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

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

Presented by:
Raymond Y. Wang, MD

Division of Metabolic Disorders, CHOC Children's Hospital / Department of Pediatrics, University of California, Irvine, CA

WORLD*Symposium*, Wednesday, February 9, 2022

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 1/2 Clinical Study Summary

NCT03580083 on ClinicalTrials.gov

Participants

Enrollment up to 11 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 + *IDS*

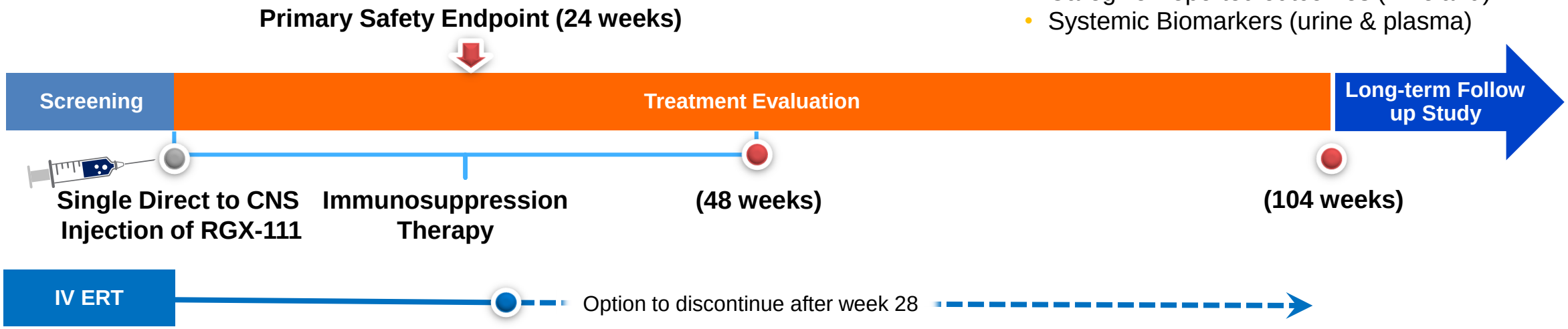
Cohort 1: 1.0 x 10^{10}
Cohort 2: 5.0 x 10^{10}

Data

Primary Endpoint is Safety

Secondary & Exploratory Endpoints Include:

- CSF Biomarkers (Heparan Sulfate)
- Neurodevelopmental Assessments (Bayley / WASI)
- Caregiver reported outcomes (Vineland)
- Systemic Biomarkers (urine & plasma)



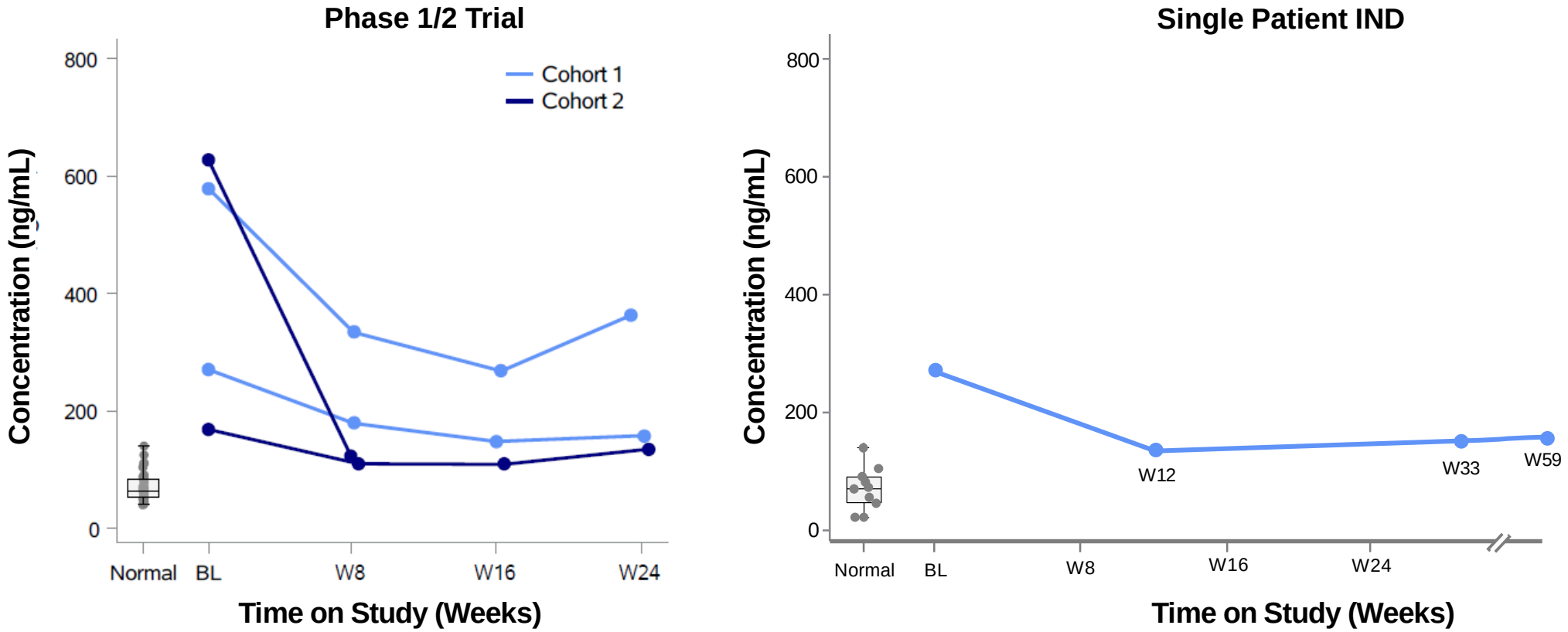
RGX-111 Phase 1/2 Trial and Single Patient Investigator-Initiated IND

- 6 participants dosed as of December 20, 2021, 5 in Phase 1/2 trial and 1 in single patient IND
- Ages at dosing from 4 months to 13 years in Phase 1/2 trial and 20 months in single patient IND
- *IDUA* Mutations among Phase 1/2 trial and single patient IND participants include nonsense/frameshift, nonsense/null variant splice site, and missense
- No SAEs related to study drug as of December 20, 2021
- Immunosuppression discontinued per protocol in one trial participant 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}	40-56 wks	1 prior HSCT+ ERT^ 1 ERT	1 completed 1 active	1 not on ERT 1 weekly
Cohort 2	3	5.0×10^{10}	3-32 wks*	1 HSCT + ERT 1 ERT 1 ERT naïve	3 active	2 weekly 1 ERT 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
* 2 participants recently dosed. Data for Cohort 2 will only include 1 or 2 participants depending on data availability
** Previously reported as 1.3×10^{10} from initial calculations for brain mass

Cerebrospinal Fluid (CSF) Biomarker
Heparan Sulfate (HS)



- **Decreased CSF heparan sulfate in all participants through last time point available**
- **Measurable CSF IDUA enzyme activity* in 3 of 4 participants in the Phase 1/2 trial and 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

Data cut December 20, 2021

Neurodevelopmental Assessments

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

n = 4*

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

n = 3

2 Phase 1/2 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 1/2 trial participant

* With at least one post-baseline assessment

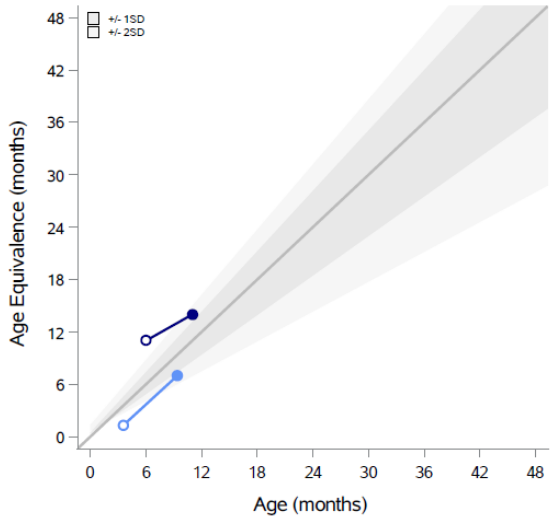
Neurodevelopmental Function BSID-III

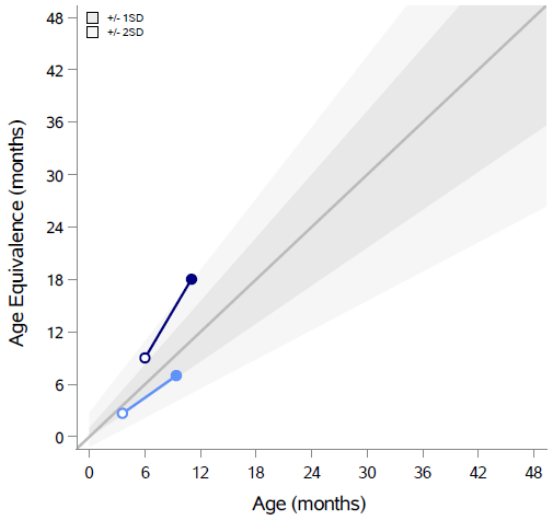
Cognition

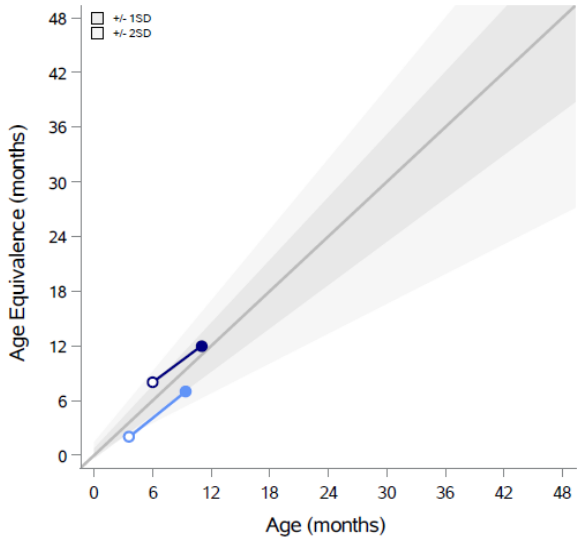
Expressive Language

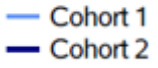
Fine Motor

Phase 1/2 Trial

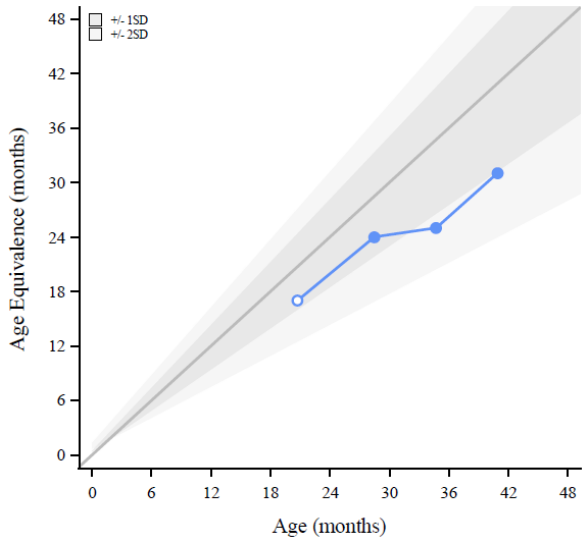


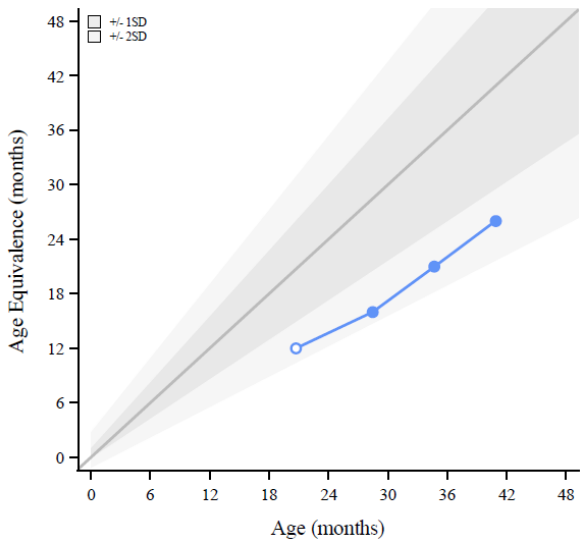


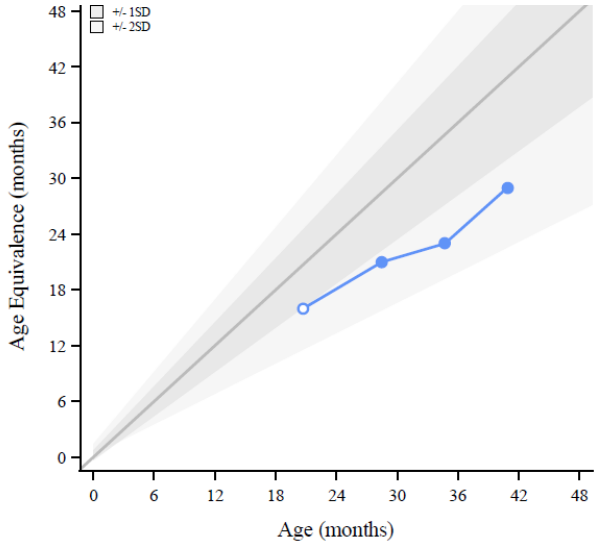




Single Patient IND





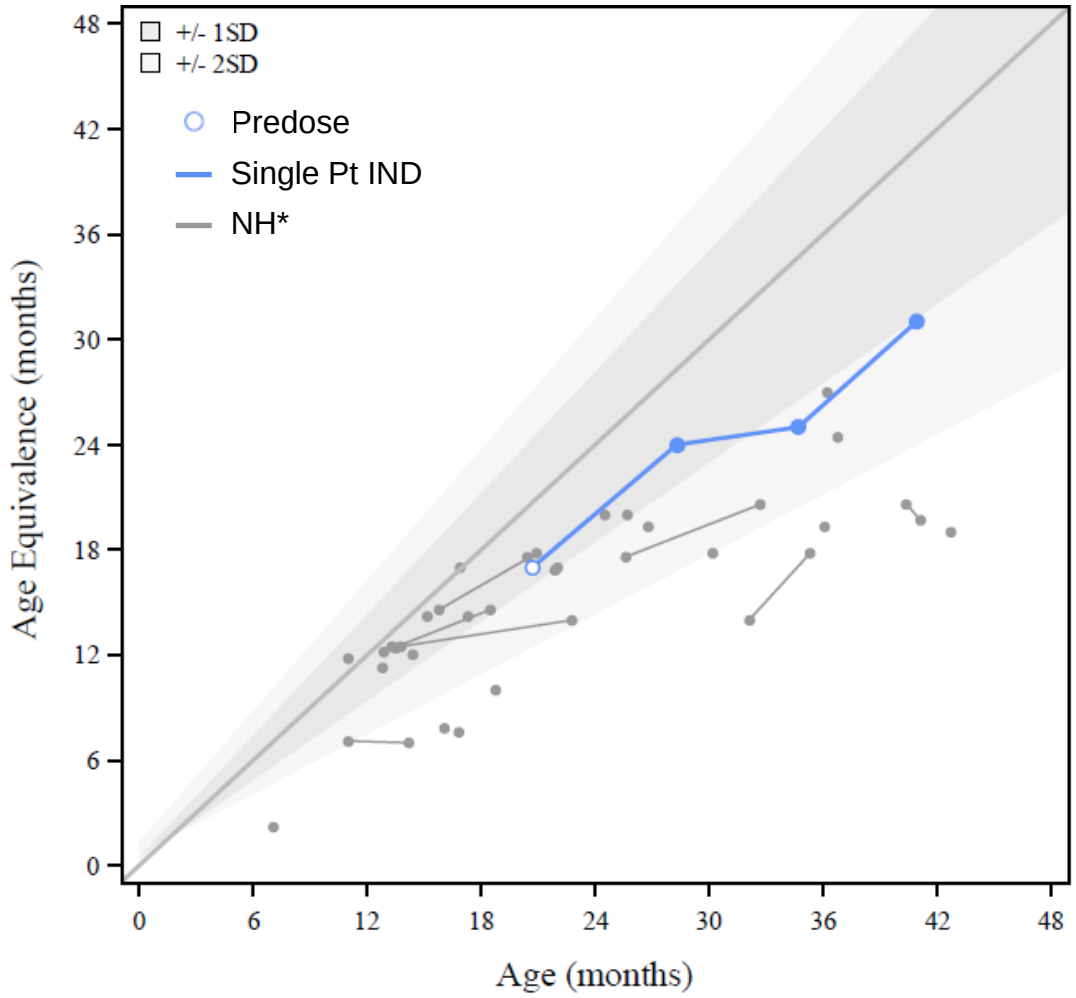


All participants showed continued skill acquisition within 2 SD of normative mean on the cognition, expressive language and fine motor subtests at last assessment

Data cut December 20, 2021

Neurodevelopmental Function BSID* Cognition

Single Patient IND Data Compared to MPS I Natural History



- **Cognitive function remains within 2 SD of normative range at the last assessment, 20 months after RGX-111 administration**
- **BSID cognition in participant approaching 42 months of age demonstrated higher age equivalent scores than available natural history data**

* Natural history data (Shapiro et al., 2018) gathered using BSID-II; RGX-111 single patient IND data gathered using BSID-III

Data cut December 20, 2021

Neurodevelopmental Function: WASI-II and VABS-III

13 year-old Phase 1/2 Trial Participant

WASI-II Full Scale Composite		
	Baseline Chronological Age 13y	Week 52 Chronological Age 14y
Mean 100 (SD 15)	**43**	**47**

VABS-III Age Equivalent Scores (year:month)		
	Baseline Chronological Age 13y	Week 52 Chronological Age 14y
Personal **(dressing, feeding, toileting, and washing/hygiene)**	**4:1**	**7:10**
Domestic	7:7	6:7
Community	7:4	6:10
Interpersonal Relationships	**5:10**	**7:4**
Play and Leisure	8:1	8:1
Coping Skill	**3:4**	**9:10**
Adaptive Behavior	**6:3**	**7:10**
Fine Motor	**5:7**	**6:4**
Gross Motor	**4:0**	**4:6**

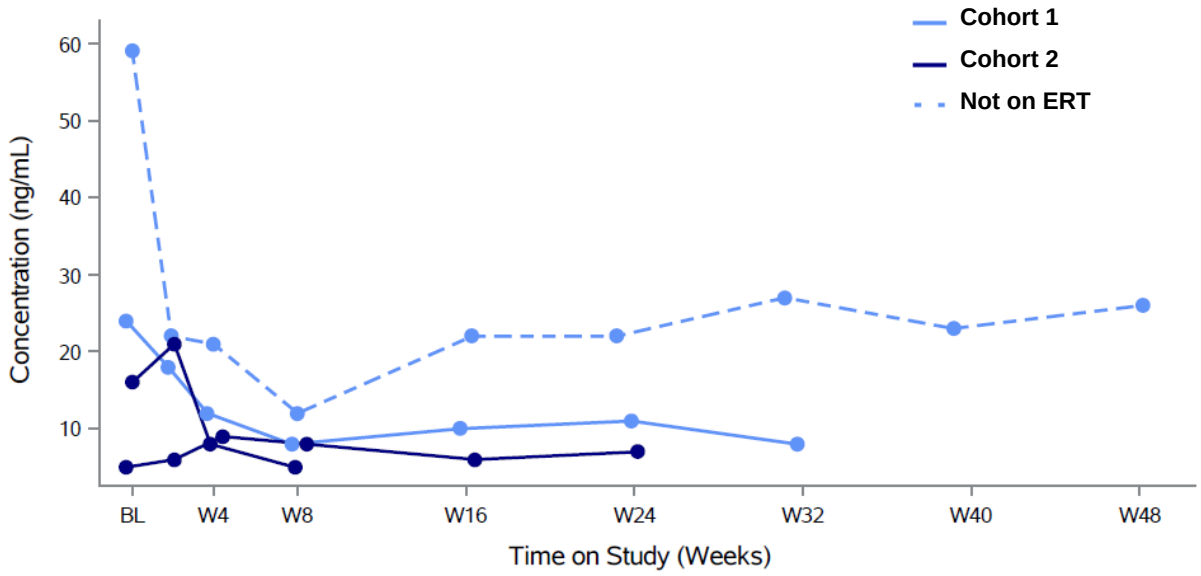
13 yr old Phase 1/2 trial participant demonstrated improvements in WASI composite and the majority of components of the VABS 52 weeks after RGX-111 administration

Data cut December 20, 2021

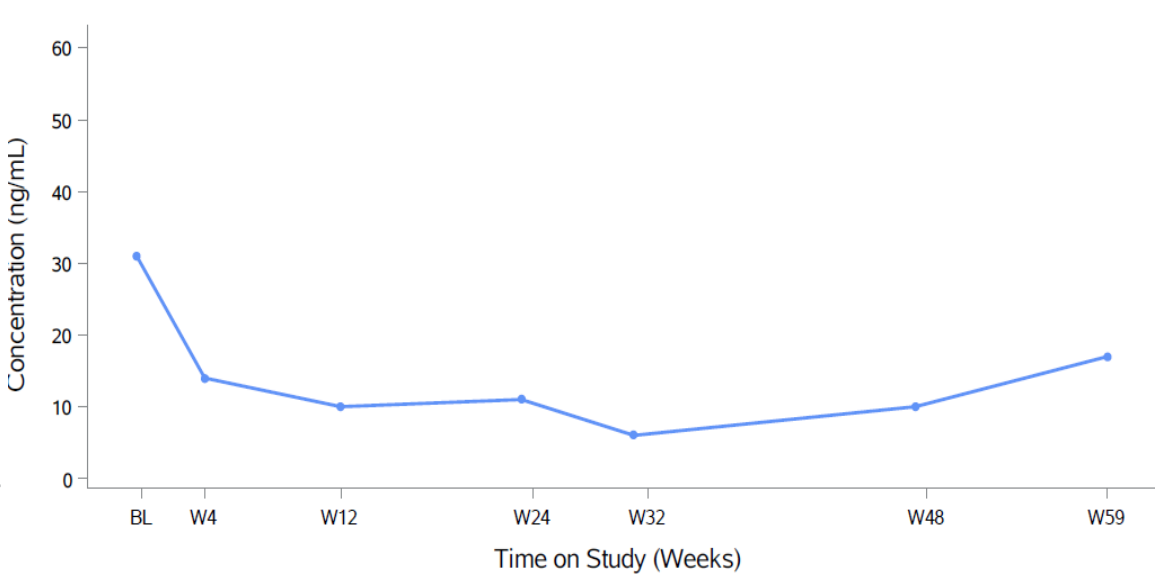
Systemic Effects: Plasma I0S6

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]

Phase 1/2 Trial



Single Patient IND



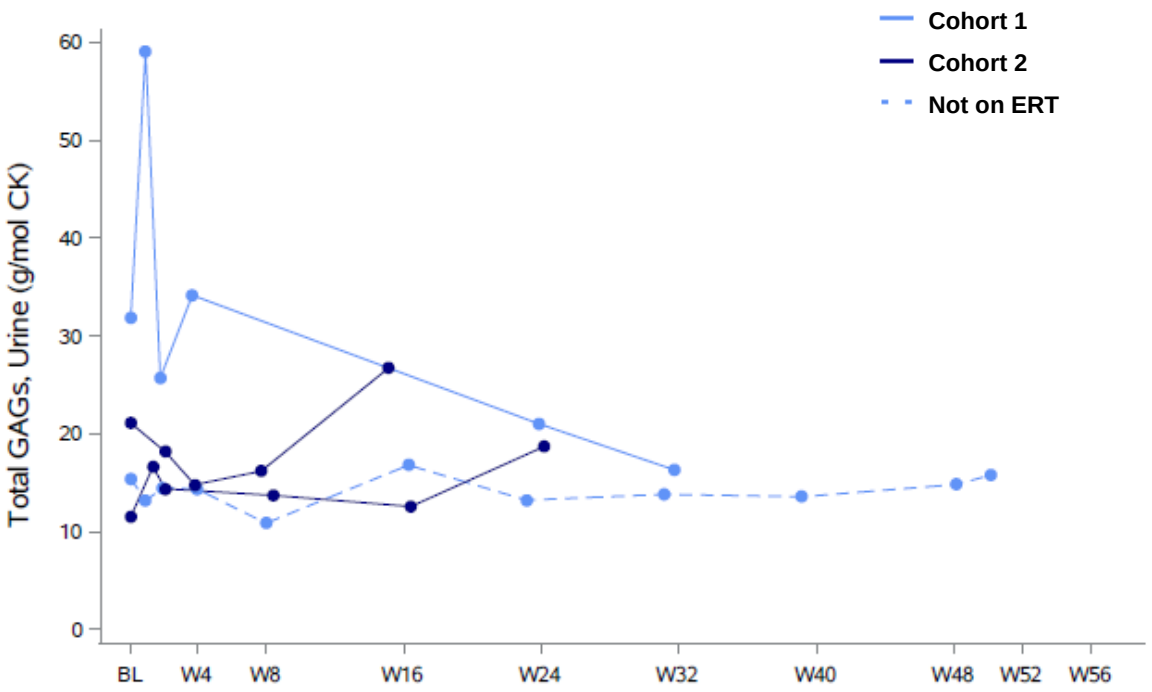
Participants with elevated I0S6 at baseline showed a decrease in I0S6 following RGX-111 administration

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

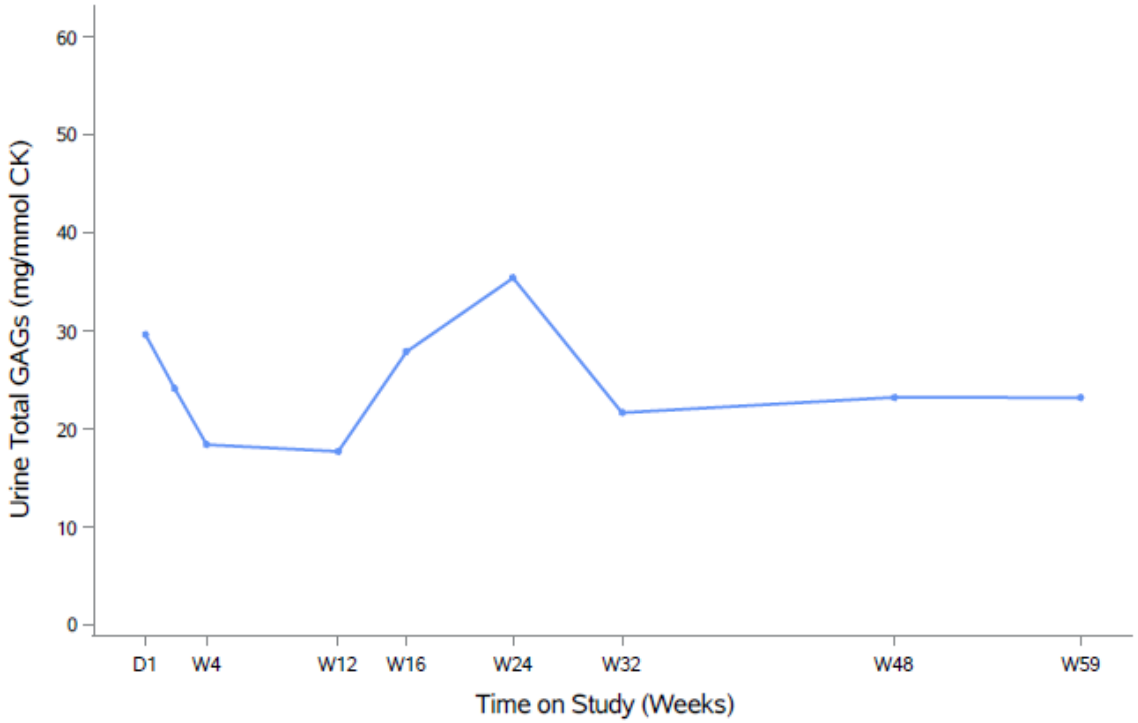
Data cut December 20, 2021

Systemic Effects: Urine Total GAGs

Phase 1/2 Trial



Single Patient IND



Total urinary GAGs remained below 30 g/mol in all participants at last time point available

Data cut December 20, 2021

RGX-111 Phase 1/2 Trial and Single Patient IND
Summary of Results

Safety: RGX-111 appeared to be well tolerated

- A total of 6 participants dosed with RGX-111 with no SAEs related to study drug

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

- **Biomarker:**
  - CSF HS reduction and IDUA enzyme activity indicate CNS biological activity
- **Neurodevelopment:**
  - Participants showed continued skill acquisition within 2 SD of normative mean on the cognition, expressive language and fine motor subtests at last assessment
  - Single patient IND participant at 42 months of age demonstrated higher age equivalent scores than available natural history data 20 months after RGX-111 administration

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

- Plasma I0S6 reductions observed following RGX-111 administration
- Low levels of urinary GAGs maintained in all participants

Data cut December 20, 2021

Acknowledgements

The RGX-111-101 Investigators

- Can Ficicioglu, Children's Hospital of Philadelphia
- Roberto Giugliani, HCPA, Porto Alegre, Brazil

REGENXBIO

- Marie-Laure Névoret
- Michele Fiscella
- Nidal Boulos
- Lin Yang
- Yoonjin Cho
- Dawn Phillips
- Michelle Gilmor
- Paulo Falabella

The Study Coordinators
(Nina Movsesyan, Harriet Chang, Ingrid Channa, Amber Morris, Larissa Pozzebon)
Research Assistants, and Study Teams at the Clinical Study Sites

The MPS I patients and their families


Thank You