RGX-111 Gene Therapy for the Treatment of Severe Mucopolysaccharidosis Type I (MPS I):

Interim Analysis of the First in Human Study and a Single Patient IND

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MPS I is a Systemic Disease Representing a Wide Spectrum of Severity

Severity of Disease Manifestations Correlates with Degree of alpha-l-iduronidase (IDUA) Deficiency

	Hurler (60%)	Hurler-Scheie (23%)	Scheie (13%)
Symptom Onset	0.5 y	3.0 y	7.8 y
Age of diagnosis	0.8 y	3.9 y	9.3 y
Cognitive	100% Regression	35% IQ < 85 14% IQ < 70	Usually normal
Somatic	Most manifestations and most severe	Intermediate number and severity	Fewest manifestations, least severe
	Coarse facial features, organomegaly, dysostosis multiplex, carpal tunnel syndrome, stiff joints, hydrocephalus, cord compression, cardiac valvular disease, recurrent upper airway infections, OAD/ sleep apnea, corneal clouding, hearing loss		
Life expectancy	Rapid progression; < 10 y	Slower progression; 30 – 40 y	Slow progression; > 40 y
SoC	HSCT	Systemic ERT	Systemic ERT
Unmet needs with SoC	Musculoskeletal/orthopedic Cardiac valve disease Corneal clouding **Neurocognitive – improved but often not normal**	Musculoskeletal/orthopedic Cardiac valve disease Corneal clouding **Neurocognitive – milder dysfunction**	N/A

Pastores (2007) Mol Genet Metab
Beck et al. (2014) Genet Med
Shapiro et al. (2015) Mol Genet Metab

RGX-111: MPS I Phase I/II Clinical Study Summary

NCT03580083 on ClinicalTrials.gov

Participants

Enrollment of 8 MPS I participants with CNS involvement or severe MPS I
(≥ 4 months of age)

May be on Standard of Care IV ERT
or
ERT Naïve

Cohorts (dose levels)

Genome copies/g brain mass

RGX-111
AAV9 + *IDUA*

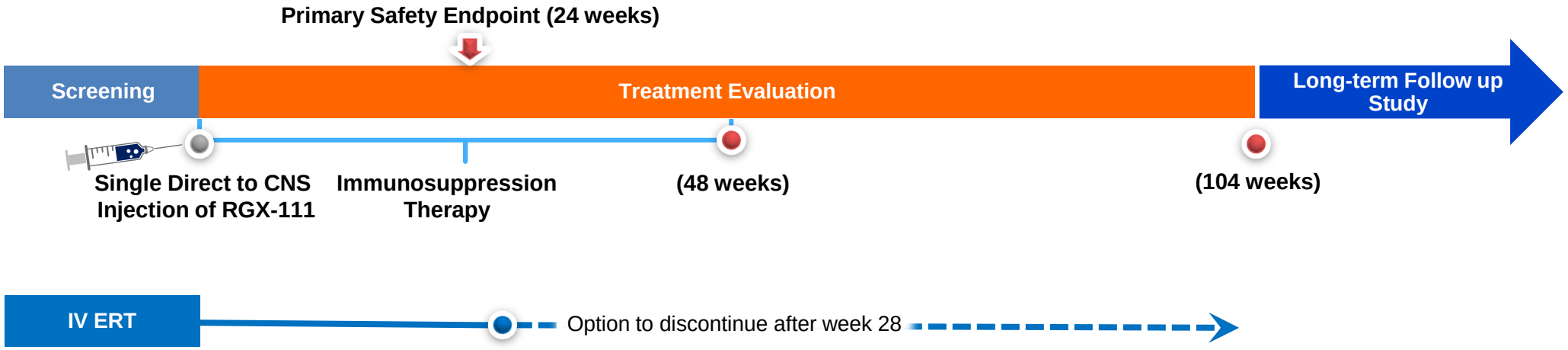
Cohort 1: 1.0 x 10^{10}
Cohort 2: 5.0 x 10^{10}

Data

Primary Endpoint is Safety

Secondary & Exploratory Endpoints Include:

- CSF GAGs (Heparan Sulfate)
- Neurodevelopmental Assessments (BSID / WASI)
- Caregiver reported outcomes (VABS)
- Systemic Biomarkers (urine & plasma)



BSID-III (Bayley Scales of Infant and Toddler Development, 3rd Edition); WASI (Wechsler Abbreviated Scale Intelligence – 2nd Edition; VABS (Vineland Adaptive Behavior Scales, 2nd Edition); SDSC (Sleep Disturbance Scale for Children)

RGX-111 Phase I/II Trial and Single Patient Investigator-Initiated IND

- As of January 17, 2023, 8 participants were dosed in the Phase I/II trial and 1 in the single patient IND protocol
- Age at dosing from 4 months to 13 years in Phase I/II trial and 20 months in single patient IND
- *IDUA* Mutations among Phase I/II trial and single patient IND participants included nonsense/frameshift, nonsense/null variant splice site, duplication, substitution and missense
- Immunosuppression discontinued per protocol in 5 trial participants and single patient IND participant

Cohort	N	Dose (GC/g Brain Mass)	Follow-Up (Weeks)	Prior / Treatment at Dosing	Immunosuppression Regimen Status	ERT (IV) Status†
Cohort 1	2	1.0×10^{10}*	79-103 wks	1 prior HSCT+ ERT^ 1 ERT	2 completed	1 not on ERT 1 weekly
Cohort 2	6**	5.0×10^{10}	7-78 wks	1 prior HSCT + ERT 4 ERT 1 ERT naïve	3 completed 3 active	4 weekly 1 discontinued 1 naïve
Single Patient IND	1	1.0×10^{10}*	87 wks	ERT	completed	weekly

† Per protocol, participants may discontinue ERT after week 28
^ Participant had <1 month of exposure to ERT
* Previously reported as 1.3×10^{10} from initial calculations for brain mass
** Data shown for 4 participants; 2 recently dosed.

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

RGX-111 Safety Summary

Phase I/II Trial and Single Patient Investigator-Initiated IND

SAE	▪ 9 serious adverse events (SAE) reported in 4 participants: None are considered related to RGX-111 ▪ SAEs reported: Bronchiolitis, bronchopneumonia, sinusitis, 2 central line infections*, COVID-19, RSV, sepsis*, otitis media* ▪ All SAEs resolved
TEAE	▪ No dose-related safety findings and no long-term safety concerns were observed ▪ All participants reported treatment emergent adverse events (TEAEs) which were predominantly mild ▪ 8 AESIs (adverse events of special interest) reported, all considered related to immunosuppression regimen, with neutropenia being the most common.

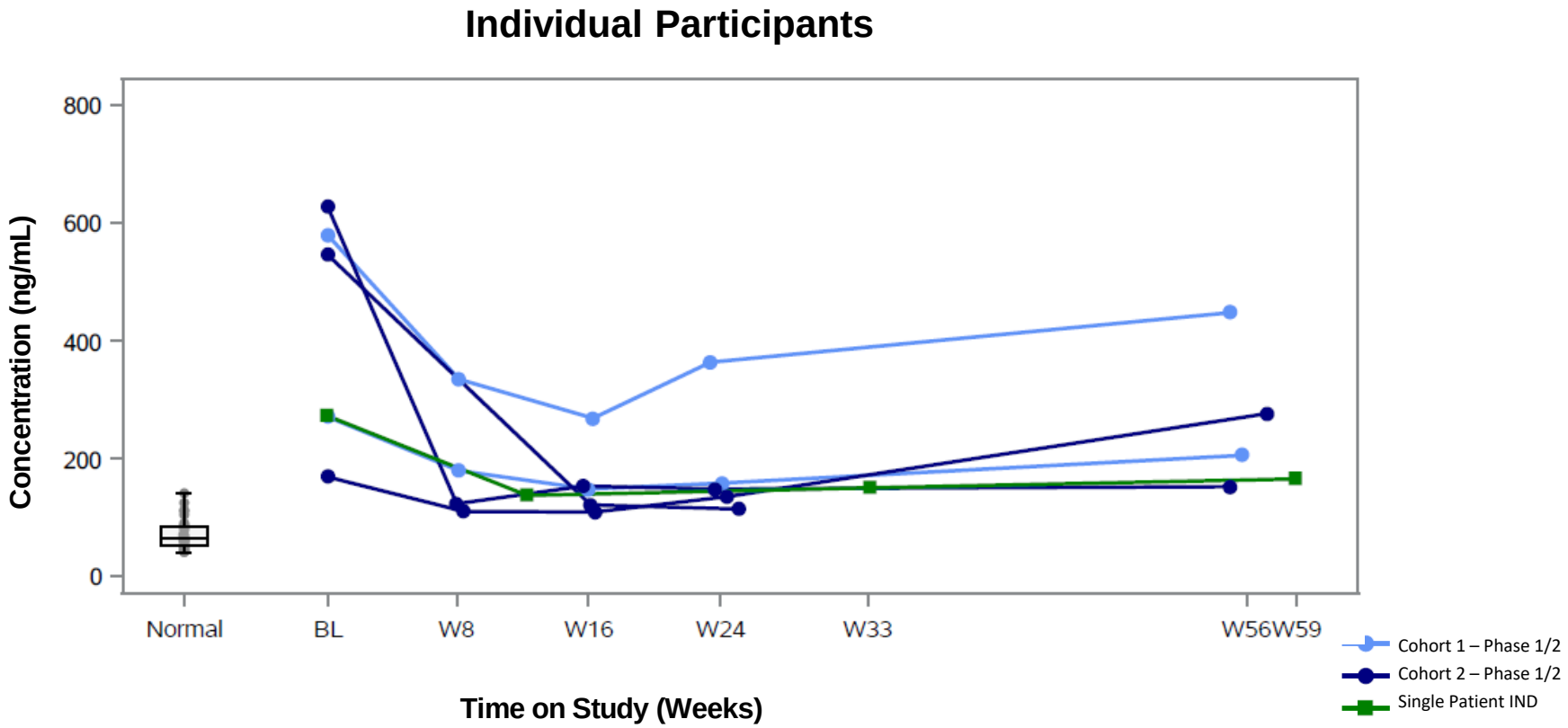
RGX-111 has been well tolerated

* Possibly related to immunosuppression (sepsis, otitis media, and 1 central line infection)

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

Cerebrospinal Fluid (CSF) GAGs

Heparan Sulfate (HS)



- Decreased CSF heparan sulfate in majority of participants through last time point available
- Measurable CSF IDUA enzyme activity* in 4 of 5 participants in the Phase I/II trial and in the single patient IND participant

Note: Normative data are based on 29 normal samples.
Age ranges from 1 mo. to 21 years of age
•Data not shown

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

Neurodevelopmental Assessments

Age and developmentally appropriate validated instruments for neurodevelopmental testing were used to evaluate all participants

n = 6 *

Bayley Scale of Infant and Toddler Development, Third Edition (BSID-III) for chronological or developmental ages 0 to 42 months

Vineland Adaptive Behavior Scale, Third Edition (VABS-III)**

n = 5

4 Phase I/II trial participants
1 single patient IND participant

Wechsler Abbreviated Scale of Intelligence (WASI-II) for chronological and development age > 6 years

Vineland Adaptive Behavior Scale, Third Edition (VABS-III)

n = 1

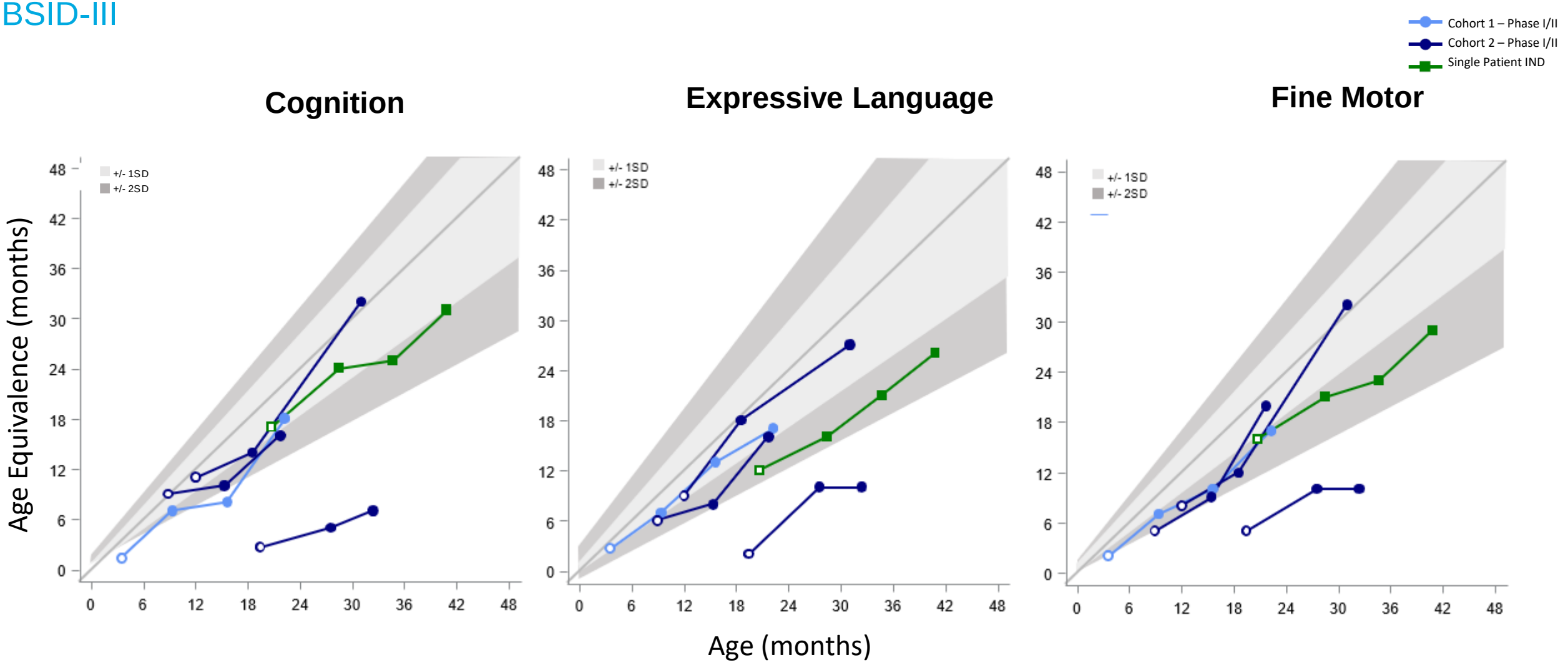
1 Phase I/II trial participant

* At least 6 months follow-up
** VABS only shown for older patient

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

Neurodevelopmental Function

BSID-III



- **All participants show continued developmental skill acquisition on all subtests**
- **At last assessment, 4 of 5 participants have function ≥ -2 SD of normative mean on the cognition, expressive language and fine motor subtests**

Includes participants (n = 5) with > 6 months of follow-up

Phase I/II Trial data cut: January 17, 2023
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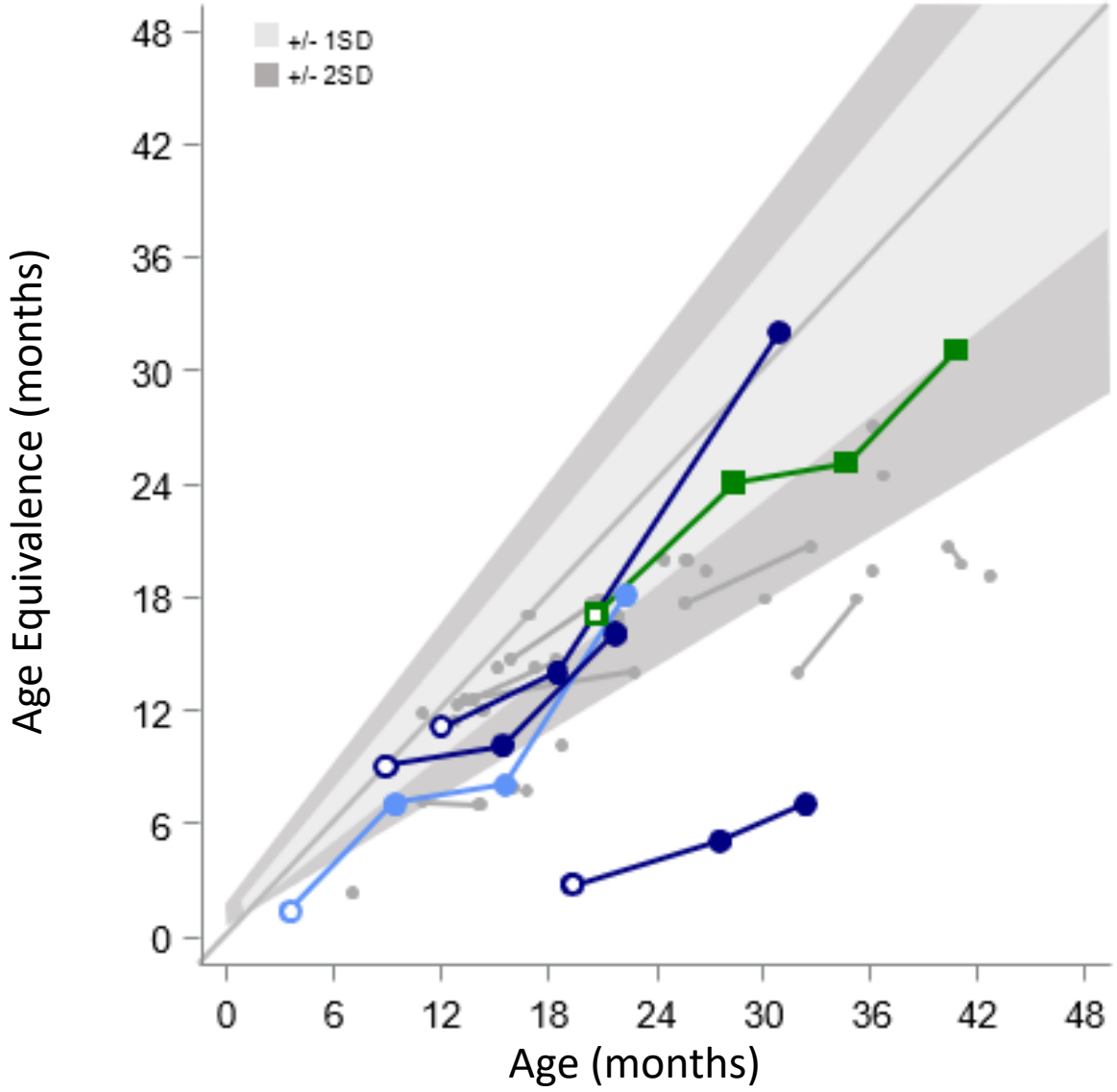
Neurodevelopmental Assessments and Function

BSID* Cognitive Subtest



BSID cognitive function in 2 participants demonstrates higher AEq than available natural history data**

Cohort 1 – Phase I/II; n = 1
Cohort 2 – Phase I/II; n = 3
Single Patient IND; n = 1

* Natural history data (Shapiro et al., 2018) gathered using BSID-I and BSID-II; RGX-111 participants evaluated with BSID-III
** 1 participant in the Phase I/II trial and the single patient IND

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

Neurodevelopmental Assessments and Adaptive Function for 13 Year Old Phase I/II Participant

WASI-II and VABS-III

WASI- II Composite Scores

Week of Assessment Age	BL 13y 2m	Week 52 14y 2m	Week 78 14y 8m
Verbal Comprehension Composite Score Mean of 100 SD15	45	55	67 ↑
Perceptual Reasoning Composite Score	49	46	59 ↑
Full Scale-4 Composite Score	43	47	61 ↑

VABS-III Age Equivalent Scores (year : month)

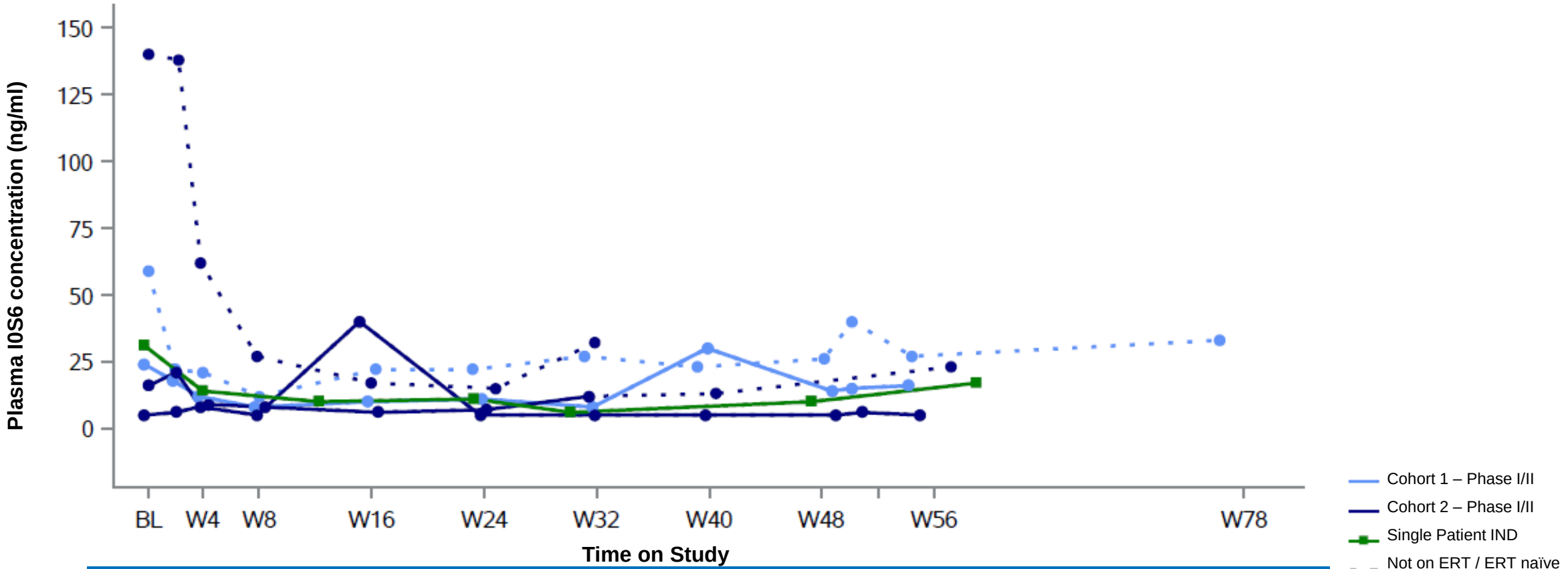
Week of Assessment Age		BL 13y 2m	Week 52 14y 2m	Week 78 14y 8m
Communication	Receptive	8:4	6:7	5:7
	Expressive	5:10	11:9	11:9 ↑
	Written	6:0	6:0	5:11
Daily Activity	Personal	4:1	7:10	4:6 ↑
	Domestic	7:7	6:7	14:9 ↑
	Community	7:4	6:10	7:11 ↑
Socialization	Interpersonal Relationships	5:10	7:4	22:0 ↑
	Play and Leisure	8:1	8:1	11:9 ↑
	Coping Skill	3:4	9:10	8:7 ↑
Adaptive Behavior	Adaptive Behavior	6:3	7:10	10:3 ↑
Motor	Fine Motor	5:7	6:4	6:3 ↑
	Gross Motor	4:0	4:6	3:2

Following RGX-111 administration, participant demonstrated improvements in WASI composite scores and the majority of the VABS-II subdomains at last assessment

Phase I/II Trial data cut: January 17, 2023

Systemic Effects: Plasma I0S6

I0S6 is a non-reducing end (NRE) disaccharide of glycosaminoglycans shown to be elevated in plasma, urine and CSF of MPS I patients[1,2,3,4,5]



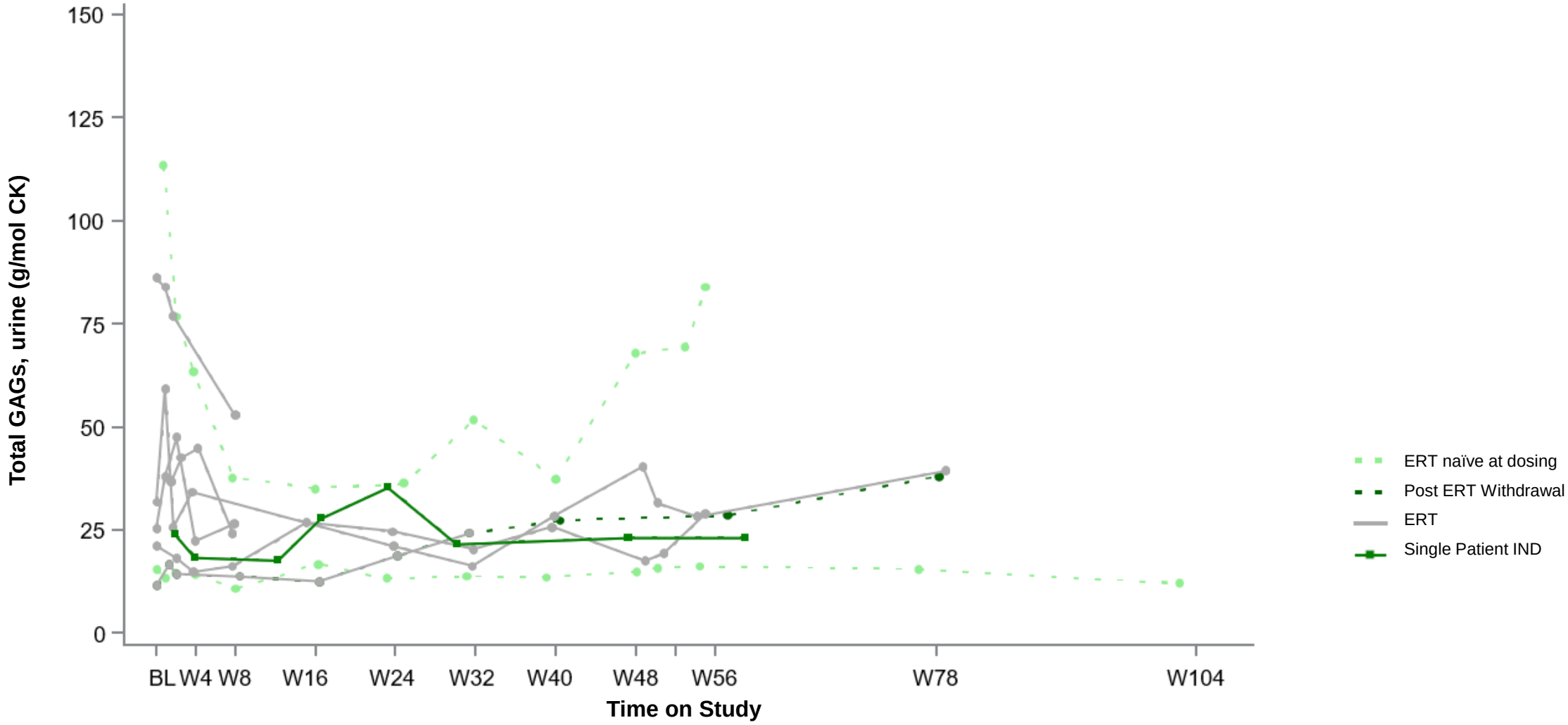
Participants with elevated I0S6 at baseline showed a decrease in I0S6 following RGX-111 administration

1. Lawrence (2012) Nat Chem Biol 2. Vera (2019) Mol Genet Metab 3. Lund (2019) Sci Rep 4. Raymond (2016) Sci Rep 5. Eisengart (2019) Genet Med

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

Systemic Effects

Urine Total GAGs



Majority of patients maintained low levels of total urine GAGs

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

RGX-111 Phase I/II Trial and Single Patient IND
Summary of Results

Safety: RGX-111 was well tolerated

- 8 participants were dosed in the Phase I/II trial and 1 in the single patient IND protocol
- RGX-111 has been well tolerated with no SAEs related to study drug

CNS: Biomarkers and neurodevelopmental assessments indicate encouraging RGX-111 CNS profile

- **Biomarker:**
  - CSF GAG reduction and IDUA enzyme activity indicate CNS biological activity
- **Neurodevelopmental Function at Last Assessment Following RGX 111 Administration:**
  - The majority of participants showed continued skill acquisition ≥ -2 SD of normative mean on the BSID-III cognition, expressive language and fine motor subtests.
    - Cognitive function in a Phase I/II trial participant and the single IND participant was higher than the age equivalent scores in the available natural history.
  - The 13 year old participant demonstrated improved neurocognition and improved personal and social skills for daily living.

Emerging evidence of systemic biomarker activity after CNS administration of RGX-111

- Plasma I0S6 reductions observed following RGX-111 administration
- Low levels of total urine GAGs maintained in majority of participants

Phase I/II Trial data cut: January 17, 2023
Single Patient IND data cut: December 12, 2021

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