive, expressive and receptive language, and fine and gross motor subtests
- BSID-III manual normative data were used to characterize ±1 and ±2 standard deviation (SD) boundaries for Age Equivalent (AEq) score[1]
- Participant data is presented for the BSID-III Cognitive, Expressive Language and Fine Motor subtests

8 Participants in Cohorts 1 and 2 with > 6 months follow-up
Separated by baseline function on cognitive subtest

Participants at baseline with cognitive function above -2 SD from the normative mean

(n = 3 Cohort 1, 1 Cohort 2)

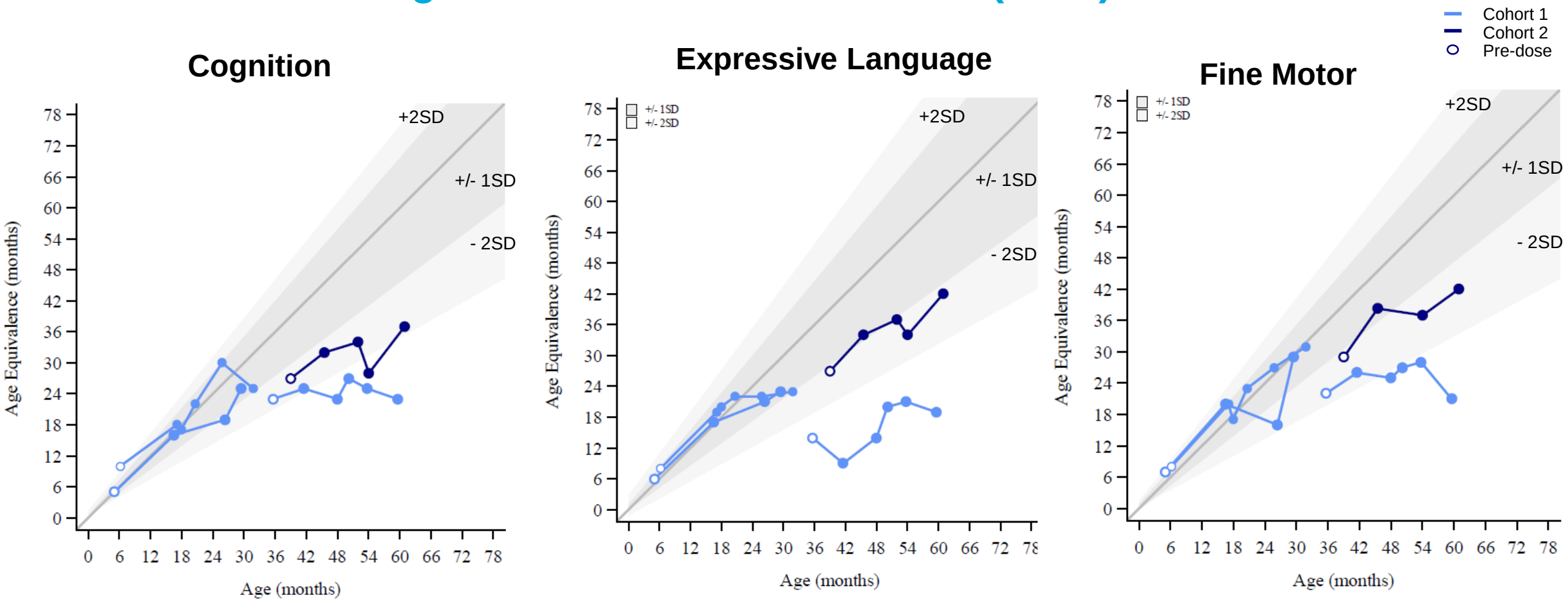


Participants at baseline with cognitive function below -2 SD from the normative mean

(n = 4 Cohort 2)

1. Cho, ICIEM Virtual Congress 2021

Neurodevelopmental Function:
Baseline BSID-III Cognitive Function Above -2 SD (n = 4)

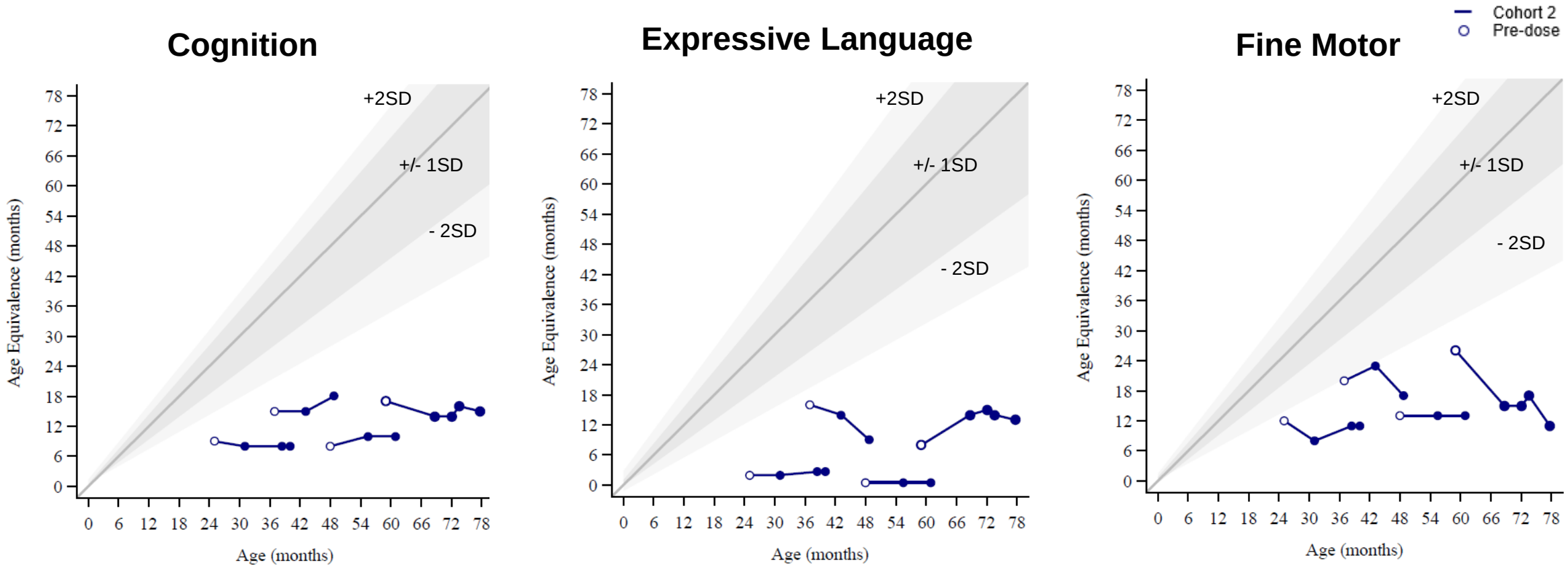


- 3 participants with cognitive function above -2 SD at baseline remained within 2 SD at the last assessment on the cognition, expressive language and fine motor subtests
- The 4th participant acquired skills on the expressive language subtest

Data cut December 20, 2021

Includes participants (n = 4) with > 6 months of follow-up
Included data from assessments that were performed before Dec 20, 2021, and have passed assessment validation and clinical review as of Jan 12, 2022

Neurodevelopmental Function:
Baseline BSID-III Cognitive Function Below -2 SD (n = 4)



Minimal skill acquisition was demonstrated in cognition for 2 participants (AEq increase of 2-3 months) and in expressive language for another participant (AEq increase of 5 months)

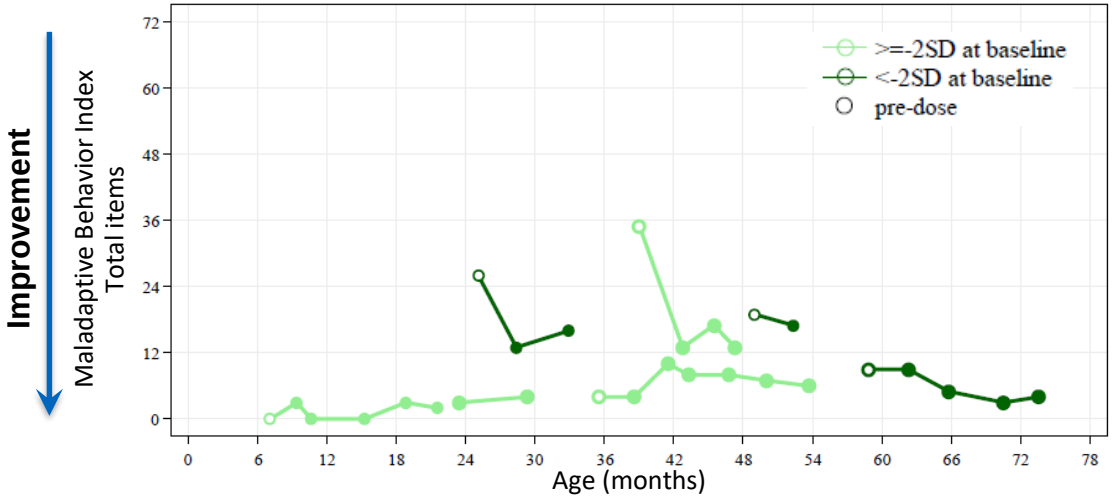
Data cut December 20, 2021

Includes participants (n = 4) with > 6 months of follow-up

Vineland Adaptive Behavior Scales-II (VABS-II)*: Maladaptive Behavior and Toileting Skills

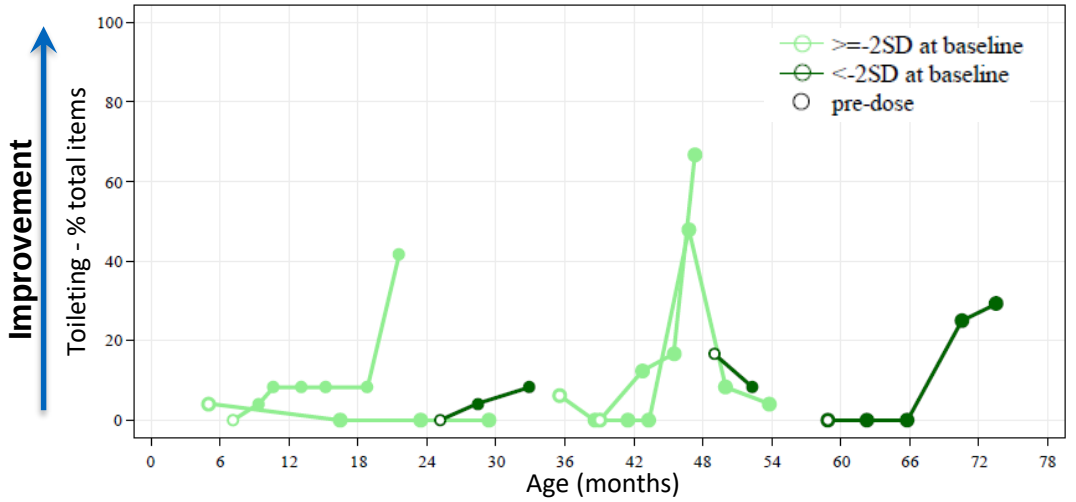
- Maladaptive behaviors and challenges with toilet training are associated with neurodegeneration
  - Maladaptive behaviors are a measure of undesirable behaviors that interfere with daily function[1]
  - Only a small minority of patients with severe MPS II achieve bowel/bladder control[2,3,4]

Maladaptive Behavior Index**



4 participants (3 with cognitive function <-2SD at baseline) show a reduction in maladaptive behaviors

Toileting



4 participants (2 with cognitive function below <-2SD at baseline) show an improvement in toileting skills

Sleep Disturbance Scale for Children*: Sleep Breathing Subtest

- Sleep disturbance includes snoring and difficulty breathing during sleep, which can be due to airway abnormalities, respiratory mechanisms and CNS involvement[3,4,5]

10 of 11 participants (5 with cognitive function <-2SD at baseline) show improved sleep breathing following RGX-121 administration

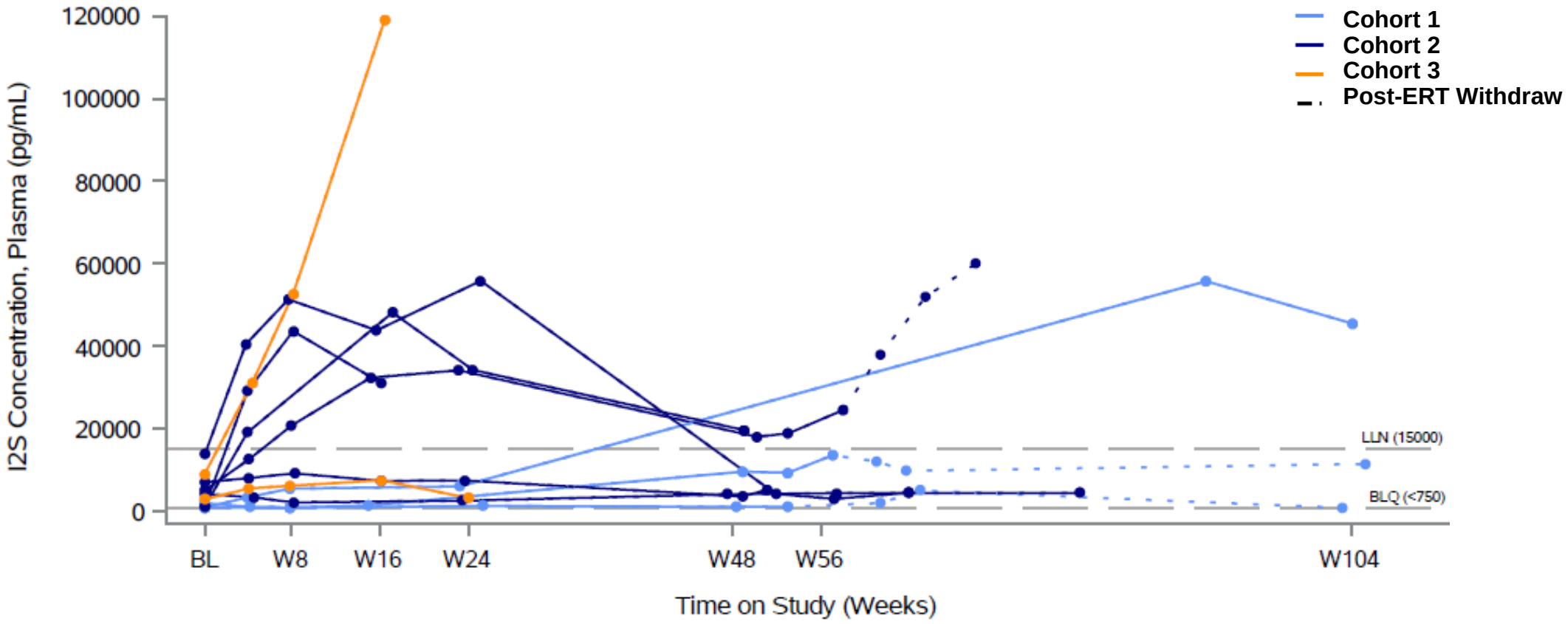
1. Sparrow (2005) Vineland II 2. Hogan (2020) Mol Genet Metab 3. Eisengart (2020) Mol Genet Metab 4. Holt (2011) J Peds 5. Barone (2018) Ital J Pediatr

*VABS-II (n=7) and Sleep Disturbance Scale for Children (n=11) data include participants with at least one post-baseline assessment

** Maladaptive Behavior Index (MBI) includes one participant without baseline data. This participant was enrolled under an earlier protocol version that did not require MBI

Data cut December 20, 2021

Systemic Effects: Plasma I2S Protein Concentration

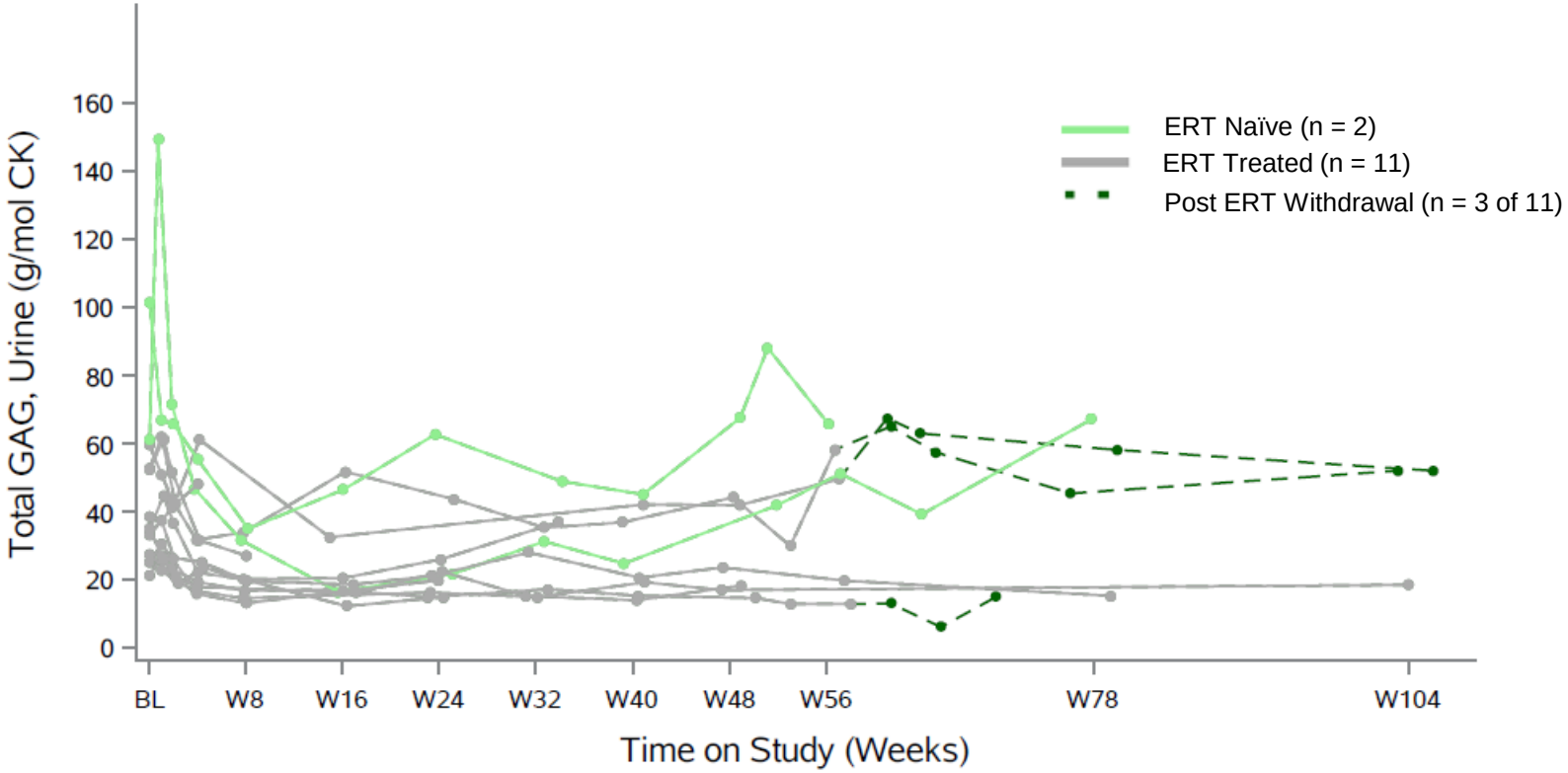


Increased plasma I2S protein concentration demonstrated in the majority of participants after RGX-121 administration

Data cut December 20, 2021

Lower Limit of Normal (LLN) is determined using the lowest result from a sample of 30 normal patients
Post-baseline measurements shown are ≥ 4 weeks post RGX-121 administration

Systemic Effects: Urine Total GAGs



Urine GAG measures showed evidence of systemic effect of RGX-121 independent of ERT treatment

- ERT Naïve: Notable decline demonstrated in urine GAGs in one of two participants through last time point available
- ERT Withdrawal: Total urine GAGs following ERT withdrawal remained relatively consistent with total urine GAGs prior to ERT withdrawal
- ERT Continuation: Total urine GAGs decreased in all participants at the last time point available

Data cut December 20, 2021

RGX-121 Phase I/II Clinical Study
Summary of Results

Safety: RGX-121 appeared to be well tolerated

- 13 patients dosed with no SAEs related to study drug

CNS: Biomarker and neurodevelopmental assessments indicate encouraging RGX-121 profile

- Dose-dependent reductions in CSF biomarkers demonstrated across cohorts
- Cohort 3 CSF D2S6 approached normal levels
- Improvements in neurodevelopmental function and caregiver reported outcomes in Cohorts 1 and 2 demonstrated CNS activity up to 2 years after RGX-121 administration

Systemic: Evidence of enzyme expression and biomarker activity after CNS RGX-121 administration

- Majority of participants demonstrated increases in plasma I2S concentration
- Urine GAG measures showed evidence of systemic effect of RGX-121 independent of ERT treatment

Data cut December 20, 2021

Acknowledgements

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