RGX-121 Gene Therapy for the Treatment of Severe Mucopolysaccharidosis Type II: CAMPSIITE™ Phase I/II/III: A Clinical Study Update

Presented by:

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Conflict of Interest Disclosure

I have the following conflicts to disclose:

Consulting Fees / Advisory Boards	Abeona, Amicus, Chiesi, Denali, Inventiva, JCR, Novartis, PTC, Protalix, REGENXBIO, Sobi
Speaker's Bureau	BioMarin, Amicus, Chiesi, Idorsia, Janssen, Novartis, Pfizer, PTC, Sanofi, Takeda
Contracted Research	Allievex, Avrobio, Azafaros, JCR, Lysogene, Paradigm, PassageBio, REGENXBIO, Sanofi, Sigilon, Takeda, Ultragenyx

Agenda

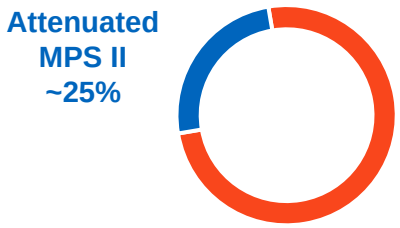
- Potential of Gene Therapy to Address Unmet Need in MPS II
- CAMPSIITE Study Part 1, Phase I/II Interim Results
- Announcing CAMPSIITE Study Pivotal Expansion
- CAMPSIITE Study Part 2, Phase III Design

AAV Gene Therapy Has the Potential to Address Unmet Need in MPS II

High Unmet Need of MPS II

Incidence of MPS II

Prevalence



- MPS II, also known as Hunter syndrome, is a rare X-linked recessive genetic disease
- 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 in severe cases

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

RGX-121 May Provide Meaningful Advantages Over Standard of Care

Potential of RGX-121 for MPS II

AAV9 Vector + *IDS* Transgene

- **One-time administration**
- Image-guided administration allows **direct delivery of *IDS* transgene to cells in the CNS**
- May **allow cells to produce functional I2S protein** and cross-correct other cells
- Potential for **long-term expression of I2S**
- **May prevent CNS disease progression**

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

RGX-121: CAMPSIITE Part 1, Phase I/II

NCT03566043 on ClinicalTrials.gov

Participants

Enrollment up to 16 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*

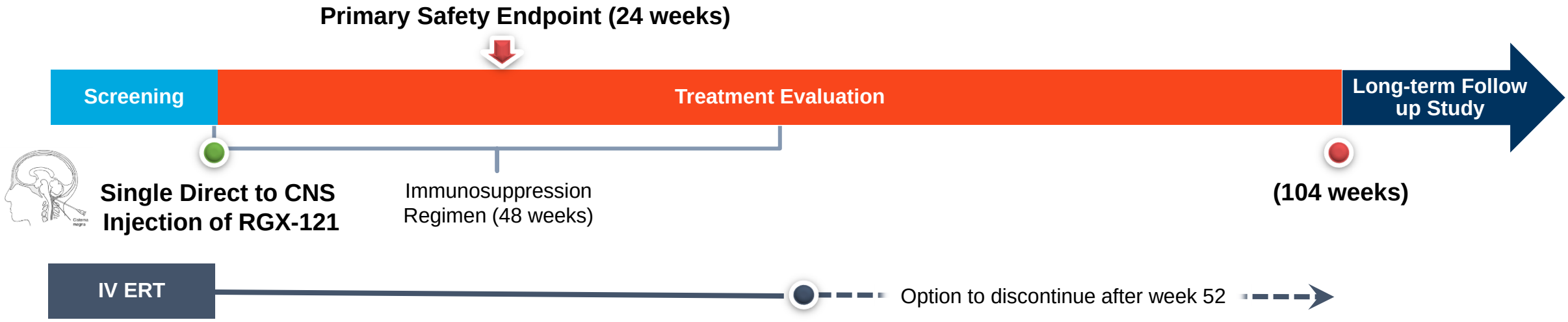
Cohort 1: 1.3 x 10^{10}
Cohort 2: 6.5 x 10^{10}
Cohort 3: 2.9 x 10^{11} *

Data

Primary Endpoint: Safety

Secondary & Exploratory Endpoints Include:

- CSF GAGs
- Neurodevelopmental Assessments (Bayley)
- Caregiver Reported Outcomes (VABS; SDSC)
- Systemic Biomarkers (urine & plasma GAGs)



VABS (Vineland Adaptive Behavior Scale; SDSC Sleep Disturbance Scale for Children
* 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 Phase I/II Cohorts

- 14 participants dosed as of August 1, 2022
- Ages at dosing range from 5 months to 59 months
- *IDS* Mutations among severe MPS II trial participants include missense, gene inversion, frameshift, deletion, substitution and splicing
- No SAEs related to study drug as of August 1, 2022
- Immunosuppression discontinued in all eligible participants (n = 11) per protocol

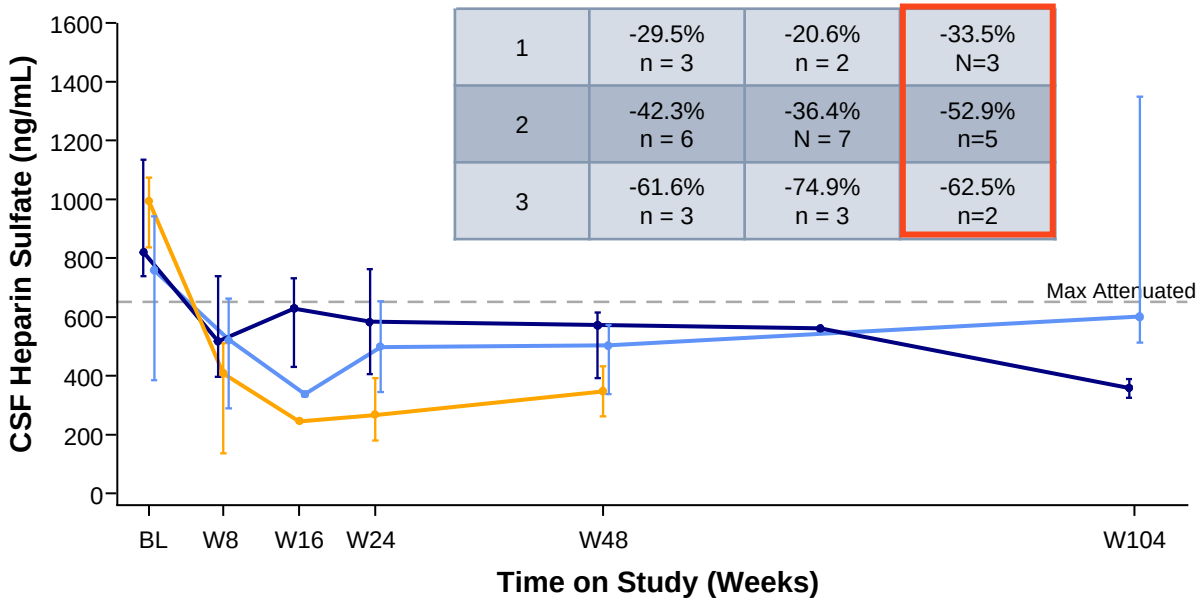
Cohort	N	Dose (GC/g Brain Mass)	Follow-Up (Weeks)	Immunosuppression Regimen Status	ERT (IV) Status†
Cohort 1	3	1.3×10^{10}	104 wk	3 completed	3 weekly*
Cohort 2	7	6.5×10^{10}	40-104 wk	6 completed 1 active	2 weekly 3 discontinued 2 naïve
Cohort 3	4**	2.9×10^{11}***	8-56 wk	2 completed 2 active	4 weekly

† Protocol allows ERT discontinuation after Week 52
* 2 subjects who discontinued restarted weekly ERT
** Data shown for 3 participants
*** 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.

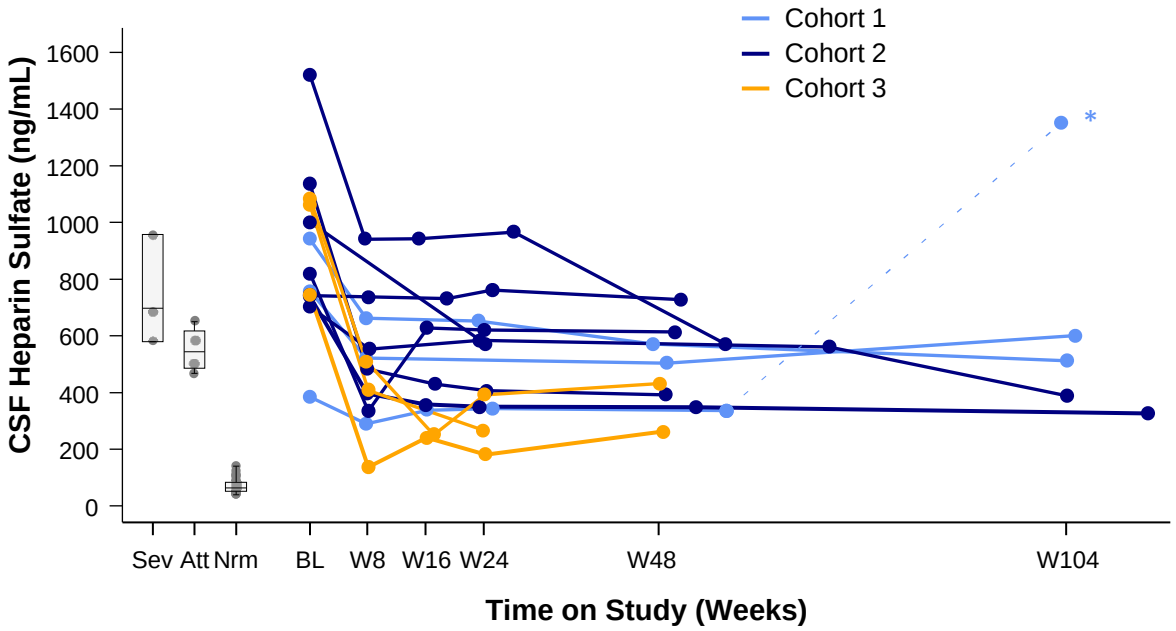
Cerebrospinal Fluid (CSF) GAGs: Heparan Sulfate (HS)

Cohorts (median†)

Cohort	Week 8	Week 24	Week 48
1	-29.5% n = 3	-20.6% n = 2	-33.5% N=3
2	-42.3% n = 6	-36.4% N = 7	-52.9% n=5
3	-61.6% n = 3	-74.9% n = 3	-62.5% n=2



Individual Participants



- **Week 48 CSF HS measurements continued to show dose-dependent reductions in Cohorts 1-3**
- **Majority of participants in all three cohorts demonstrated decreased CSF HS at last time point available**

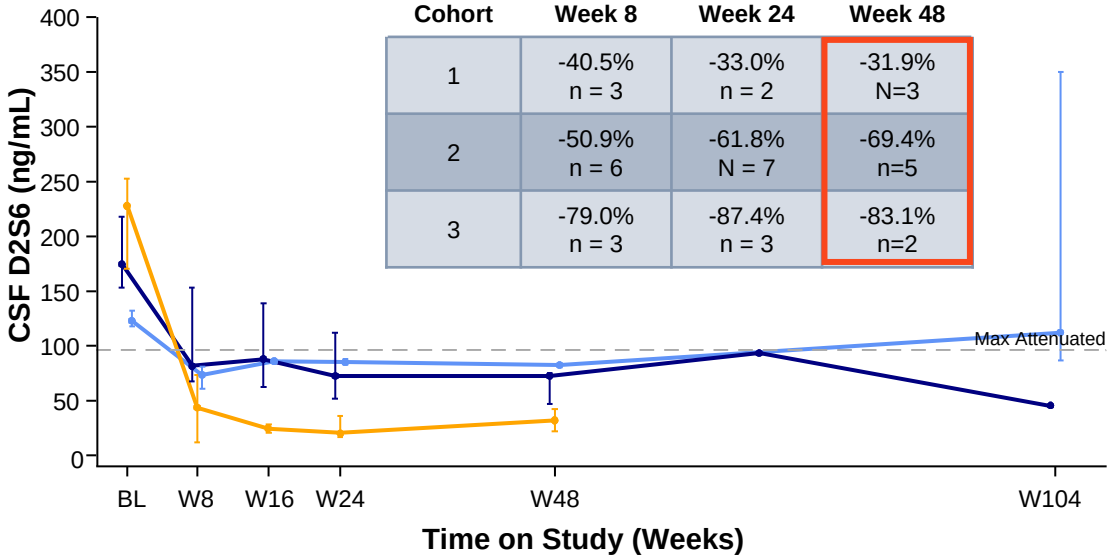
* CNS related clinical event (ventriculoperitoneal shunt infection) took place on Day 522 post RGX-121 administration in this Cohort 1 patient that was deemed unrelated to study drug
† Median CSF HS concentration +/- Q1 and Q3 per cohort.
Normative data are based on 29 normal samples. The ages for 9 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 GAGs: HS D2S6 Disaccharide

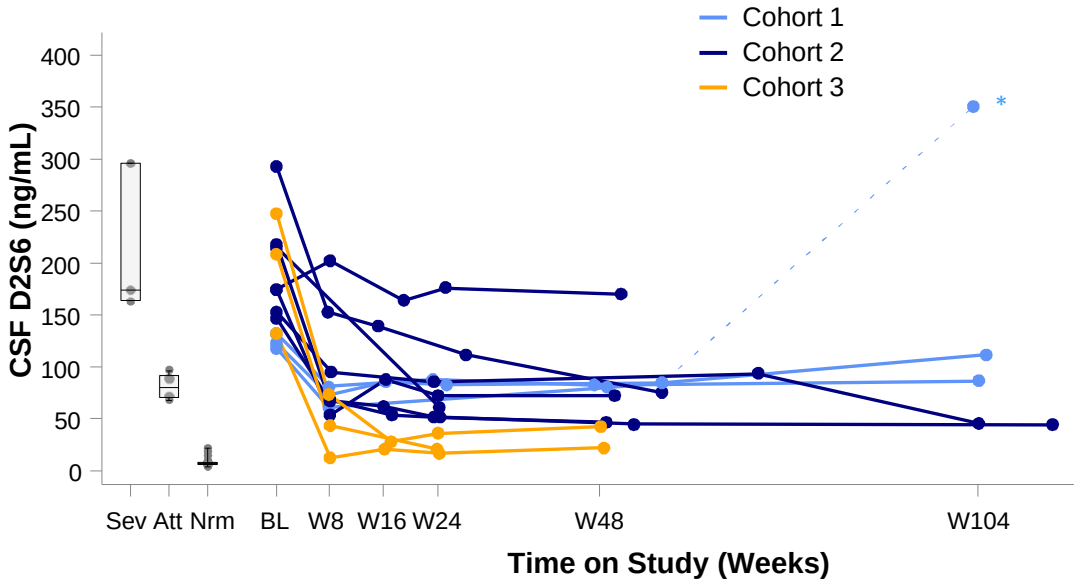
D2S6 is a Correlate of Neuropathology Phenotype in Severe MPS II[1-3]

Cohorts (median†)

Cohort	Week 8	Week 24	Week 48
1	-40.5% n = 3	-33.0% n = 2	-31.9% N=3
2	-50.9% n = 6	-61.8% N = 7	-69.4% n=5
3	-79.0% n = 3	-87.4% n = 3	-83.1% n=2



Individual Participants



- **Week 48 CSF HS D2S6 measurements continued to show dose-dependent reductions across cohorts, with Cohort 3 participants approaching normal levels**
- **Majority of participants in all three cohorts demonstrated decreased CSF HS D2S6 at last time point available**
- **Measurable CSF I2S protein concentration in Cohort 2 & 3 participants after RGX-121 administration (range 747 – 5080 pg/mL)****

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

* 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

** Data not presented

† Median CSF D2S6 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.

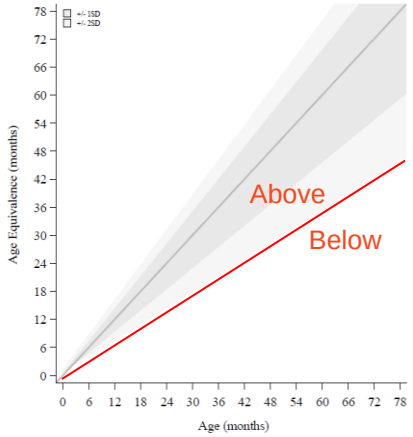
Neurodevelopment Assessments:
Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III)

- 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, n = 1 Cohort 2)

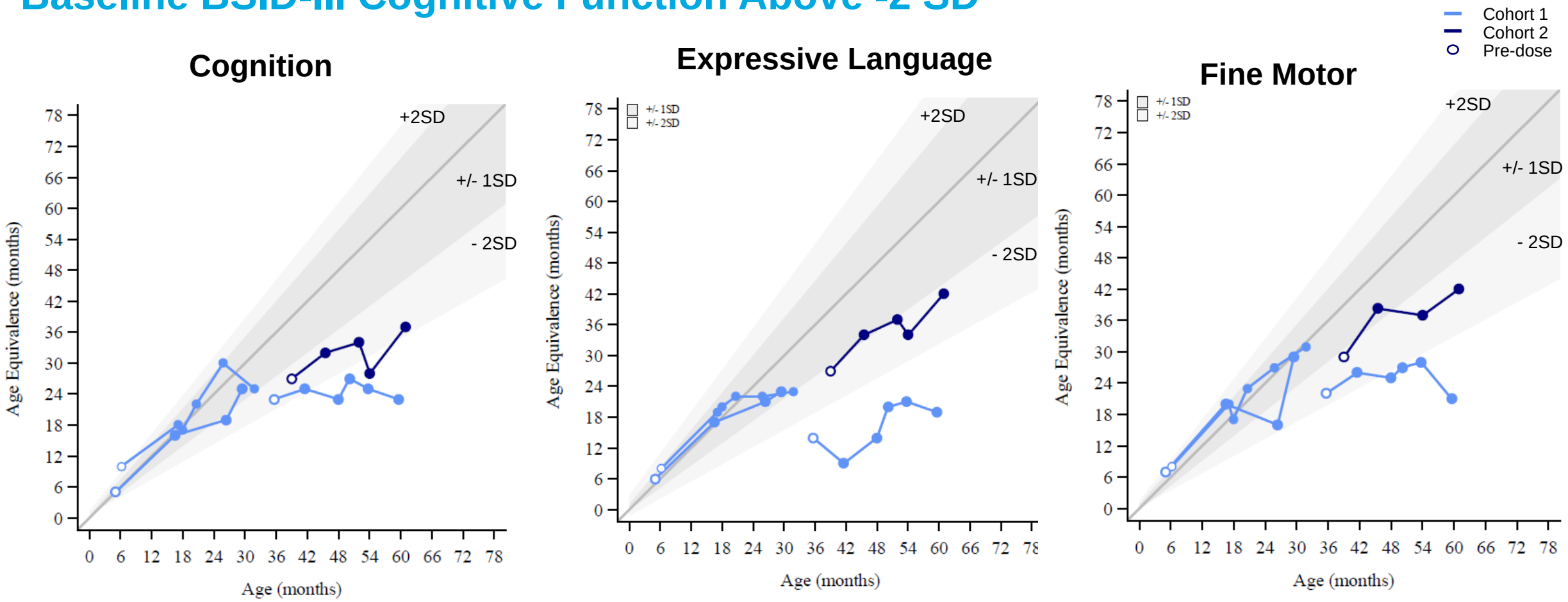


Participants at baseline with cognitive function below -2 SD from the normative mean

(n = 4 Cohort 2)

Neurodevelopmental Function:

Baseline BSID-III Cognitive Function Above -2 SD



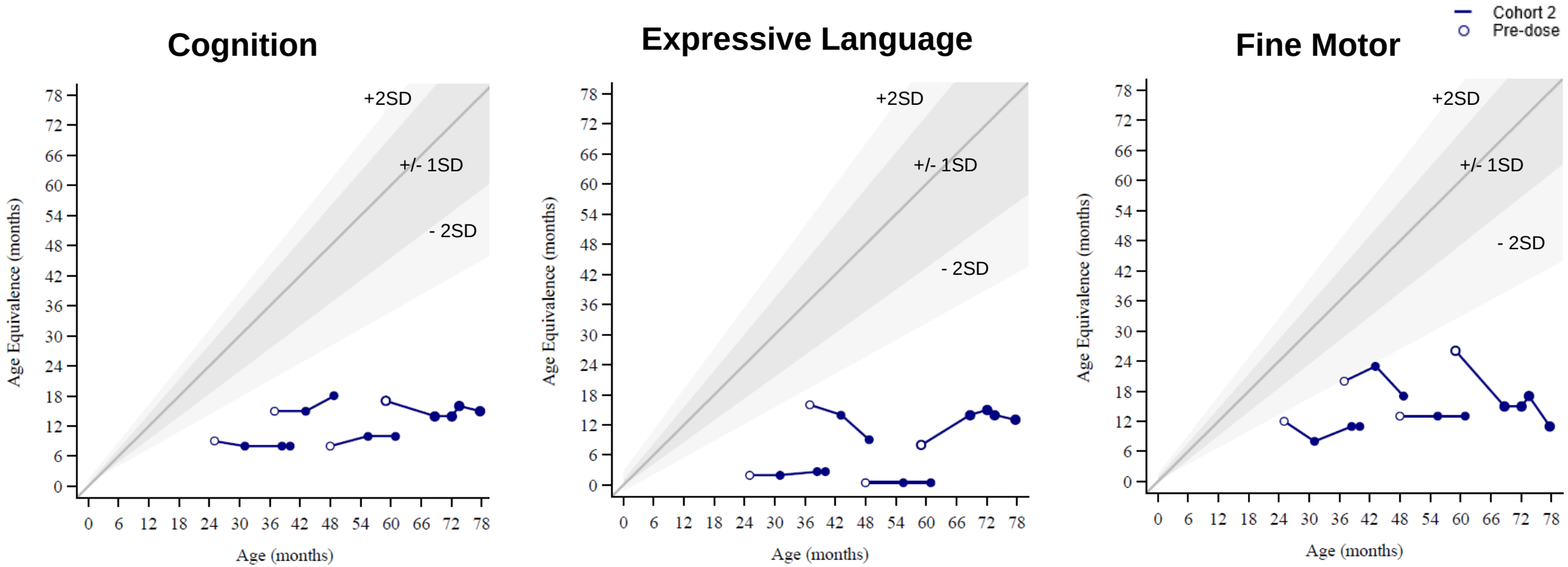
3 of 4 participants with cognitive function above -2 SD at baseline remained within 2 SD at the last assessment on the cognition, expressive language and fine motor subtests

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

Data cut December 20, 2021

Neurodevelopmental Function:

Baseline BSID-III Cognitive Function Below -2 SD



Participants with cognitive function below -2SD at baseline demonstrated minimal skill acquisition

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

Data cut December 20, 2021

Presented at WORLDSymposium, February 9, 2022

RGX-121 CAMPSIITE Part 1, Phase I/II

Summary of Results

Safety: RGX-121 appeared to be well tolerated[1]

- As of August 1, 2022, 14 patients have been dosed with no SAEs related to study drug

CNS: CSF GAGs and neurodevelopmental assessments continue to indicate an encouraging RGX-121 profile[1,2]

- **Dose-dependent reductions in CSF GAGs demonstrated across cohorts[1]**
- **Cohort 3 CSF HS D2S6 approached normal levels at 48 weeks[1]**
- Improvements in neurodevelopmental function and caregiver reported outcomes* in Cohorts 1 and 2 demonstrated CNS activity up to 2 years after RGX-121 administration[2]

Systemic: Evidence of enzyme expression and biomarker activity after CNS RGX-121 administration[2*]

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

Based on these data, REGENXBIO is taking Dose 3 into a pivotal program

1. Data cut August 1, 2022
2. Data cut December 20, 2021; Presented at WORLDSymposium, February 9, 2022

* Caregiver reported outcomes, I2S concentration, and Urine GAG data not shown

RGX-121 Pivotal Program for Patients with MPS II

REGENXBIO has announced:[1]

- Expansion of the Phase I/II trial of RGX-121 into a pivotal Phase I/II/III trial
- Intention to file a Biologics License Application (BLA) in the U.S. using the accelerated approval pathway for RGX-121
- Enrollment of up to 10 patients to support a BLA filing in 2024

RGX-121 has the potential to be considered for accelerated approval as it may:[2]

1) Treat a serious condition
2) Provide a meaningful advantage over available therapies
3) Demonstrate an effect on a surrogate endpoint (CSF GAGs) that is reasonably likely to predict clinical benefit

Should RGX-121 be approved under the accelerated approval pathway, confirmatory trials will be conducted

For more information on U.S. Accelerated Approval Pathway see reference 2

1. https://regenxbio.gcs-web.com/news-releases/news-release-details/regenxbio-announces-intention-file-biologics-license-application
2. https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development#:~:text=A%20surrogate%20endpoint%20is%20a,to%20predict%20that%20clinical%20benefit

RGX-121: CAMPSIITE Part 2, Phase III

NCT03566043 on ClinicalTrials.gov

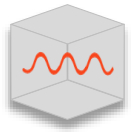
Participants

Enrollment up to 30 neuronopathic MPS II patients
(≥ 4 months to < 5 years of age)

May be on Standard of Care IV ERT
or
ERT Naïve

If MPS II Phenotype Unknown:
Serial neurodevelopmental assessments up to 12 Months;
May screen for intervention if neuronopathic confirmed

Dose



RGX-121
AAV9 + *IDS*

2.9 x 10^{11} *
Genome copies/g brain mass

Data

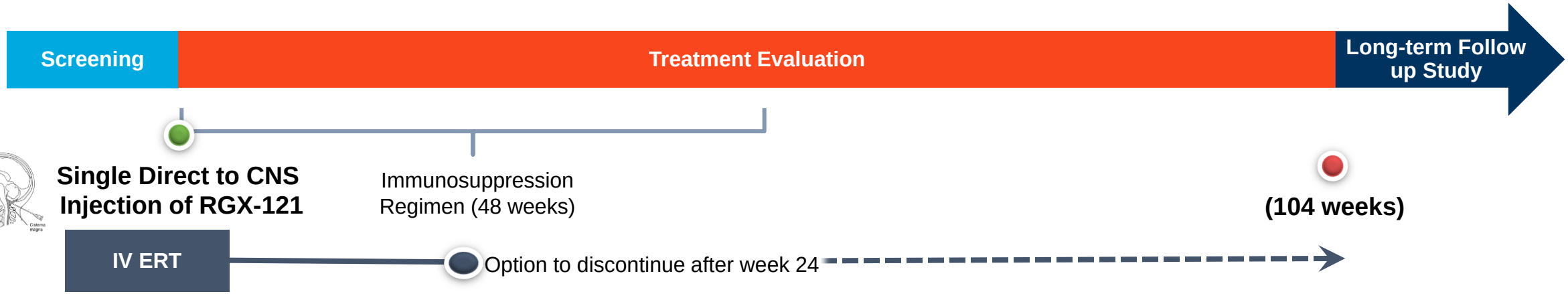
Primary Endpoint: CSF GAGs

Co-primary Endpoint:

- Neurodevelopmental Assessments (Bayley, Mullen)

Secondary Endpoints:

- Safety
- Caregiver Reported Outcomes (VABS)
- Systemic Biomarkers (I2S, GAGs)
- MRI



- Dose is the same as Cohort 3 in CAMPSIITE Part 1 (Phase I/II).
- VABS: Vineland Adaptive Behavior Scales

Acknowledgements

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