CAMPSIITE® Phase I/II/III: Interim clinical update of clemidsogene lanparvovec (RGX-121), an investigational gene therapy for treatment of neuronopathic mucopolysaccharidosis type II (MPS II)

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RGX-121 is an investigational product that has not been approved by the FDA. No conclusions regarding safety and efficacy can be made.

AAV Gene Therapy Has the Potential to Address the High Disease and Treatment Burden in MPS II

High Unmet Need in MPS II

- 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
  - Two-thirds of MPS II patients exhibit neuronopathic disease
  - Leads to somatic manifestations, neurodegeneration and early death
- Standard of care includes IV enzyme replacement therapy (ERT), which **does not address CNS disease involvement and has high burden of treatment**

Newborn screening for MPS II provides an opportunity to treat CNS manifestations prior to the onset of symptoms

RGX-121 May Provide Meaningful Advantages Over Standard of Care as a One-time Treatment

Potential of RGX-121 for MPS II

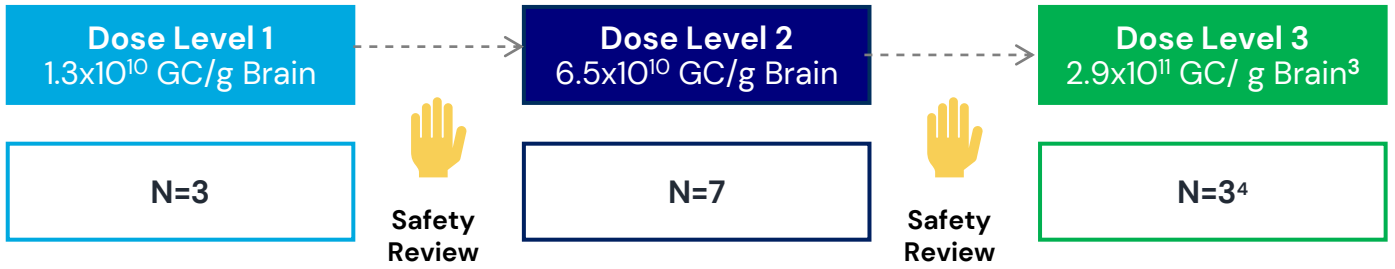
AAV9 Vector + *IDS* Transgene

- **One-time administration**
- Image-guided administration allows **direct delivery of *IDS* transgene to cells in the CNS**
- Potential for **long-term expression of functional I2S**
- **May prevent CNS disease progression**
- **D2S6* has been shown to distinguish between attenuated and neuronopathic MPS II**
- **The RGX-121 development program is using CSF D2S6 as a surrogate endpoint reasonably likely to predict clinical benefit**

*D2S6 is a trisulfated disaccharide component of heparan sulfate.

CAMPSIITE® Phase I/II/III Study of RGX-121 as a Potential One-Time Treatment for MPS II

CAMPSIITE Part 1[1], Dose-Finding (n = 13) Used to Inform Pivotal Design

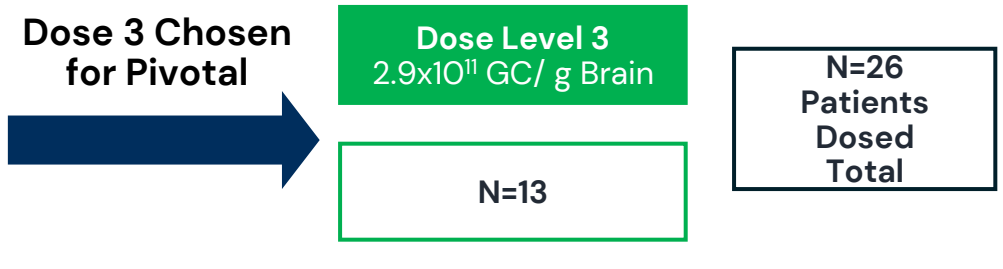


Primary Endpoint:
Safety through week 24

Secondary Endpoints[5]:

- Safety (through 2 years)
- Biomarkers (CSF, Plasma, Urine)
- Neurodevelopmental Function (BSID-III) and Effects on Daily Living Skills (VABS)
- Vector Shedding

CAMPSIITE Part 2[2] (n = 13) Pivotal for BLA



Primary Endpoint:
Proportion of patients with CSF HS D2S6 below maximum attenuated level at week 16

Secondary Endpoints[5]:

- Neurodevelopmental Function (BSID-III) and Effects on Daily Living Skills (VABS)
- MRI (Brain Volume)
- Safety up to 2 years
- Biomarkers (CSF, Plasma, Urine)

1. Part 1 includes patients dosed with hyperstack material.
2. Part 2 includes all patients dosed with bioreactor (BRX), commercial-ready material.
3. 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.
4. 2 patients initially dosed in part 1 with BRX material are assessed as part of pivotal.
5. Not all endpoints listed or presented

BSID-III, Bayley Scale of Infant and Toddler Development, 3rd Edition; VABS, Vineland Adaptive Behavioral Scales Version 2

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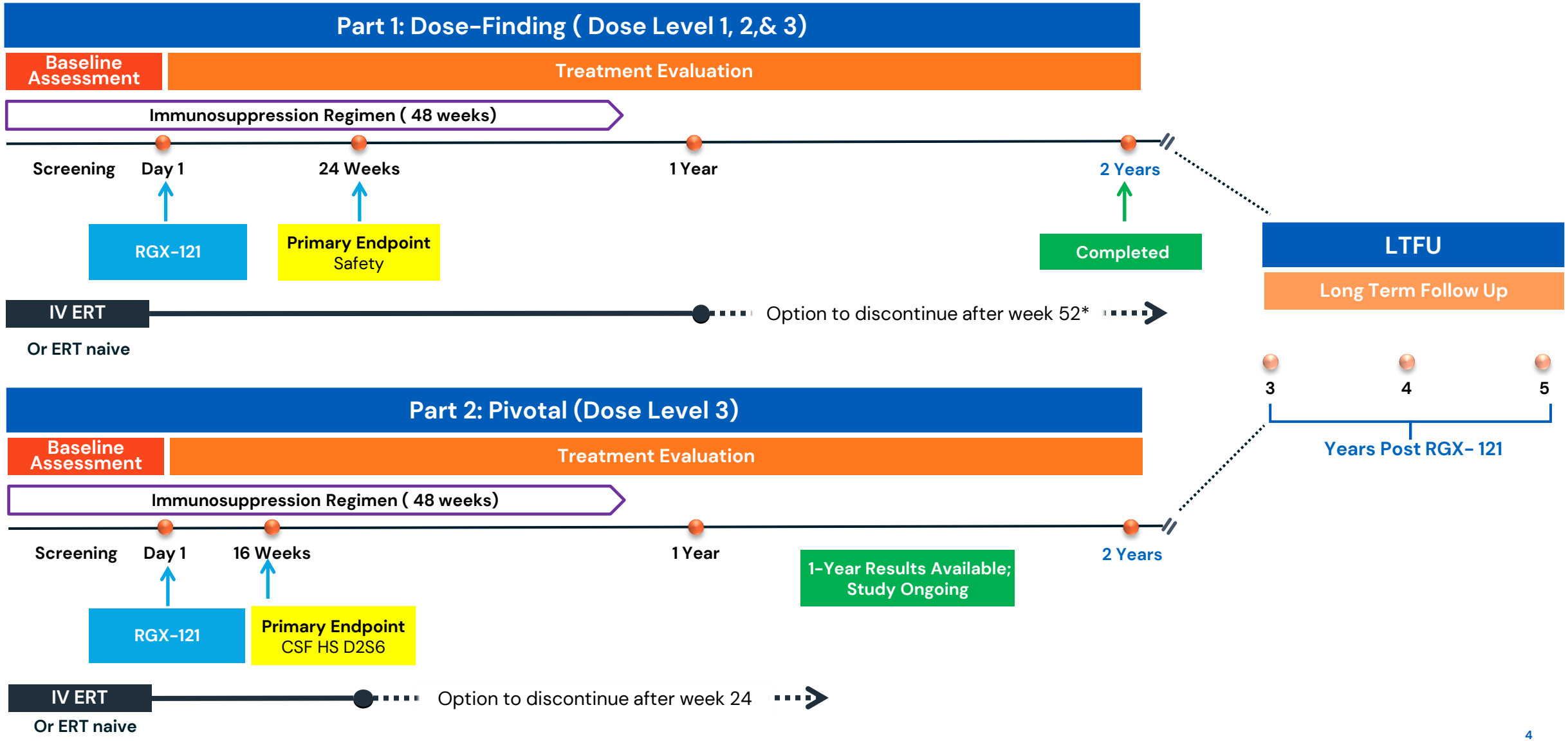
CAMPSIITE® Phase I/II/III Study Design

Severe (Neuronopathic MPS II Participants) ≥4 Months to < 5 Years of Age



* Option to discontinue was changed to 24 weeks in May 2022 via protocol update

CAMPSIITE Study – Demographics

- 26 neuronopathic MPS II participants dosed (13 dose-finding & 13 pivotal)
- Age at dosing ranged from 5 months to 59 months
- *IDS* mutations included deletion, frameshift, gene inversion, insertion, missense, splicing, and substitution

Trial Phase	Cohort	N	Dose (GC/g Brain)	IC / IVR[1] Route of Administration
Dose-Finding	Dose 1	3	1.3×10^{10}	n = 3 / 0
	Dose 2	7	6.5×10^{10}	n = 7 / 0
	Dose 3[2]	3	2.9×10^{11}	n = 2 / 1
Pivotal	**Dose 3**	**13**	**2.9×10^{11}**	**n = 8/5**

2 patients initially dosed in part 1 with Dose 3 BRX material are assessed as part of pivotal
1. Intracerebroventricular (IVR) administration is alternate route of administration if IC administration is not possible
2. 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$\times 10^{11}$ GC/g of brain mass using a transgene-specific PCR assay

Clemidsogene Lanparvovec (RGX-121) Was Well Tolerated

Treatment Emergent Adverse Events	Dose-Finding (n = 13)		Pivotal (n = 13)
	Week 24 (Primary Endpoint) n = participants (%)	2 years (End of Study) n = participants (%)	≥ 1 Year* n = participants (%)
All SAEs	3 (23%)	6 (46%)	5 (38%)
RGX-121 Related SAEs	0	0	1 (8%)[1]
RGX-121 Related AEs	4 (31%)	5 (38%)	6 (46%)
Administration Procedure Related AEs	2 (15%)	2 (15%)	1 (8%)
IS[2] Related AEs	4 (31%)	6 (46%)	6 (46%)
Most Common AEs[3]	Vomiting 6(46%) Gastroenteritis 4 (31%) Pyrexia 4 (31%)	Cough 8 (62%) Vomiting 8 (62%) Pyrexia 7 (54%)	Gastroenteritis 6 (46%) Vomiting 6 (46%) Diarrhea 5 (39%)

- No single AE was experienced by all participants, and no clear dose-response relationship (increased incidence of AEs with increasing dose) could be discerned
- One SAE leading to death[4] in pivotal was unrelated to RGX-121
- The majority of AEs were mild to moderate

Related adverse events define as those rated probable or possible as determined by sponsor
1. One SAE possibly related to clemidsogene lanparvovec, elevated liver enzymes, resolved with steroid treatment
2. IS (immune suppression): prednisone/prednisolone, tacrolimus, sirolimus
3. Most common TEASs defined as top 3 TEAEs
4. Died of an abdominal infection >1.5 years after dosing. Participant was not on immunosuppression at the time and there was a known infectious outbreak in the area. Death was not consider related by the PI or Sponsor.

* Data cut date August 20, 2024

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

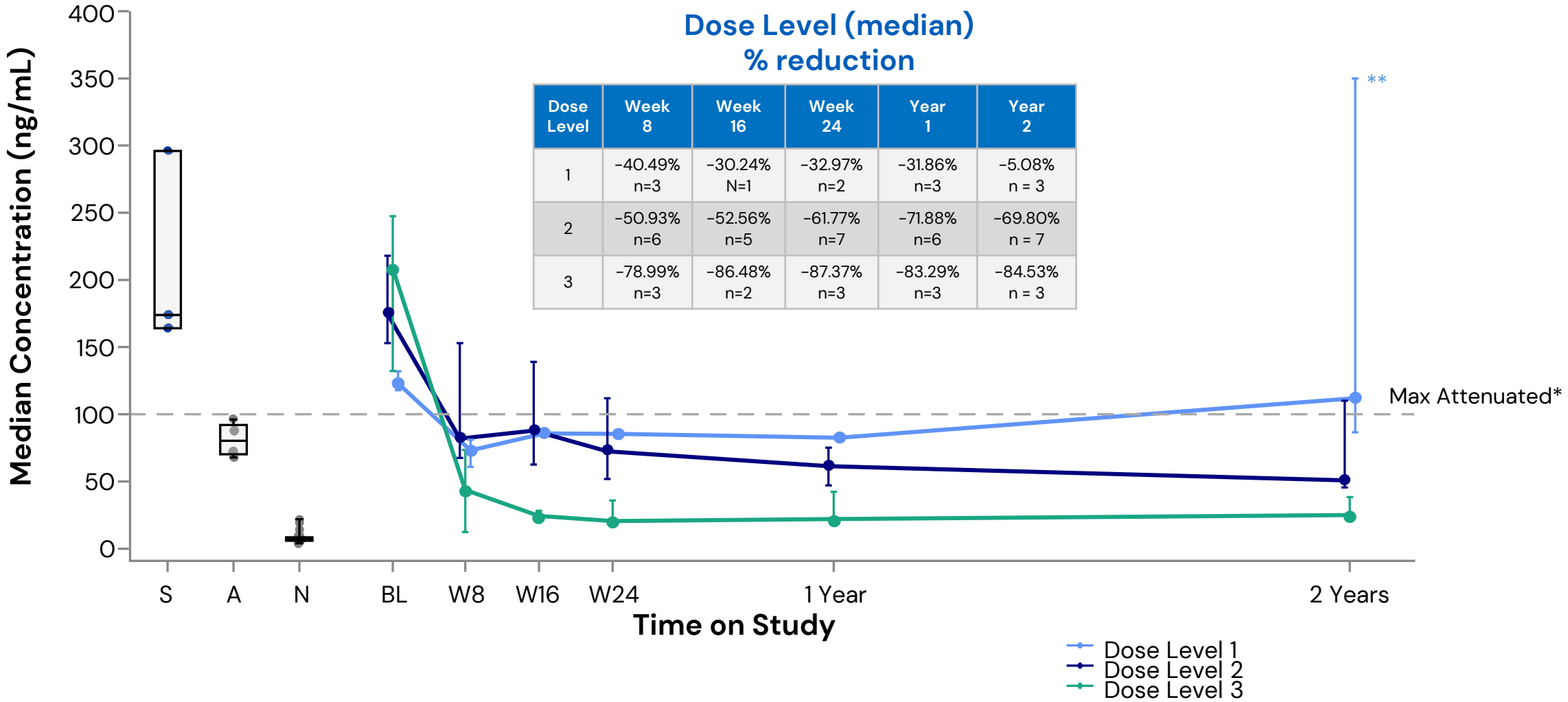
CSF HS D2S6
Biomarker Endpoint

Dose-Finding: Sustained Dose-Dependent Decreases in CSF HS D2S6 at 2 Years

CSF HS D2S6 is a Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit in Neuronopathic MPS II

Dose Level (median) % reduction

Dose Level	Week 8	Week 16	Week 24	Year 1	Year 2
1	-40.49% n=3	-30.24% N=1	-32.97% n=2	-31.86% n=3	-5.08% n = 3
2	-50.93% n=6	-52.56% n=5	-61.77% n=7	-71.88% n=6	-69.80% n = 7
3	-78.99% n=3	-86.48% n=2	-87.37% n=3	-83.29% n=3	-84.53% n = 3



S=Severe; A=Attenuated; CSF=Cerebrospinal Fluid; BL=Baseline, defined, for each participant, as the average of the pre-dose values; W=Week.
Attenuated and severe data are based on samples from Brazil which were analyzed by Frontage assay. The ages of the 3 severe samples range from 4 years 8 months to 10 years old. The ages of 4 attenuated samples range from 11 years to 29 years old.
* MPS II attenuated reference point (~ 100 ng/mL) based on analysis presented in Boulos N, World Symposium, 2022
** CNS related clinical event (ventriculoperitoneal shunt infection with subsequent revision) deemed unrelated to study drug took place at 1.5 years post RGX-121 administration

Pivotal: Primary Endpoint Achieved with Sustained Reduction in CSF D2S6 through 1 Year

CSF HS D2S6 is a Surrogate Endpoint Reasonably Likely to Predict Clinical Benefit in Neuronopathic MPS II

	Week 16	Week 24	1 Year
Proportion of Participants with CSF HS D2S6 at or below maximum attenuated level	**9/13 Primary Endpoint ($p < 0.0001$)***	**10/13**	**8/11****
% Median Reduction of CSF HS D2S6	**-81 %**	**-82 %**	**-82 %**

MPS II attenuated reference point ≤ 100 ng/mL based on analysis presented in Boulos N, World Symposium, 2022
* Primary endpoint was compared to the margin of 20%
** Samples could not be obtained from 2 participants at 1 year

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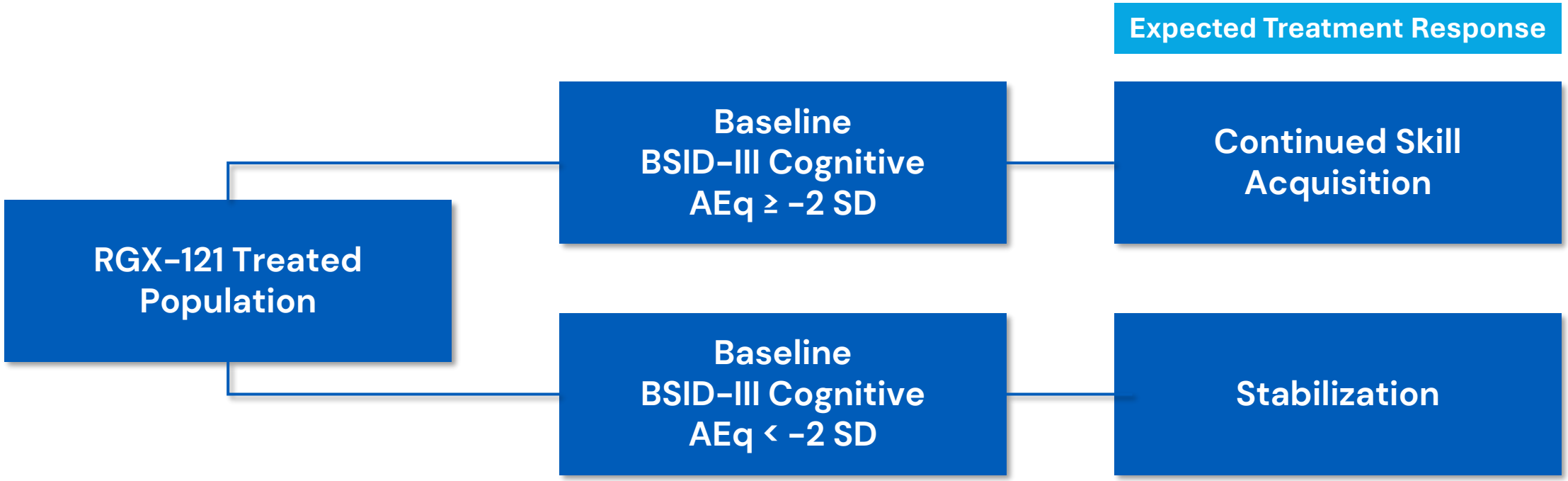
RGX-121 Gene Therapy for the Treatment of Severe Mucopolysaccharidosis Type II (MPS II):

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

BSID-III Used to Determine Baseline Status and Measure Neurodevelopmental Change After Dosing

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

- Natural history suggest different phases of disease reflected in neurodevelopmental trajectory
- Participants were stratified by baseline cognitive function as a clinical biomarker for disease stage
- Expectations of treatment-response differ depending upon stage of disease at the time of dosing

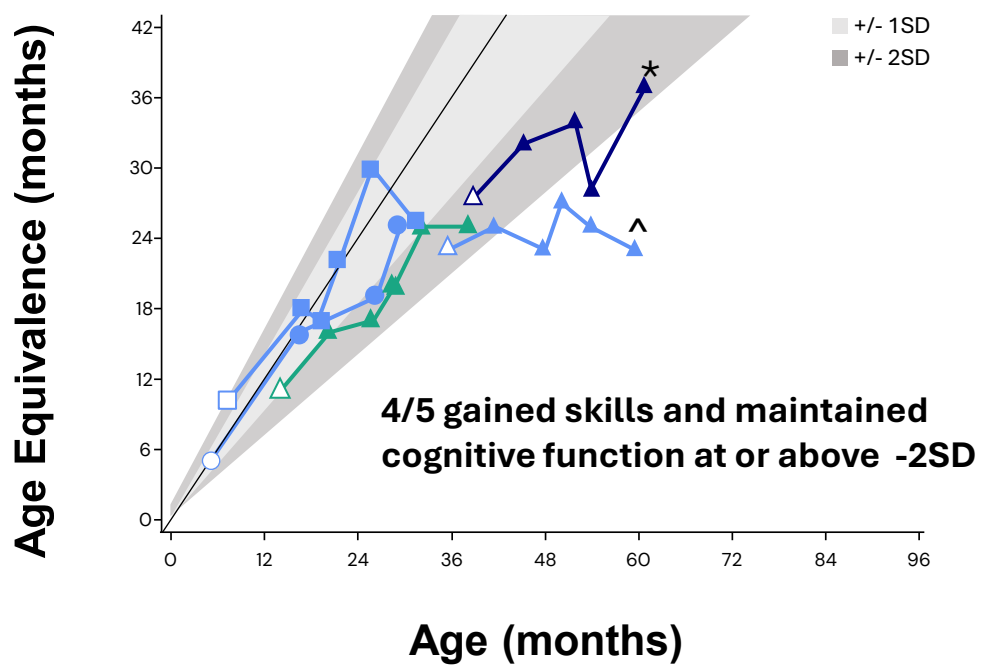


Shapiro (2017) *Molecular Genetics and Metabolism*

Dose-Finding: Continued Neurodevelopmental Skill Acquisition or Stability in the Majority of Participants at 2 Years

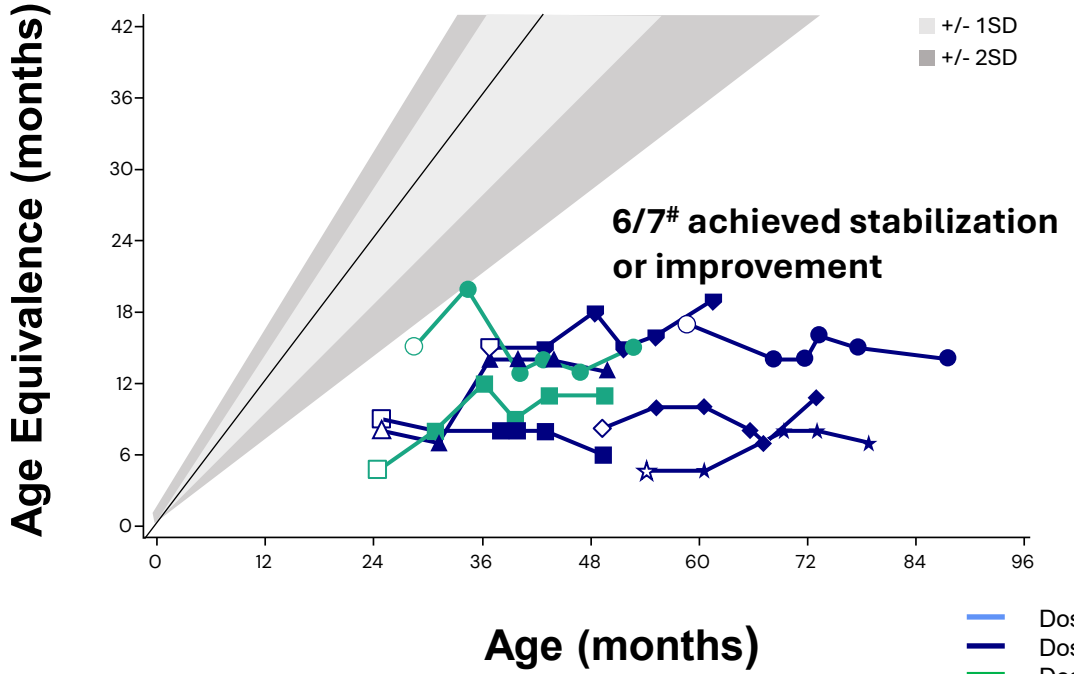
Majority of Participants Continued to Gain Skills

Baseline BSID-III Cognitive Function ≥ -2SD



Majority of Participants Stabilized

Baseline BSID-III Cognitive Function < -2SD



Cognitive function measured via the Bayley Scale of Infant and Toddler Development, 3rd Edition (BSID-III) Cognitive Subtest
*Patient reached maximum ceiling effect based on BSID-III manual and reached ceiling effect at subsequent visit.
^ CNS related clinical event (ventriculoperitoneal shunt infection with subsequent revision) deemed unrelated to study drug took place at 1.5 years post RGX-121 administration
#One patient missed their 2-year visit and is not included

Pivotal: Neurodevelopmental Skill Acquisition or Stability on all BSID-III Subscales in Participants at 1 year

	Above/Equal to -2SD AEq (SE) N = 5			Below -2SD AEq (SE) N = 8		
BSID-III Subscale	Baseline	Year 1	**Change from Baseline**	Baseline	Year 1	**Change from Baseline**
Cognitive	15.7 (6.0)	24.2 (4.4)	**+ 8.5** (3.3)	13.9 (3.1)	16.6 (2.9)	**+ 2.7** (1.5)
Fine motor	16.1 (6.6)	22.6 (4.3)	**+ 6.5** (3.5)	14.2 (2.4)	16.5 (2.9)	**+ 2.3** (2.5)
Gross Motor	13.6 (5.3)	18.8 (2.8)	**+ 5.2** (2.8)	12.3 (1.9)	15.5 (1.2)	**+ 3.2** (1.5)
Receptive Language	14.7 (5.4)	19.8 (3.7)	**+ 5.1** (1.9)	9.7 (3.3)	11.2 (2.7)	**+ 1.5** (1.9)
Expressive Language	14.3 (5.2)	19.0 (3.6)	**+ 4.7** (2.1)	12.3 (3.6)	12.5 (2.6)	**+ 0.2** (1.6)

BSID-III, Bayley Scale of Infant and Toddler Development, 3rd Edition

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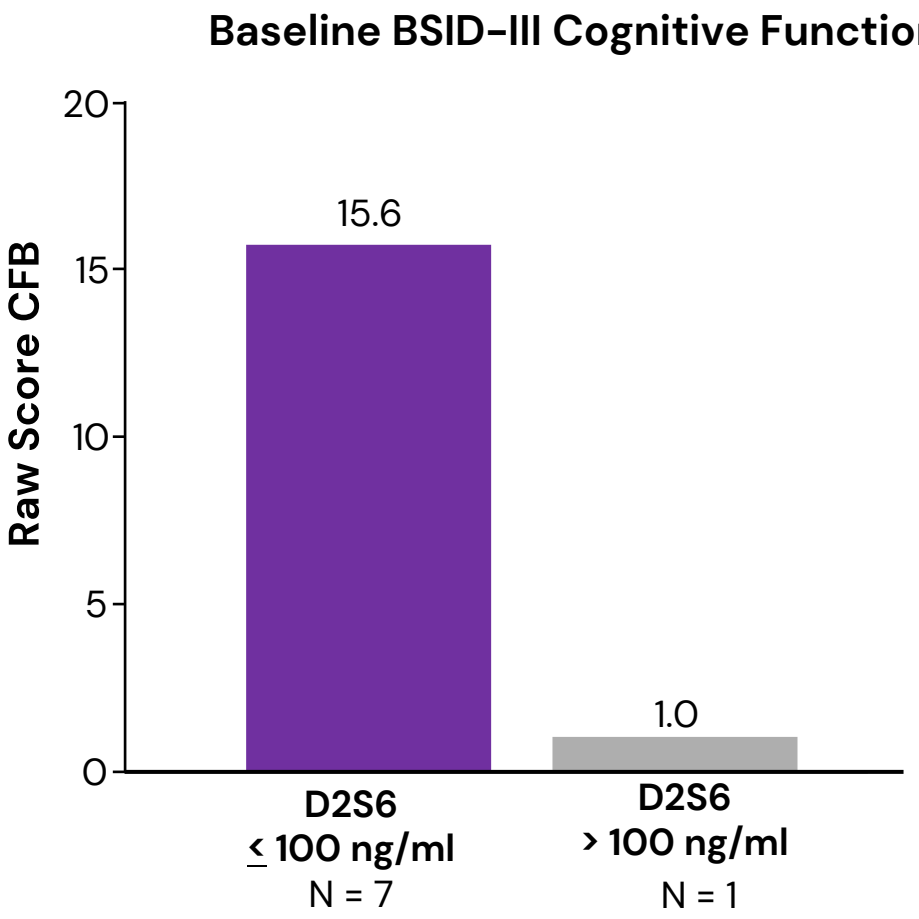
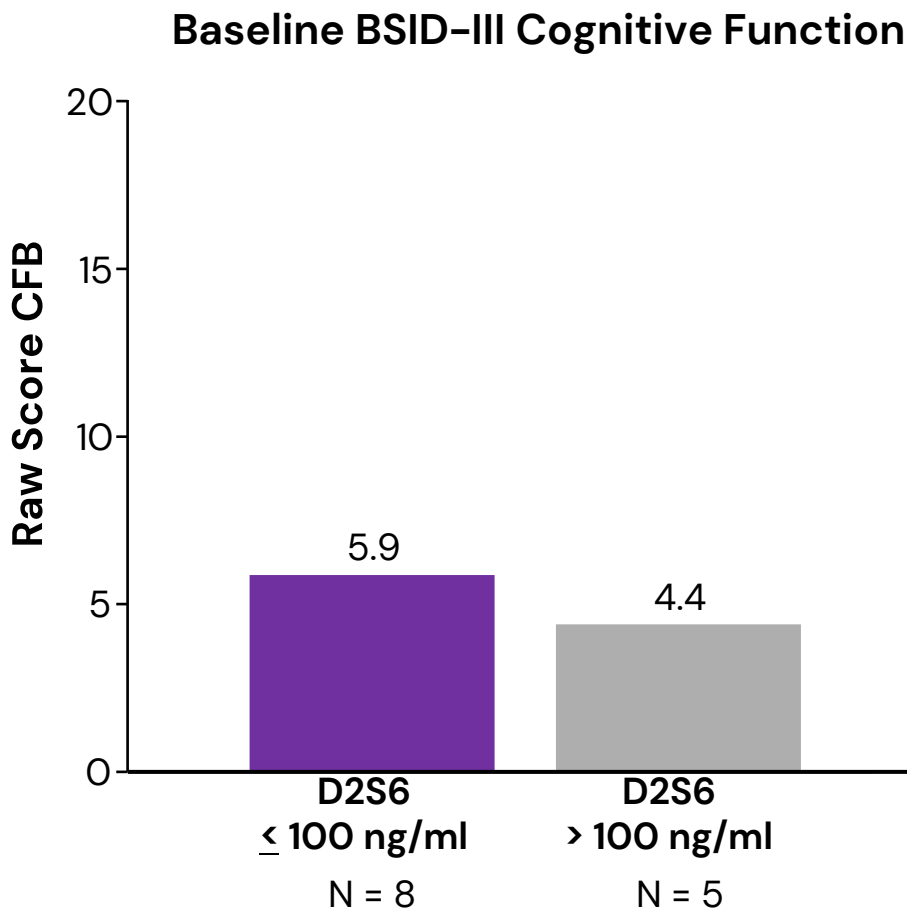
CSF HS D2S6 at Week 16 and Neurocognitive Outcomes in Participants Show Correlation at 1 Year





CFB, Change from Baseline
Analysis includes participants from dose-finding (all doses) and pivotal
2 Dose Level 1 participants did not have a week 16 value
Max. attenuated D2S6 level: ≤ 100ng/ml

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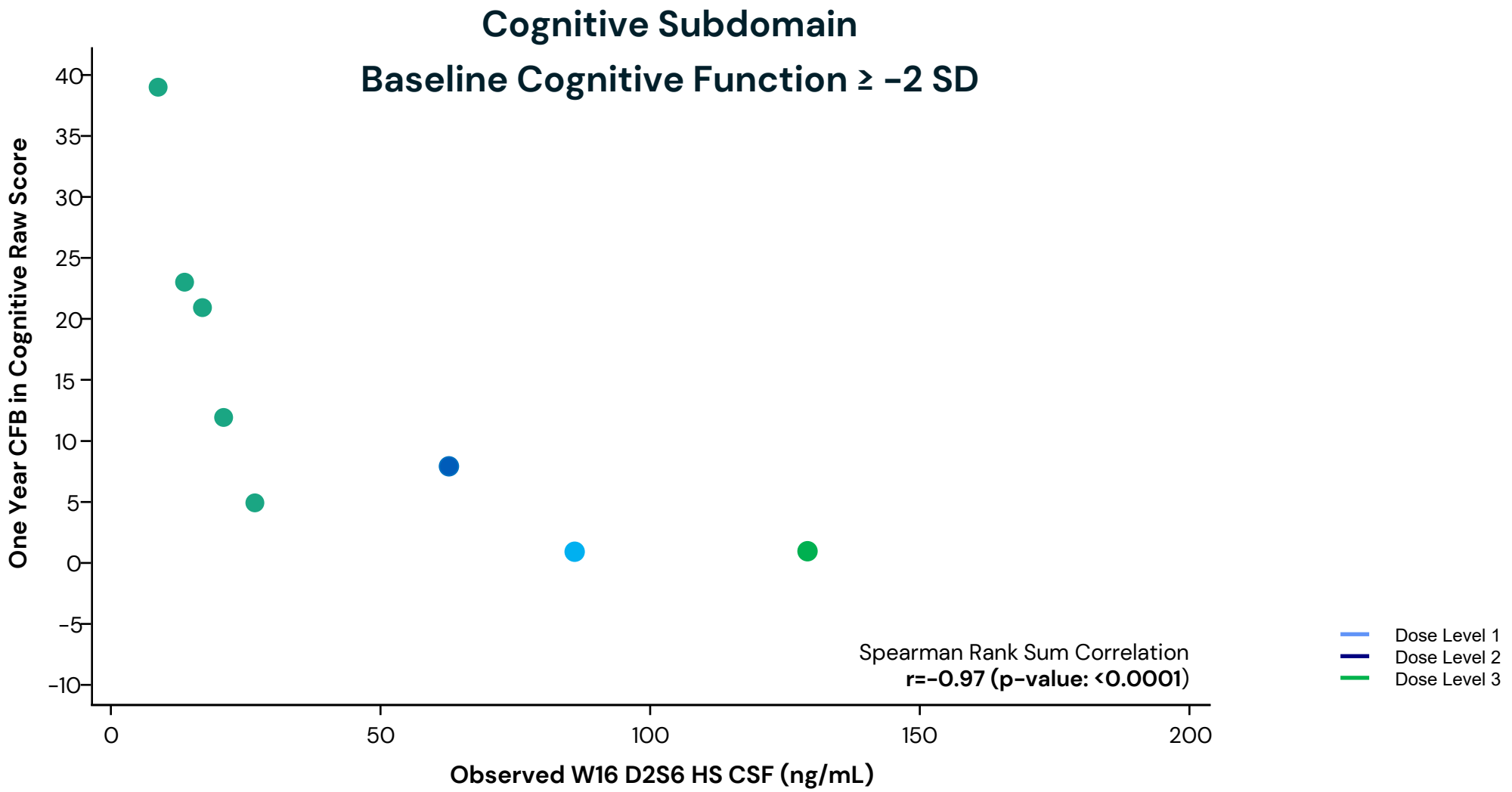
Significant Correlation Between 1 Year Developmental Outcomes and Measured CSF HS D2S6 Level at Week 16



CFB, Change from Baseline
Participants from dose-finding and pivotal with baseline BSID cognitive subscale score ≥ -2SD at baseline
n = 8; 2 Dose Level 1 participants did not have a week 16 value

Data cut date August 20, 2024

Summary of CAMPSIITE Study

- Clemidsogene lanparvovec (RGX-121) was well tolerated in 26 patients
- Pivotal primary endpoint (CSF HS D2S6 at 16 weeks) was met with sustained reductions through 1 year
- Continued neurodevelopmental skill acquisition or stabilization demonstrated post RGX-121 administration*
- Correlation between CSF HS D2S6 at week 16 and neurocognitive outcomes at 1 year
- Interim results support early measurable reductions in D2S6 are reasonably likely to predict long-term neurodevelopment in children with neuronopathic MPS II

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* Dose-finding participants at 2 years, pivotal participants at 1 year

Data cut date August 20, 2024

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