RGX-121 Gene Therapy for Severe Mucopolysaccharidosis Type II (MPS II):

Interim Results of an Ongoing First in Human Trial

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Disclosures

Marie-Laure Névoret is an employee of REGENXBIO

Objectives

- Mucopolysaccharidosis Type II (MPS II) and RGX-121 as a therapeutic candidate
- Overview of RGX-121-101 First in Human Study
- Biochemical and Clinical Interim Analysis
- Conclusions and Program Outlook of Gene Therapy for MPS II

Mucopolysaccharidosis Type II (MPS II)

MPS II is also known as Hunter syndrome

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

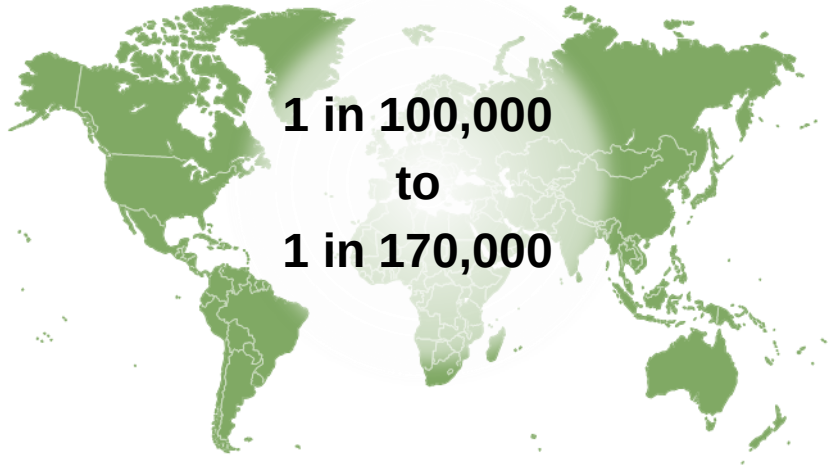
Caused by a deficiency of iduronate-2-sulfatase (I2S), an enzyme required for the degradation of the glycosaminoglycans (GAGs)

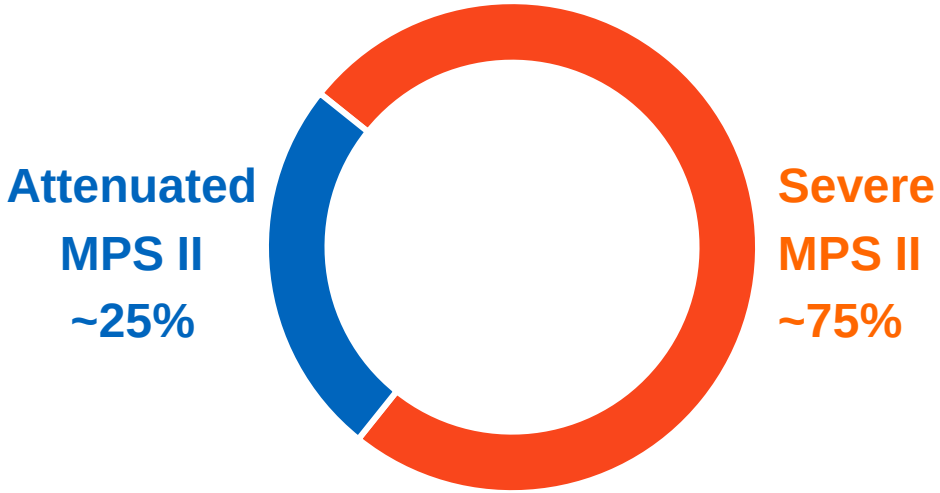
GAG build-up causes:

- Systemic Symptoms
- Frequent Neurodegeneration
- Early Death

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

Incidence





Prevalence

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

RGX-121-101: MPS II Phase 1/2 Clinical Study Summary

NCT03566043 on ClinicalTrials.gov

Patients

Approximately 12 MPS II patients

(≥ 4 months to < 5 years of age)

RGX-121
AAV9 + *IDS*

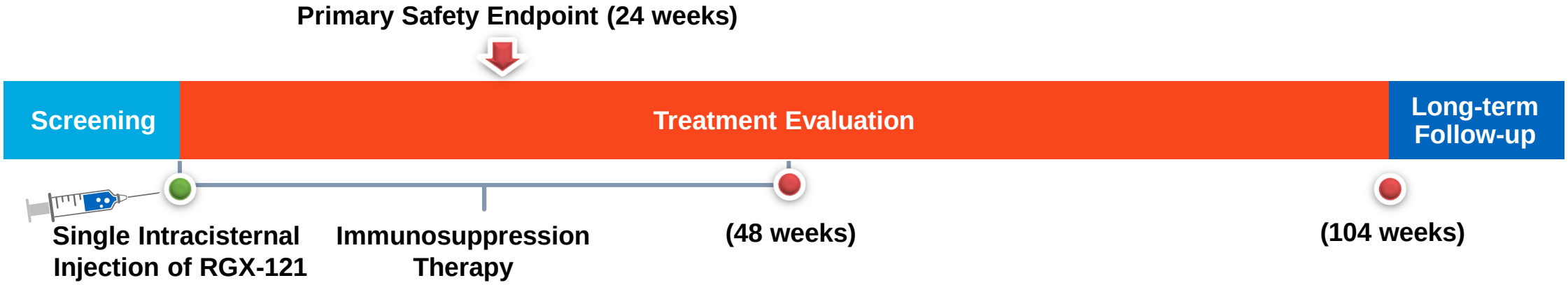
Cohorts (dose levels)

Genome copies/g brain mass

Cohort 1: 1.3 x 10^{10}
Cohort 2: 6.5 x 10^{10}
Cohort 3: 2.0 x 10^{11}

Data

Primary endpoint is safety; secondary endpoints include signs of efficacy



RGX-121-101: Patient overview

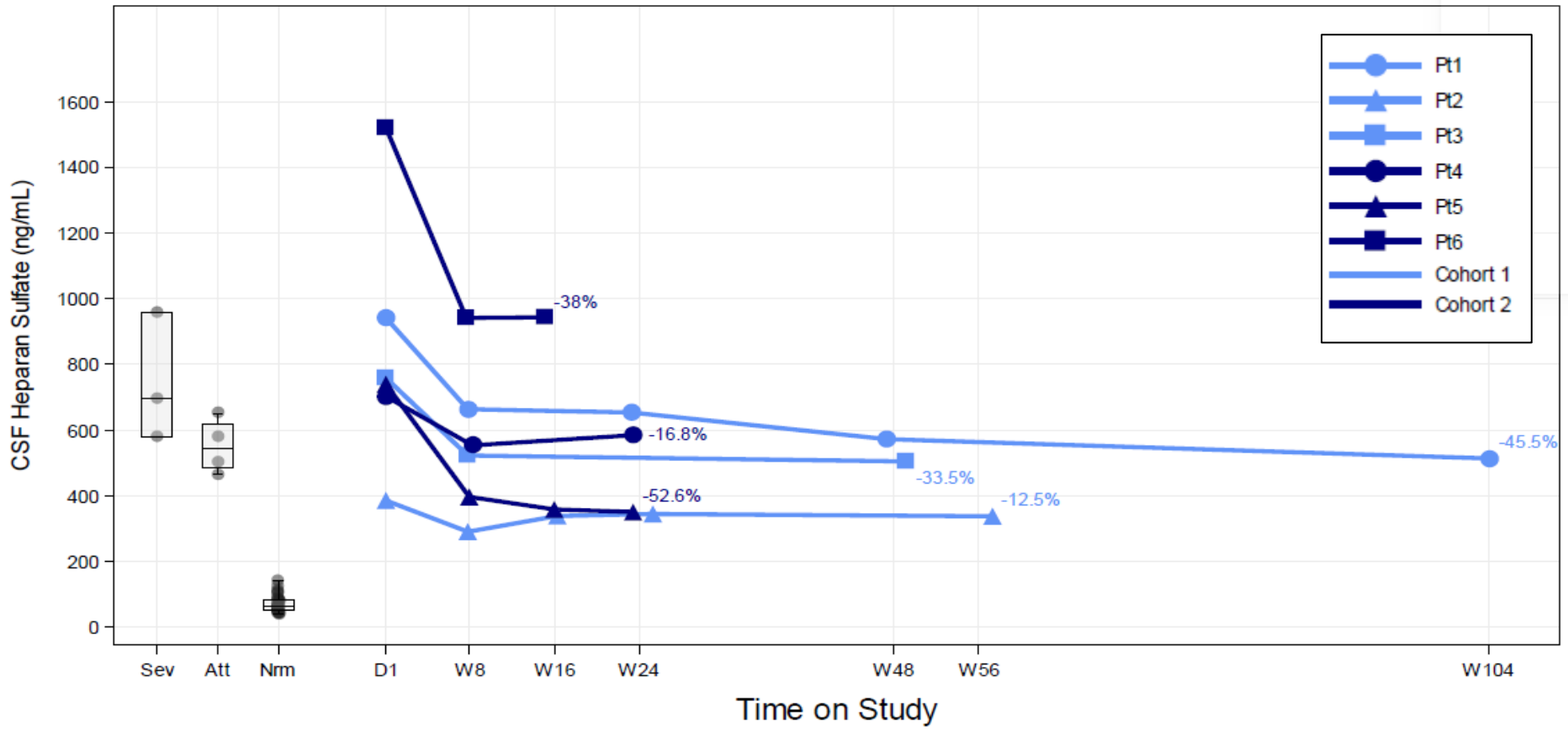
- No SAEs related to study drug as of 04 January 2021
- Immunosuppression discontinued per protocol in first 4 patients
- 8 patients dosed to date
- Ages at dosing: 5 months to 59 months
- Mutations among patients: 3 missense, 2 gene inversions, 3 frameshifts

	Patient	Dose (GC/g brain mass)	Follow-Up (weeks)	Immunosuppression Regimen Status	ERT (IV) status†
Cohort 1	1	1.3×10^{10}	104	Complete	Weekly
	2	1.3×10^{10}	78	Complete	**Discontinued**
	3	1.3×10^{10}	64	Complete	**Discontinued**
Cohort 2	4	6.5×10^{10}	56	Complete	Weekly
	5	6.5×10^{10}	32	Tapering	Weekly
	6	6.5×10^{10}	24	Tapering	**Naïve**
	7*	6.5×10^{10}	8	Active	Weekly
	8*	6.5×10^{10}	4	Active	**Naïve**

* Limited data available for Patients 7 and 8

† Protocol allows ERT discontinuation only after Week 52

Cerebral spinal fluid (CSF) Biomarker: Heparan Sulfate (HS)

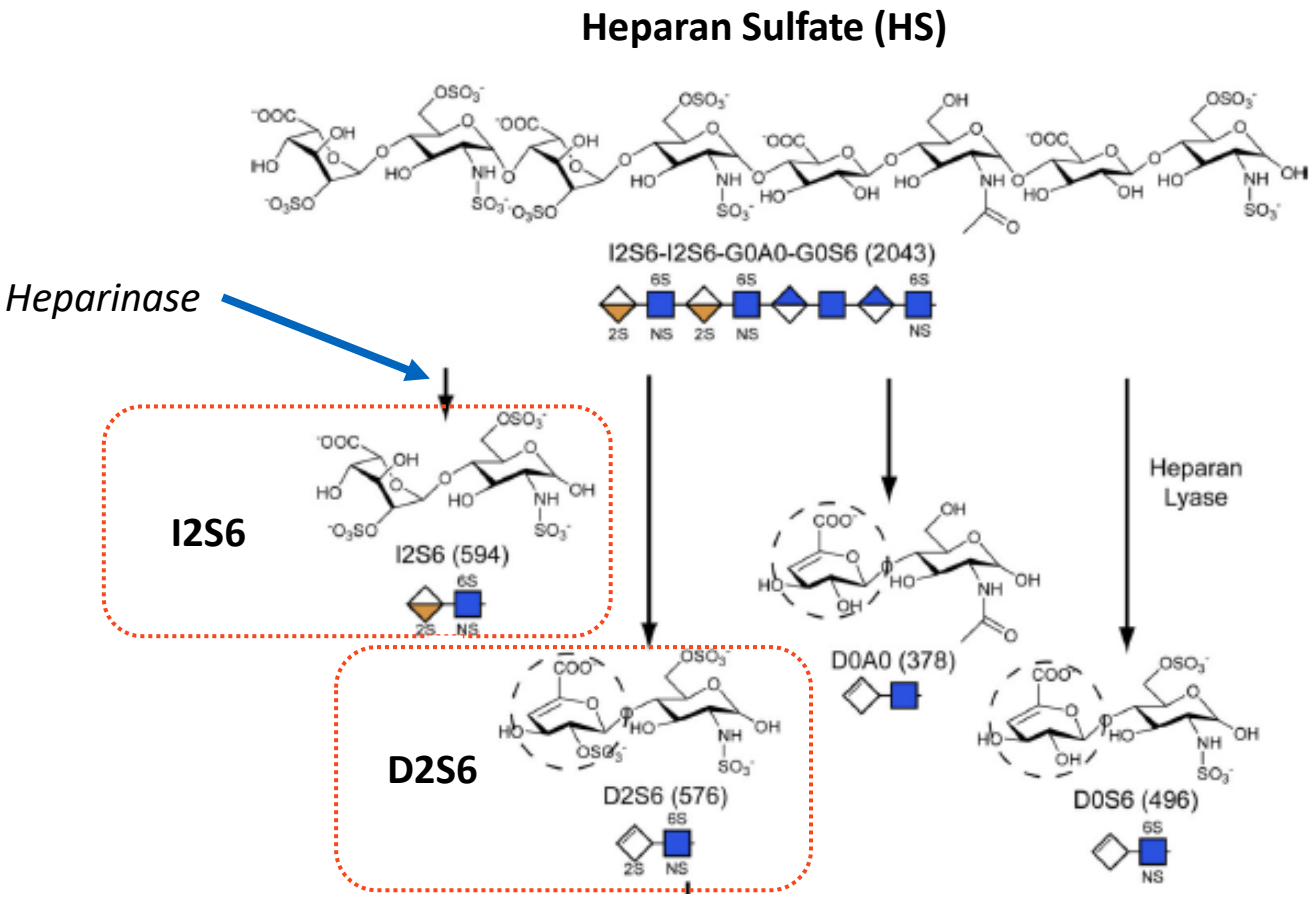


Consistent Heparan Sulfate decrease in the CSF after RGX-121 dosing

- The median change from baseline at week 8 (N=6) is -30.3% and p-value is 0.03*
- The median change from baseline at the last available timepoint (N=6) is -35.8% and p-value is 0.03*
- Measurable CSF I2S enzyme concentration in cohort 2 after RGX-121 administration (range 1170-1940 pg/mL)

* p-values are from Wilcoxon signed rank test

HS Digestion with Heparinase



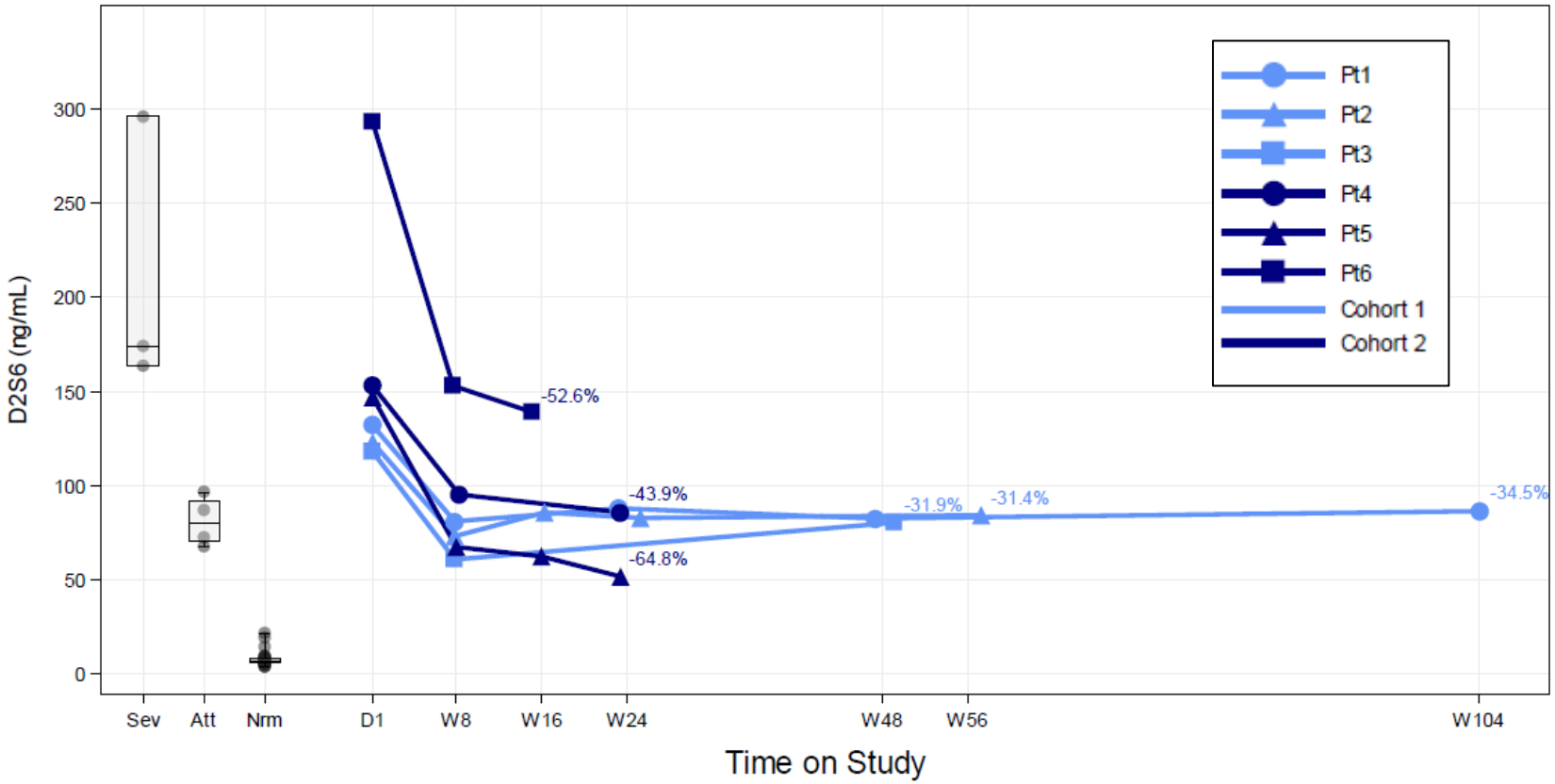
I2S6 and D2S6 are products of heparinase digestion

- I2S enzyme cleaves sulfates from HS in the lysosome
- Absence of I2S causes long chains of fully sulfated D2S6 to accumulate in HS
- Quantitative measurement of D2S6 is reflective of I2S enzyme activity level

Adapted from Lawrence 2012. *Nat Chem Biol*. ; 8(2): 197–204.

CSF Biomarker: HS D2S6 Disaccharide

- HS sulfation has been correlated with pathogenesis in neurodegenerative disorders[1-3]



Consistent decrease in CSF D2S6, a correlate of neuropathology phenotype in severe MPS II[4-6]

- The median change from baseline at week 8 (N=6) is -44.2% and p-value is 0.03*
- The median change from baseline at the last available timepoint (N=6) is -39.2% and p-value is 0.03*

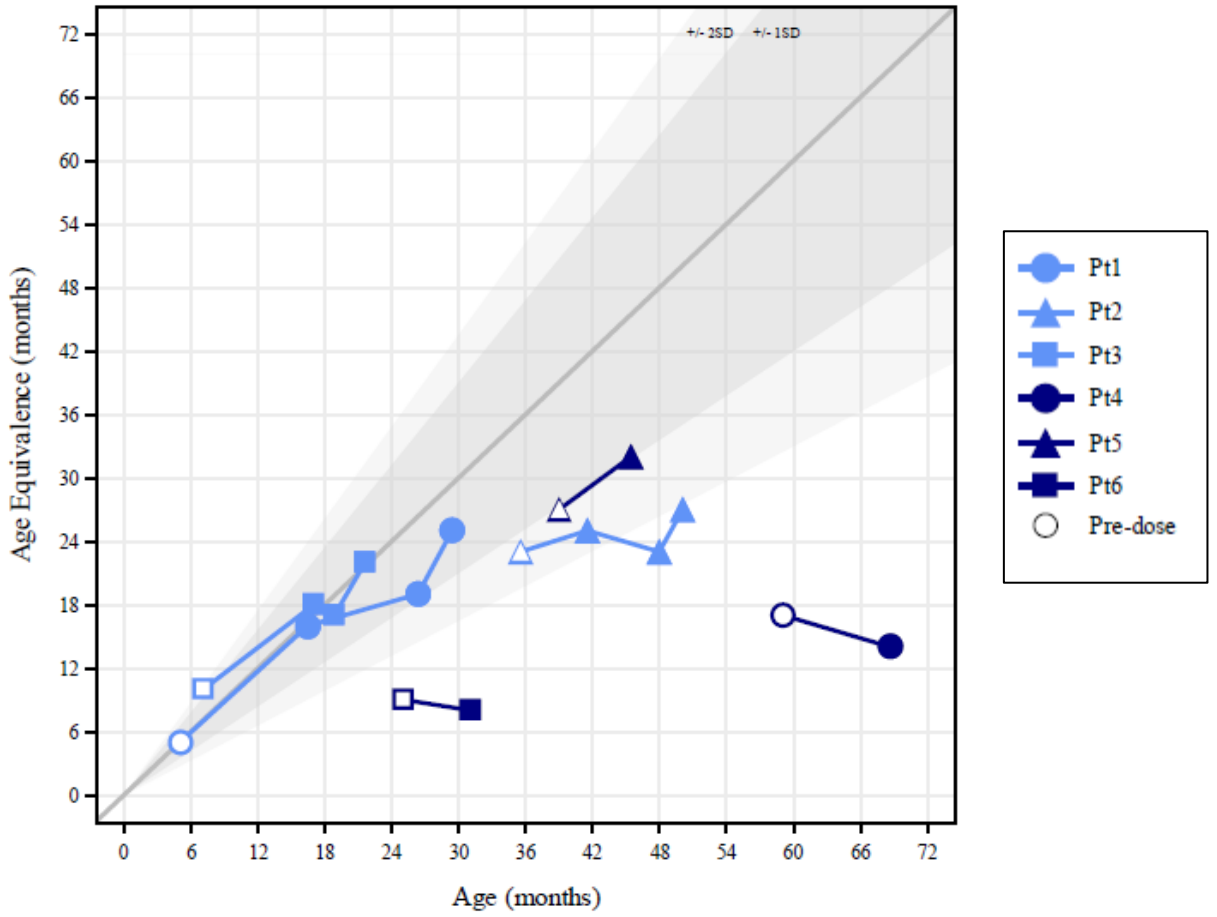
* p-values are from Wilcoxon signed rank test

[1]Rauch 2018, Sci Rep. 23;8(1):6382. [2]Stopschinski 2018, J Biol Chem. 6;293(27):10826-10840. [3]Huyhn 2019 PLoS One. 4;14(1):e0209573.
[4]Holley 2011, J Biol Chem. 28;286(43):37515-24. [5]Wilkinson 2012, PLoS One. 7(4):e35787. [6]Gleiz 2018, EMBO Mol Med. 10(7):e8730.

Neurodevelopment Function: Age Equivalence (Cognitive)

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

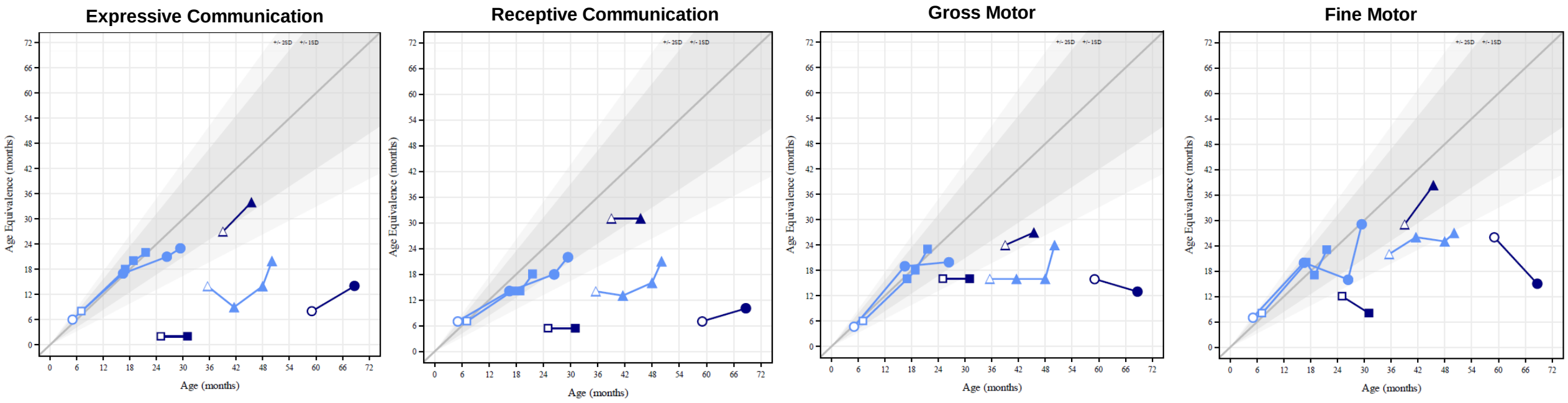
- Patients 1, 3 and 5 demonstrate continued cognitive development within a normal range
- Patients 2 and 4 presented with significant cognitive delay at baseline
  - Patient 2 has continued cognitive development
  - Patient 4 acquired expressive and receptive language skills (see next slide)



Continued cognitive development in 4 of 5 patients with > 6 months of follow-up

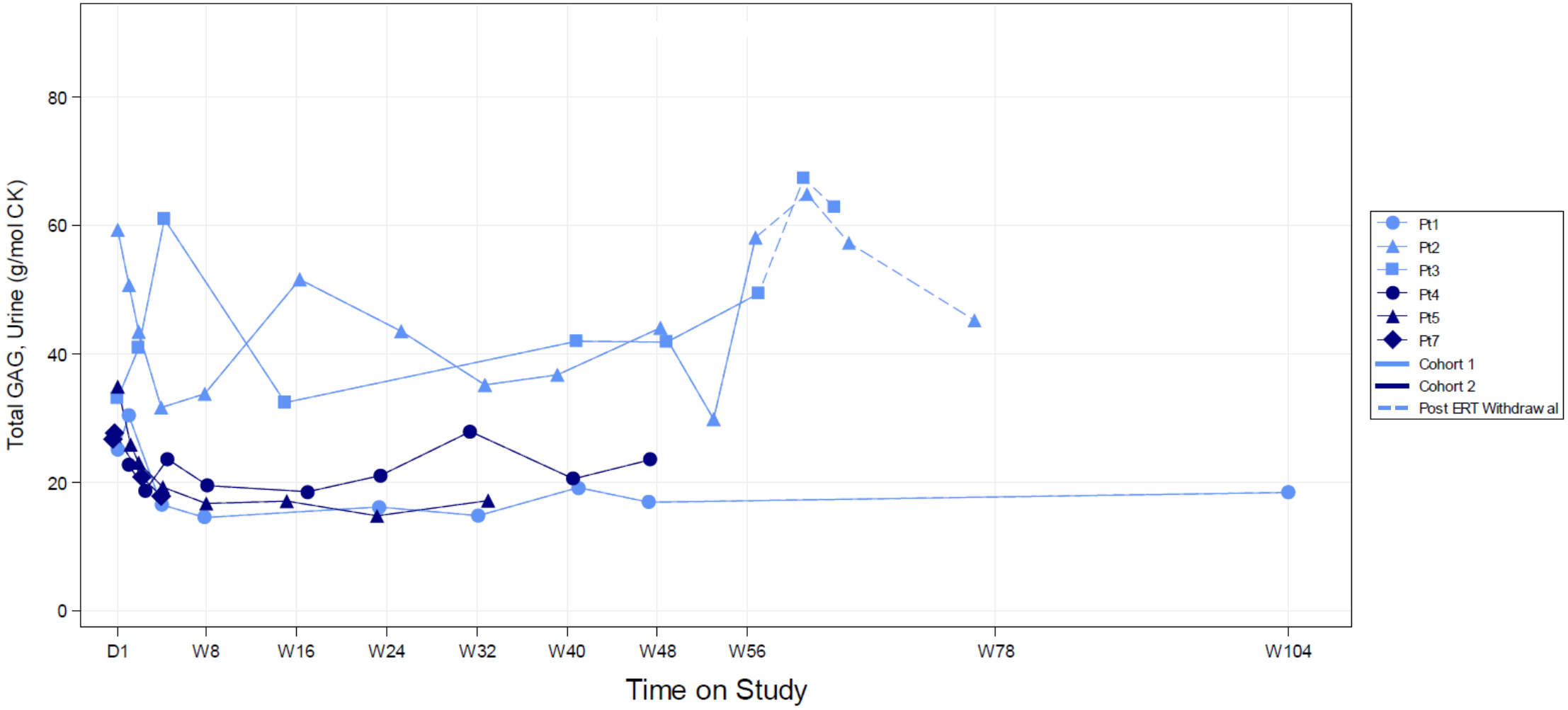
Neurodevelopment Function: Language and Motor Domains

BSID-III



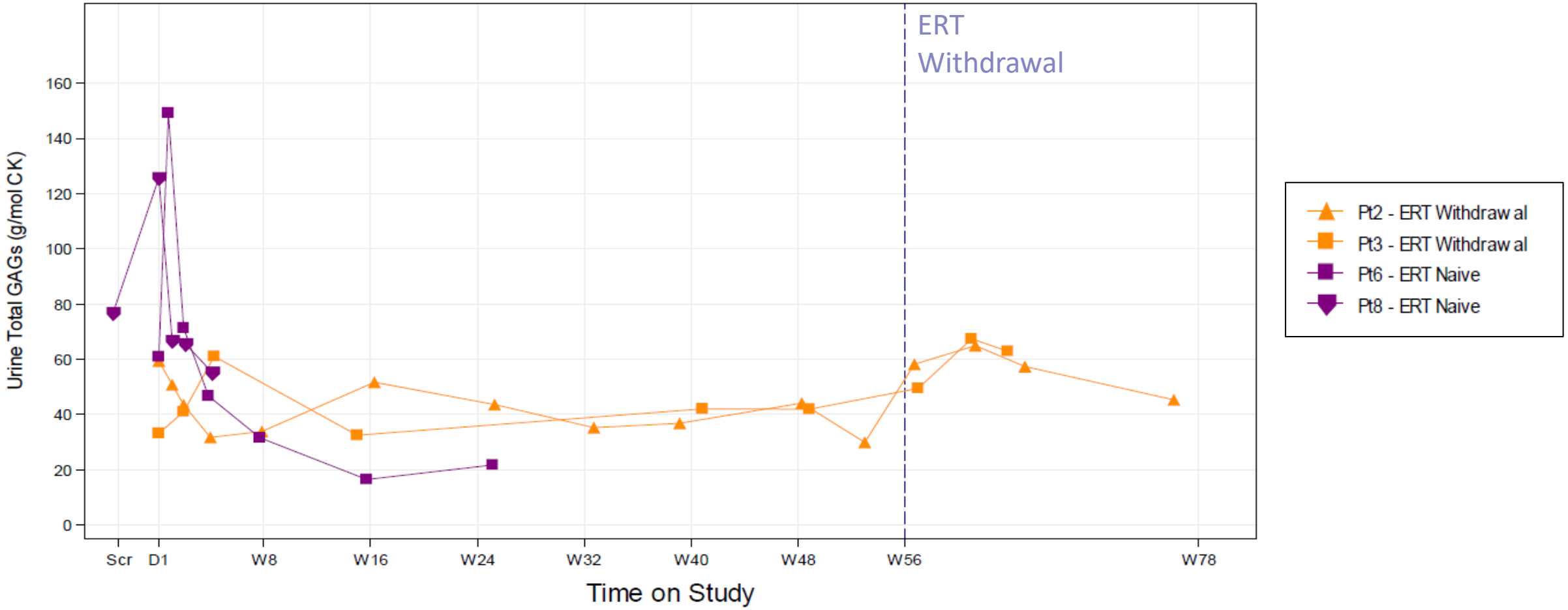
Continued language and/or motor skills acquisition in patients with > 6 months of follow-up

Systemic Efficacy: Urine Total GAGs
ERT-Treated Patients



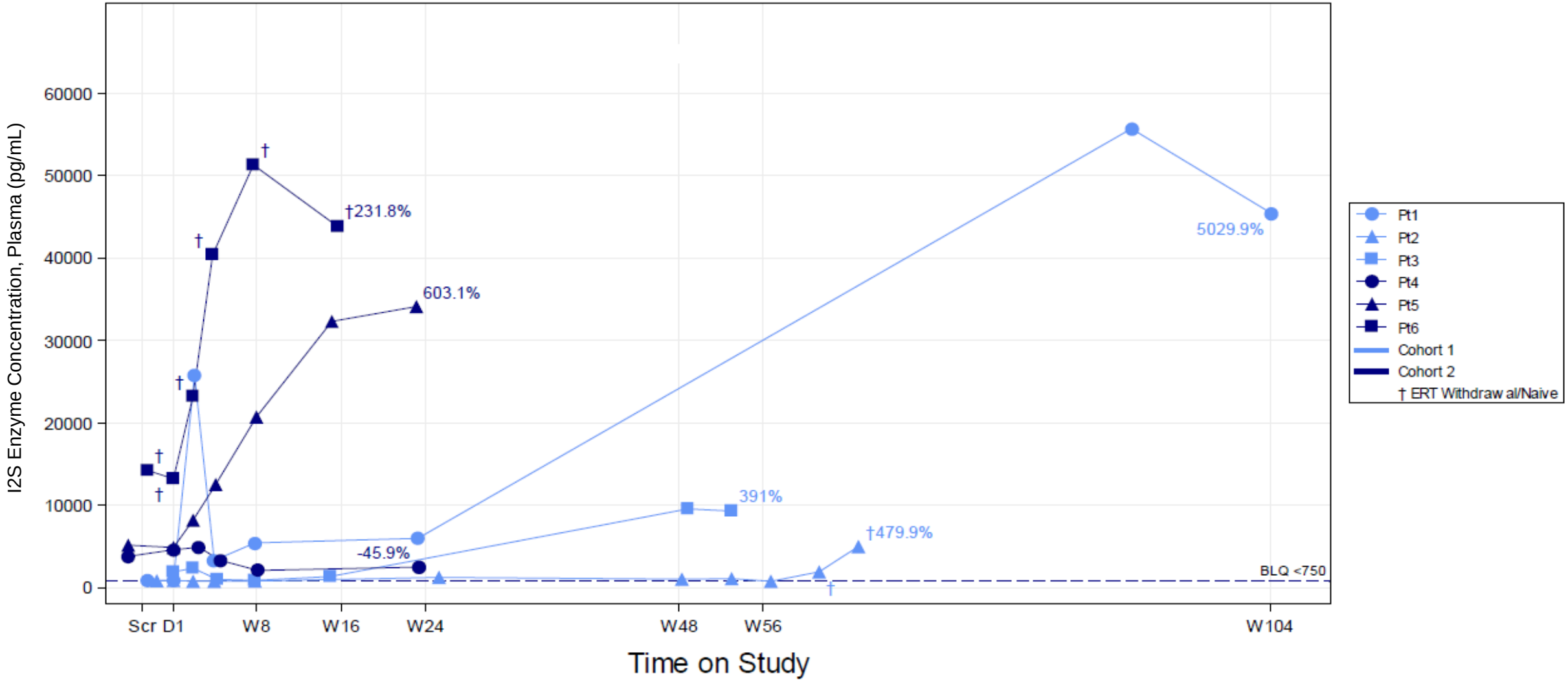
Sustained decrease in urine GAG levels across all patients receiving ERT

Systemic Efficacy: Urine Total GAGs
ERT Naïve and ERT Discontinued Patients



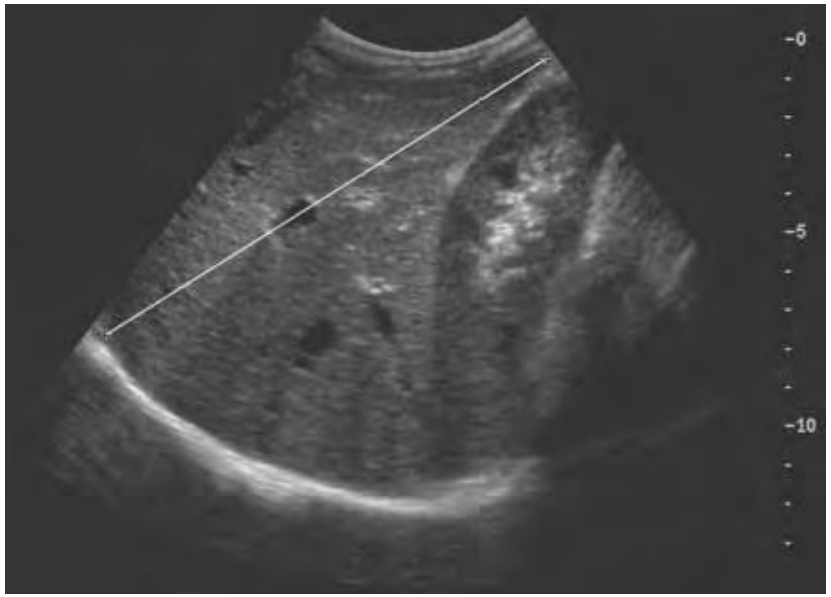
Rapid decrease in urine GAGs in ERT-naïve patients after RGX-121 administration; absence of urine GAG rebound post ERT withdrawal

Systemic Efficacy: Plasma I2S Enzyme Concentration



General increase in plasma I2S enzyme levels in 5 out of 6 patients after RGX-121 administration

Systemic Efficacy: Liver and Spleen Ultrasounds
ERT Naïve Patient



Kratzer 2003

- Hepatosplenomegaly occurs almost universally in untreated MPS II[1]
- Patient 6, who never received ERT, demonstrated clear reduction in liver and spleen dimensions 24 weeks after receiving RGX-121

Patient	**Follow-Up** (weeks)	**Liver Diameter** (cm)	**Spleen Length** (cm)	**Spleen Height** (cm)	**Spleen Width** (cm)
6	Screening	12.0	9.0	6.0	7.2
	24	10.8	7.6	4.0	4.0

Decreased liver and spleen dimensions in ERT-naïve patient 24 weeks after RGX-121 administration

[1] *Wraith et al. Genetics in Medicine.10,508–516(2008)*

RGX-121-101: Summary of Results

RGX-121 appeared to be well tolerated

- 8 patients dosed with no SAEs related to study drug (as of 04January2021)
- Immunosuppression discontinued in first 4 patients according to protocol

Biomarker and neurodevelopmental function indicate encouraging RGX-121 CNS activity

- Consistent reductions in HS in the CSF up to 2 years
- CSF I2S enzyme concentration measurable in all cohort 2 patients
- Continued cognitive development in 4 of 5 patients with > 6 months of follow-up
- Continued language and/or motor skills acquisition in patients with > 6 months of follow-up
- Continued acquisition of cognitive and/or language skills in patients with cognitive delay prior to dosing

Emerging evidence of systemic enzyme expression and biomarker activity of RGX-121

- Plasma I2S enzyme levels increased in 5 of 6 patients
- Rapid urine GAG reduction in ERT naïve patients
- Decreased liver and spleen dimensions in ERT naïve patient
- Absence of urine GAG rebound in the 2 patients who have discontinued ERT

Acknowledgements

MPS II patients and their families

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- **Dr Can Ficicioglu**, Children's Hospital of Philadelphia, USA
- **Dr Roberto Giugliani**, Hospital de Clínicas de Porto Alegre, Brazil
- **Dr Paul Harmatz**, University of California San Francisco, USA

MPS II Program:

RGX-121-101: NCT03566043

Age 5-18 years: NCT04571970

Observational: NCT04591834

MPS I Program:

First in human:
NCT03580083

REGENXBIO, the sponsor of the RGX-121-101 trial