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

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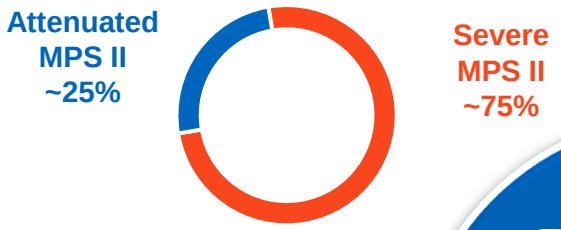
AAV Gene Therapy Has the Potential to Address Unmet Need in MPS II

High Unmet Need in 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) which results in GAG accumulation
  - Causes systemic symptoms, neurodegeneration and leads to early death

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 partcipants
(≥ 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*

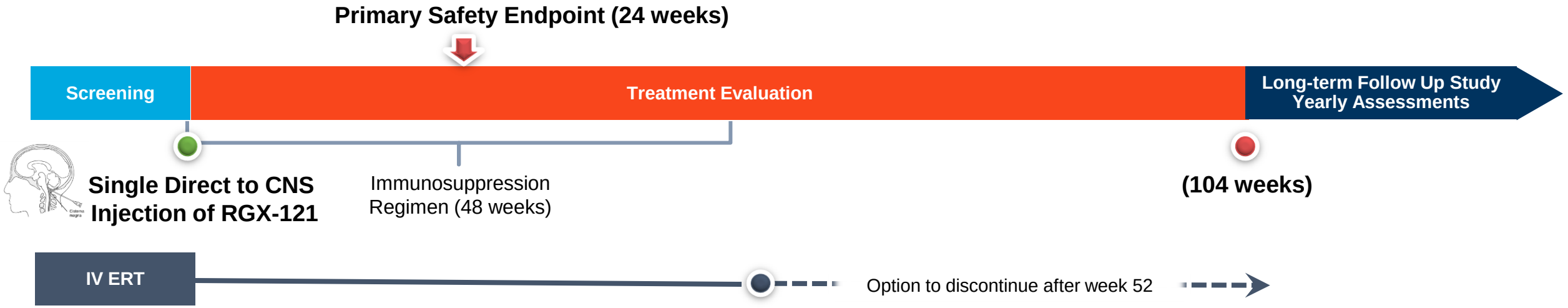
Cohort 1: 1.3 x 10^{10}
Cohort 2: 6.5 x 10^{10}
Cohort 3: 2.9 x 10^{11} *

Data

Primary Endpoint: Safety

Secondary & Exploratory Endpoints Include:

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



Bayley (Bayley Scales of Infant and Toddler Development, 3rd Edition); VABS (Vineland Adaptive Behavior Scales, 2nd Edition); 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

- 15 participants dosed as of January 3, 2023
- Age at dosing ranged from 5 months to 59 months
- *IDS* Mutations among severe MPS II trial participants included deletion, frameshift, gene inversion, insertion, missense, splicing, and substitution
- Study duration 104 weeks. At the end of the study, participants were invited to participate in a long-term follow-up study for a total of 260 weeks (5 years)
- Immunosuppression discontinued in all eligible participants (n = 13) 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}	154-208 wk	3 completed	3 weekly*
Cohort 2	7	6.5×10^{10}	61-160 wk	7 completed	2 weekly 4 discontinued 1 naïve
Cohort 3	5**	2.9×10^{11}***	8 to 78 wk	3 completed 2 active	3 weekly 1 discontinued 1 naïve

† Protocol allows ERT discontinuation after Week 52
* 2 participants who discontinued restarted weekly ERT
** Limited data shown for 2 recently dosed 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.

CAMPSIITE Safety Summary

SAE	▪ 12 serious adverse events (SAE; 8 in main study, 4 in LTFU) reported in 7 participants: None are considered related to RGX-121 ▪ SAEs reported in main study: HSV gingivostomatitis*, fever requiring hospitalization, infection of VP shunt, viral meningitis*, hydrocephalus, laryngospasm, cerebellar/cerebral infarction, seizures ▪ SAEs reported in LTFU: Tonsillitis, Pharyngitis, Viral URI, URI ▪ 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 ▪ 6 AESIs (adverse events of special interest) reported, all considered related to immunosuppression regimen, all resolved, with HSV gingivostomatitis being the most common

RGX-121 has been well tolerated

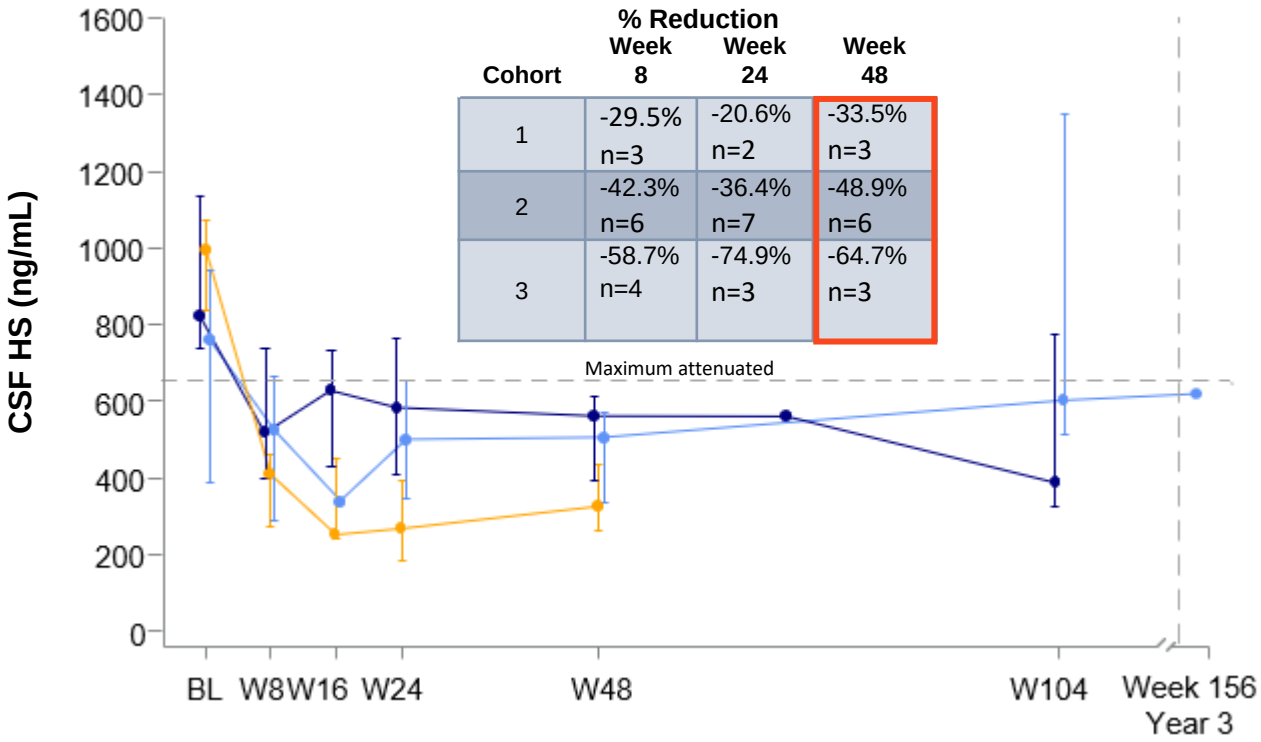
* Possibly related to immunosuppression

Data cut January 3, 2023

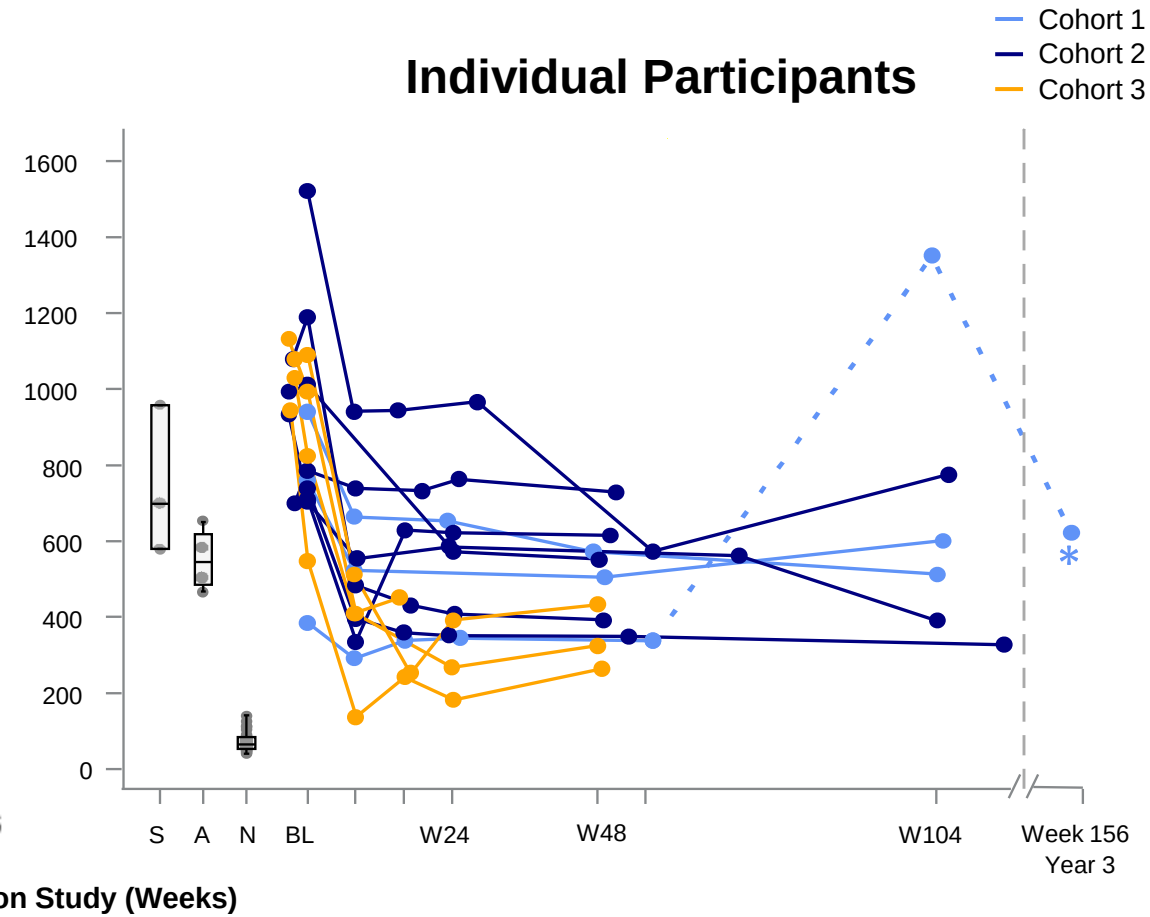
Cerebrospinal Fluid (CSF) GAGs: Heparan Sulfate (HS)

Cohorts (median†)

Cohort	% Reduction 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	-48.9% n=6
3	-58.7% n=4	-74.9% n=3	-64.7% n=3



Individual Participants

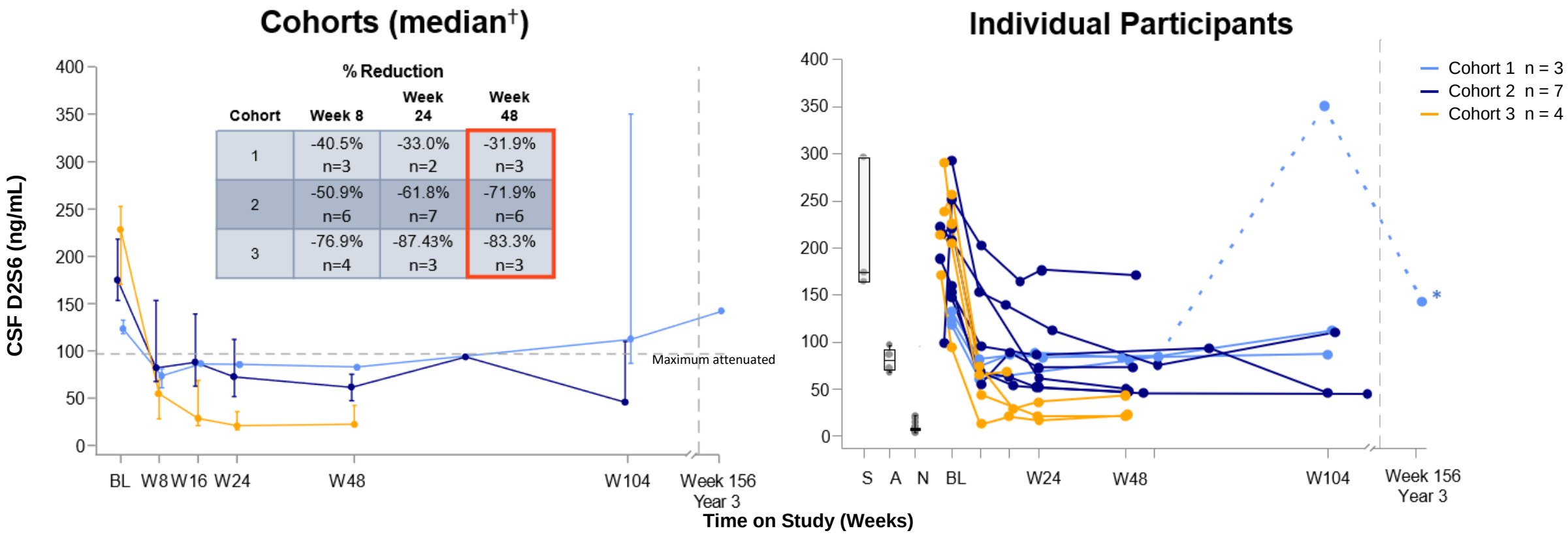


- **Week 48 CSF HS measurements continued to show dose-dependent reductions in Cohorts 1-3**
- **13 of 14 participants in all three cohorts demonstrated decreased CSF HS from baseline at last time point available***

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

CSF GAGs: HS D2S6, a Trisulfated Disaccharide

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



- **Week 48 CSF HS D2S6 measurements continued to show dose-dependent reductions across cohorts, with Cohort 3 participants approaching normal levels**
- **13 of 14 of participants in all three cohorts demonstrated decreased CSF HS D2S6 from baseline at last time point available***
- **Measurable CSF I2S protein concentration in 10 of 11 Cohort 2 & 3 participants after RGX-121 administration**

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

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

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Neurodevelopment Assessments

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

- Participants were assessed using the BSID-III
- Age Equivalent (AEq) data is presented for the BSID-III Cognitive, Expressive Language and Fine Motor subtests
- BSID-III manual normative data were used to characterize ±1 and ±2 standard deviation (SD) boundaries for the AEq score[1]
  - Participants were separated by baseline BSID-III cognitive function
- AEq change from baseline (CFB) is defined by:
  - Increase of ≥3 mo on AEq
  - Stability: change from -3 mo to +3 mo AEq
  - Decline ≥3 mo AEq

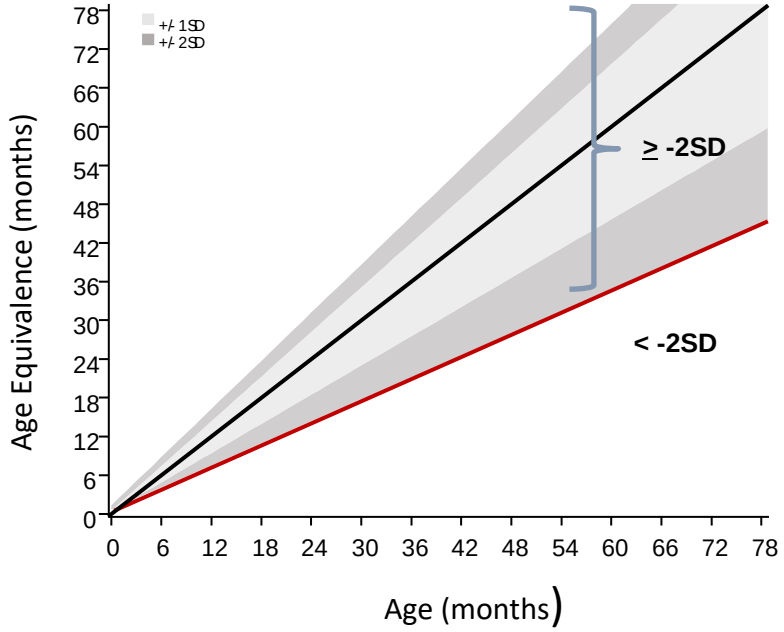
13 Participants with > 6 months follow-up separated by baseline function on cognitive subtest

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

Cohort 1, n = 3
Cohort 2, n = 1
Cohort 3, n = 1

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

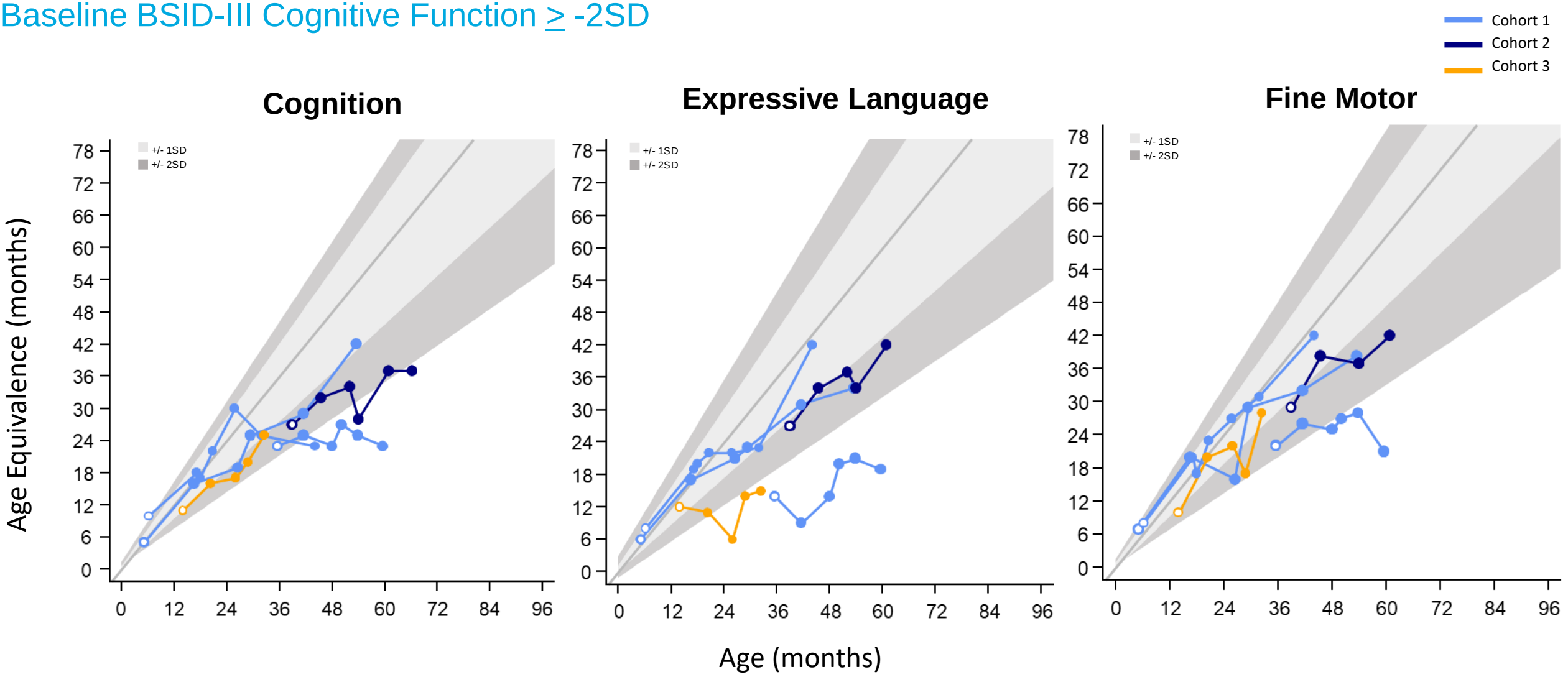
Cohort 2, n = 6
Cohort 3, n = 2



Cho, ICIEM Virtual Congress 2021

Neurodevelopmental Function

Baseline BSID-III Cognitive Function ≥ -2SD

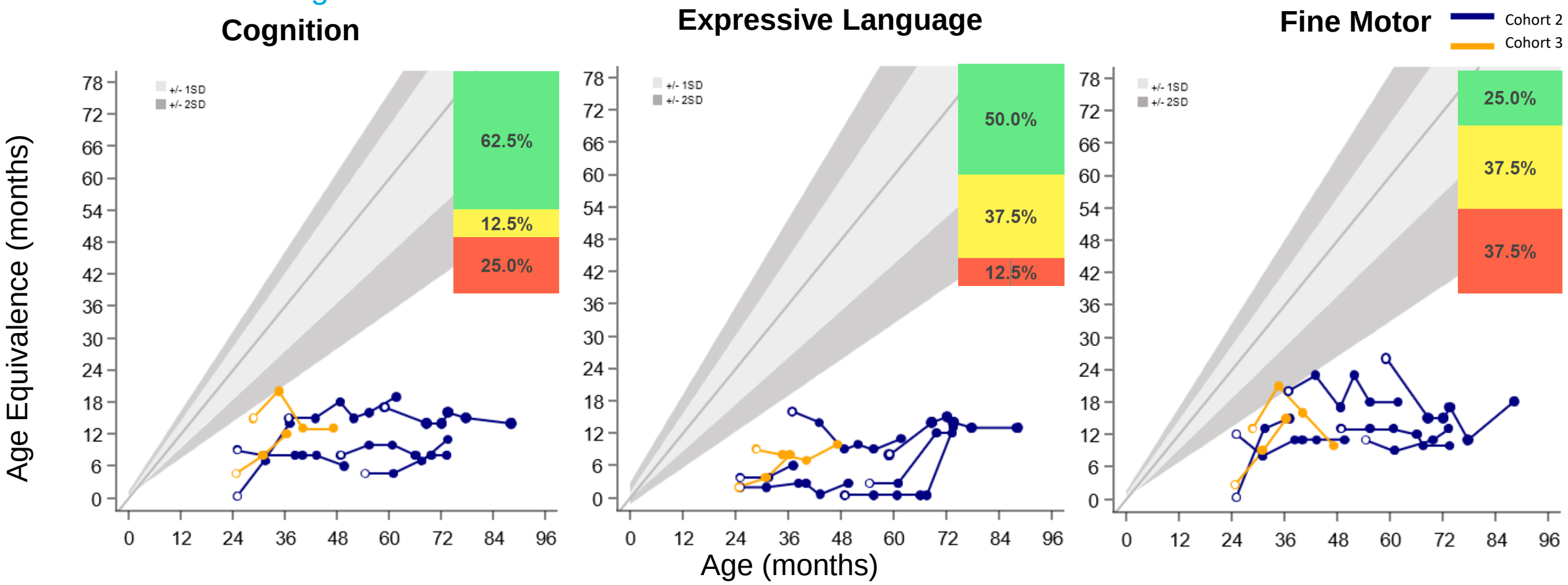


The majority of participants with baseline function ≥-2SD have developmental function that remained within that range on at least 2 domains

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

Neurodevelopmental Function

Baseline BSID-III Cognitive Function Below -2 SD



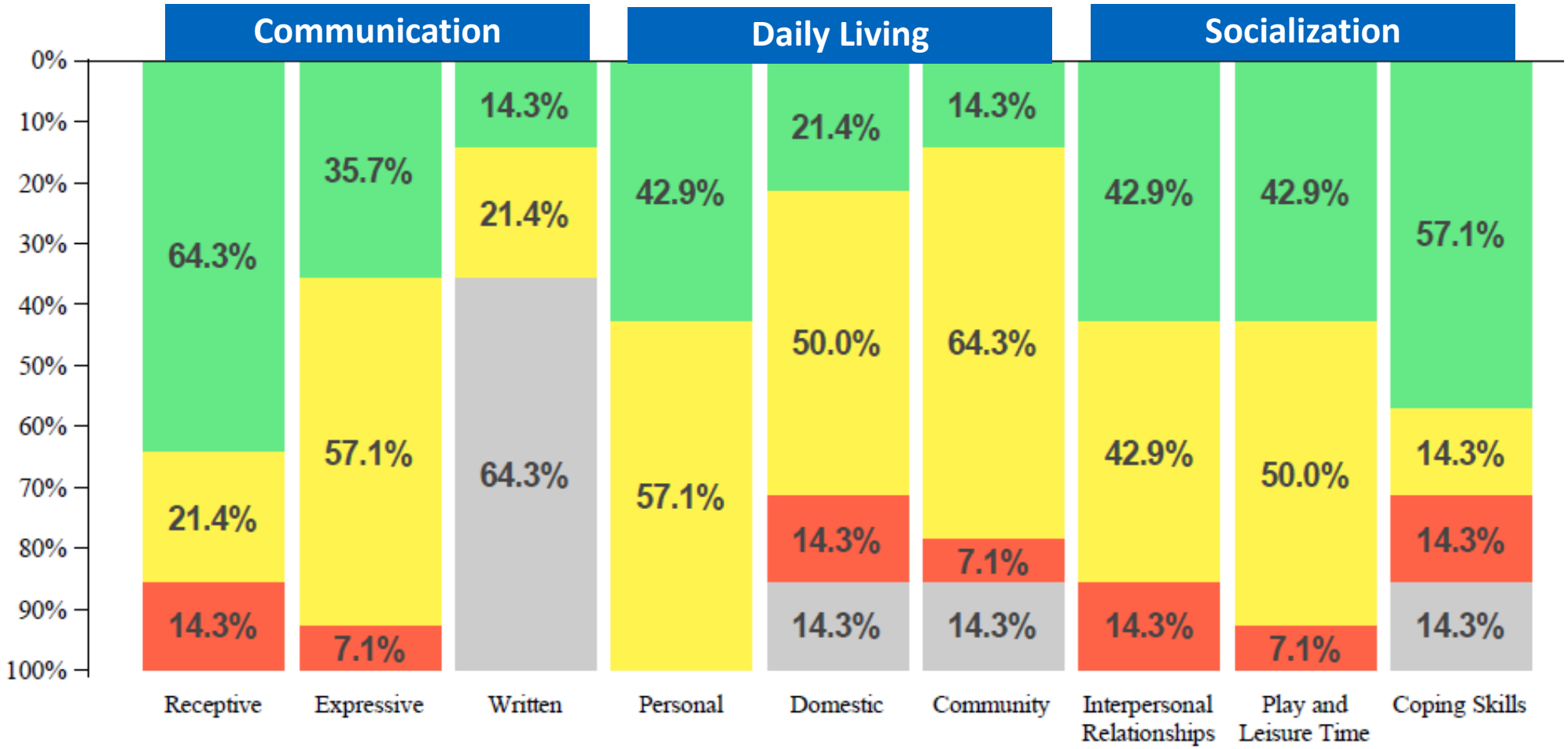
The majority of participants with baseline function below -2SD stabilized or had an increase of ≥ 3 mo in AEq on cognitive, expressive, language or fine motor subtests

Includes participants (n = 8) with > 6 months of follow-up

Change from baseline (CFB) is defined as: Increase ≥ 3 mo AEq; Stabilization -3 < CFB < 3 mo AEq; Decrease ≤ -3 mo AEq

Vineland Adaptive Behavior Scales Second Edition (VABS-II)

VABS measures adaptive behavior, defined as the personal and social skills for everyday living*



The majority of participants demonstrated stabilization or ongoing skill acquisition on age-appropriate subtests of communication, daily living and socialization

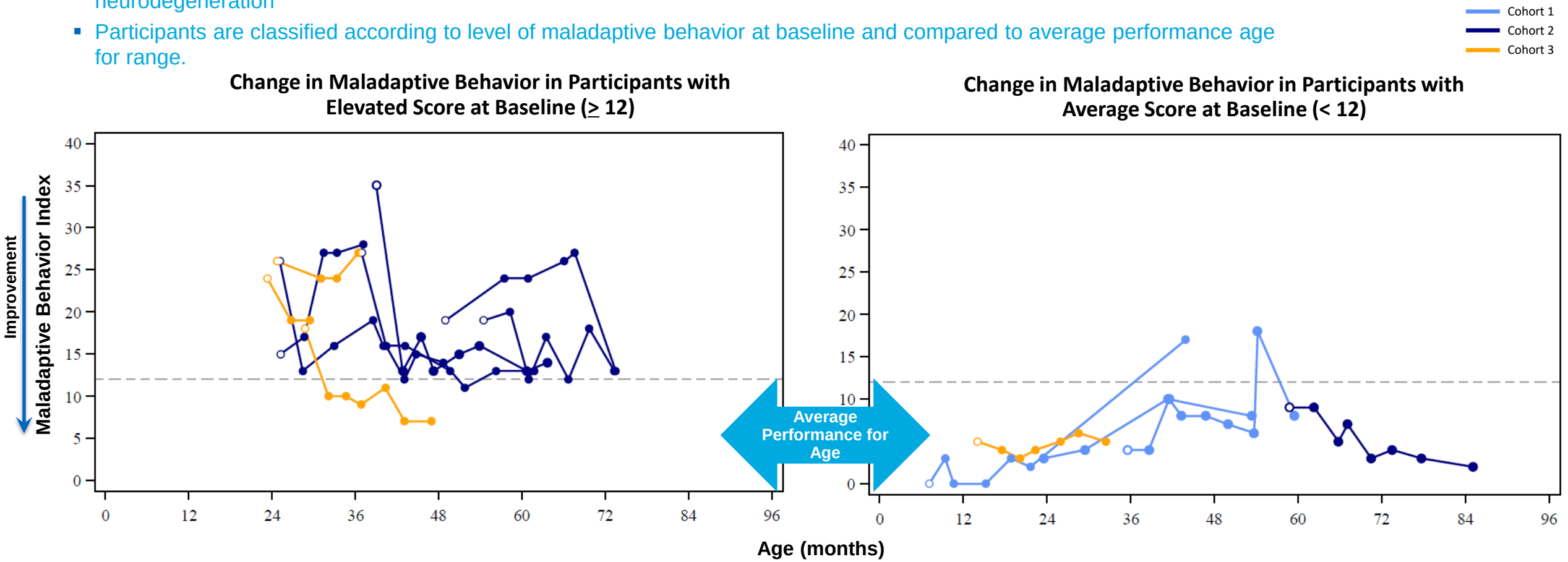
Includes participants (n = 14) with > 6 months of follow-up

* The percent of participants for whom the subtest was not able to be assessed due to age

Change from baseline (CFB) is defined as: Increase ≥ 3 mo AEq; Stabilization -3 mo< CFB < 3 mo AEq; Decrease ≤ -3 mo AEq

VABS-II Maladaptive Behavior Index

- Maladaptive behaviors, a measure of undesirable behaviors that interfere with daily functions, are associated with neurodegeneration
- Participants are classified according to level of maladaptive behavior at baseline and compared to average performance age for range.



At last time point assessed

- **7 of 9 participants with elevated maladaptive behavior at baseline achieved a reduction in maladaptive behavior score**
- **4 of 5 participants with average maladaptive behavior for age at baseline maintained average maladaptive behavior score**

1. Sparrow (2005) Vineland II

VABS-II data include participants with at least one post-baseline assessment OR Includes participants (n = 14) with > 6 months of follow-up

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

RGX-121 CAMPSIITE Part 1, Phase I/II

Summary of Results

Safety: RGX-121 was well tolerated

- As of January 3, 2023, 15 participants have been dosed with RGX-121
- RGX-121 has been well tolerated across 3 cohorts with no SAE related to study drug

CNS: CSF GAGs and neurodevelopmental assessments continue to indicate an encouraging RGX-121 profile

- Dose-dependent, durable reductions in CSF GAGs demonstrated across cohorts
- Cohort 3 CSF HS D2S6 approached normal levels at 48 weeks
- Neurodevelopmental and daily activity skill acquisition was observed up to 3 years after RGX-121 administration
  - Treatment response appeared to be dependent on the extent of neurologic deficits at baseline

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 not presented

RGX-121: CAMPSIITE Part 2, Phase III

NCT03566043 on ClinicalTrials.gov

Participants

Enrollment up to 30 neuronopathic MPS II participants
(≥ 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*

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

Data

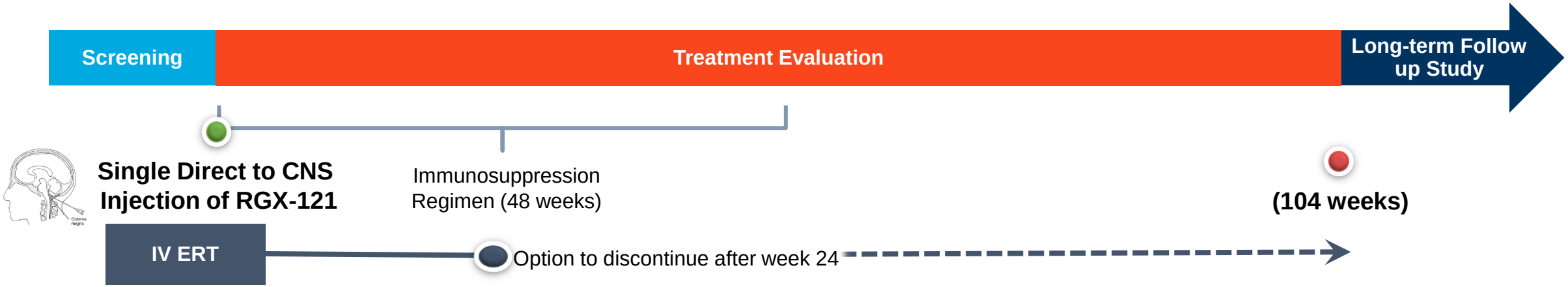
Primary Endpoint: CSF GAGs

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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