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 CNS Need 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
  - Causes systemic symptoms, neurodegeneration and leads to early death
  - Two-thirds of MPS II patients exhibit neuronopathic phenotype
- Standard of care includes IV enzyme replacement therapy (ERT), which **does not address CNS disease involvement**

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

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.

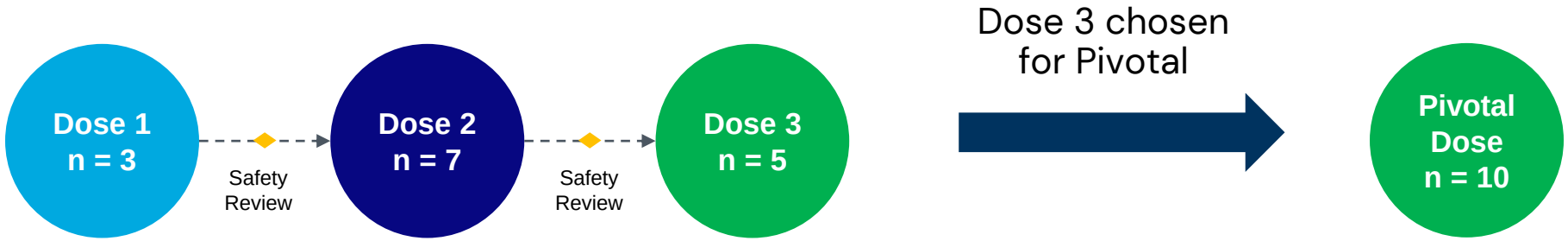
CAMPSIITE™ Phase I/II/III Study of RGX-121 as a Potential Treatment for MPS II

CAMPSIITE Part 1, Dose-Finding, Used to Inform Pivotal Design

- **Safety**
- **CSF GAGs: D2S6, a surrogate biomarker reasonably likely to predict clinical benefit**
- **Neurodevelopment: Bayley**
- **ERT Free Status**

CAMPSIITE Part 2, Pivotal

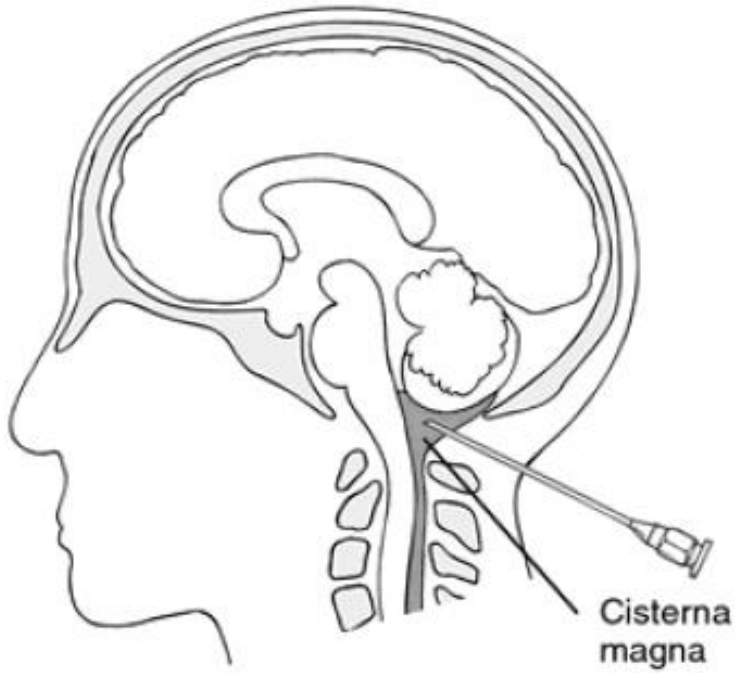
- **CSF GAGs: D2S6**
- **Safety**



Numerous Clinical Trials Worldwide Utilize Image Guided Intracisternal (IC) Direct to CNS Administration

IC administration results in widespread distribution in the brain

Neurodegenerative Disease	Sponsor	Clinicaltrial.gov Identifier
MPS II	REGENXBIO	NCT03566043
MPS I	REGENXBIO	NCT03580083
Parkinson's Disease (PD-GBA)	Prevail / Eli Lilly	NCT04127578
Infantile GM1 gangliosidosis	Lysogene	NCT04273269
Frontotemporal dementia (FTD-GRN)	Prevail / Eli Lilly	NCT04408625
Infantile/Juvenile GM2 (Tay-Sachs)	University of Massachusetts	NCT04669535
Frontotemporal dementia (FTD-GRN	Passage Bio	NCT04747431
Early Infantile Krabbe	Passage Bio	NCT04771416



Clinicaltrials.gov accessed January 23, 2024

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

Dose Escalation Data
CAMPSIITE Part 1, Dose-Finding

CAMPSIITE Part 1, Dose-Finding Study Design

Participants

Enrolled 15 severe (neuronopathic) MPS II participants
(≥ 4 months to < 5 years of age)

May be on Standard of Care IV ERT or ERT Naïve

Dose Levels

Genome copies/g brain

RGX-121
AAV9 + *IDS*

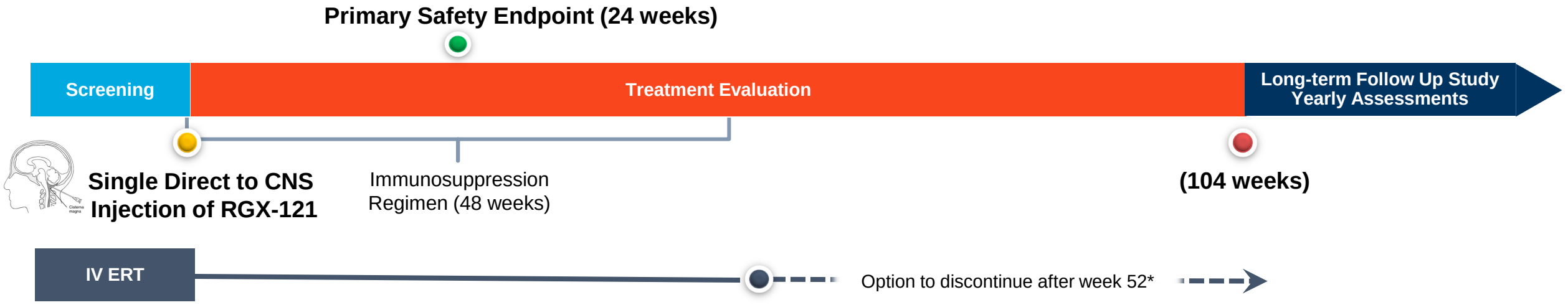
Dose 1: 1.3 x 10^{10}
Dose 2: 6.5 x 10^{10}
Dose 3: 2.9 x 10^{11}

Data

Primary Endpoint: Safety

Secondary & Exploratory Endpoints Include:

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



NCT03566043 on ClinicalTrials.gov

Bayley (Bayley Scales of Infant and Toddler Development, 3rd Edition); VABS (Vineland Adaptive Behavior Scales, 2nd Edition); SDSC (Sleep Disturbance Scale for Children)

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

CAMPSIITE Part 1, Dose-Finding Cohorts

- 15 neuronopathic MPS II participants dosed as of June 20, 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
- Immunosuppression discontinued in all eligible participants (n = 14) per protocol

Cohort	N	Dose (GC/g Brain)	Follow-Up Initial Study = 2 yrs LTFU = 3 yrs	IC / ICV[1] Route of Administration
Dose 1	3	1.3×10^{10}	3.0-4.0 yrs	n = 3 / 0
Dose 2	7	6.5×10^{10}	1.5-3.2 yrs	n = 7 / 0
Dose 3 / Pivotal[2]	5	2.9×10^{11}	0.5-2.0 yrs	n = 4 / 1

1. Intracerebroventricular (ICV) administration is alternate route of administration if IC administration is not possible
2 Cohort 3 / pivotal dose participants received RGX-121 produced by a proprietary bioreactor platform process

CAMPSIITE Part 1, Dose-Finding Interim Safety Summary

SAE	▪ 14 serious adverse events (SAE; 8 in main study, 6 in LTFU) reported in 8 participants: **None are considered related to RGX-121 or administration procedure** ▪ 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, Femoral neck fracture, tonic/clonic seizures ▪ 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

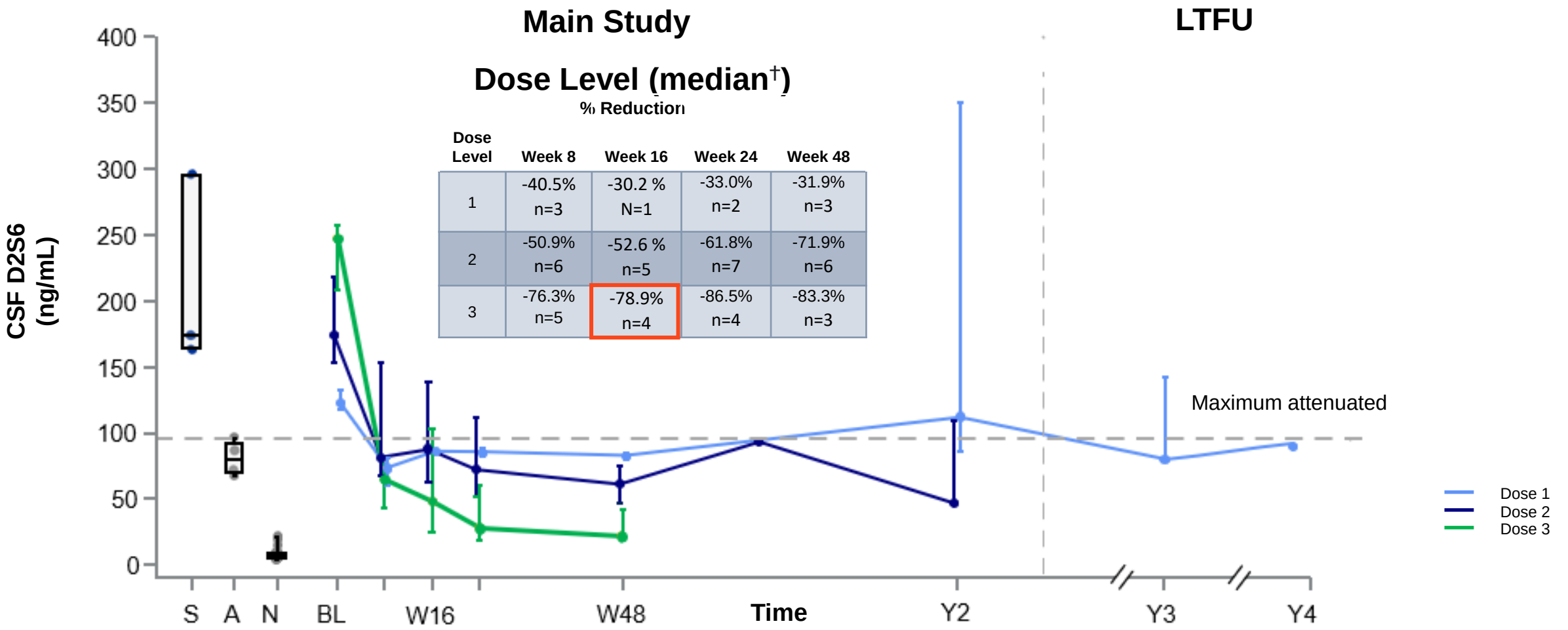
RGX-121 has been well tolerated at all dose levels

LTFU: Long Term Follow-up
* Possibly related to immunosuppression

Data cut June 20, 2023

Dose-Dependent Decreases in CSF D2S6 up to 4 years

D2S6 is a surrogate endpoint reasonably likely to predict clinical benefit in neuronopathic MPS II



Dose 3 (Pivotal Dose) levels approach normal levels

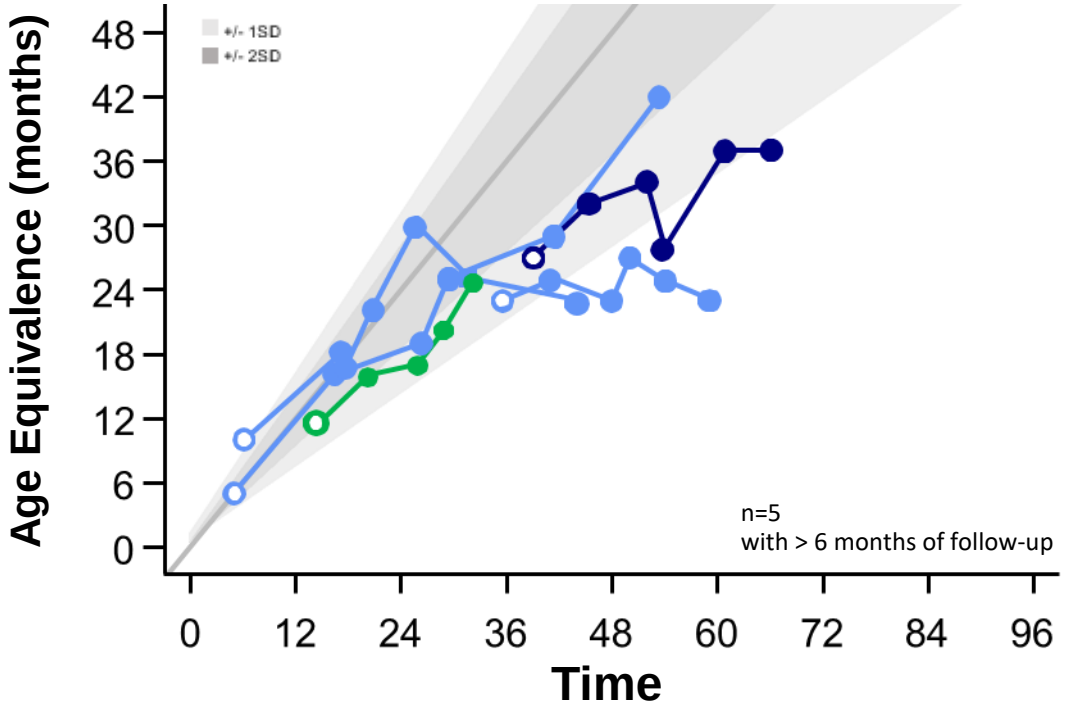
Median CSF D2S6 concentration +/- Q1 and Q3 per cohort.
Normative data are based on 29 samples (N) . Attenuated (A) defined as IQ ≥ 70. The ages of 4 attenuated samples range from 11 years to 29 years old
Severe (S) defined as IQ < 70. The ages of 3 severe samples range from 4 years 8 months to 10 years old.

Data cut June 20, 2023

Neurodevelopmental Assessments Demonstrate Continued Skill Acquisition or Stability in the Majority of CAMPSIITE Dose-Finding Participants

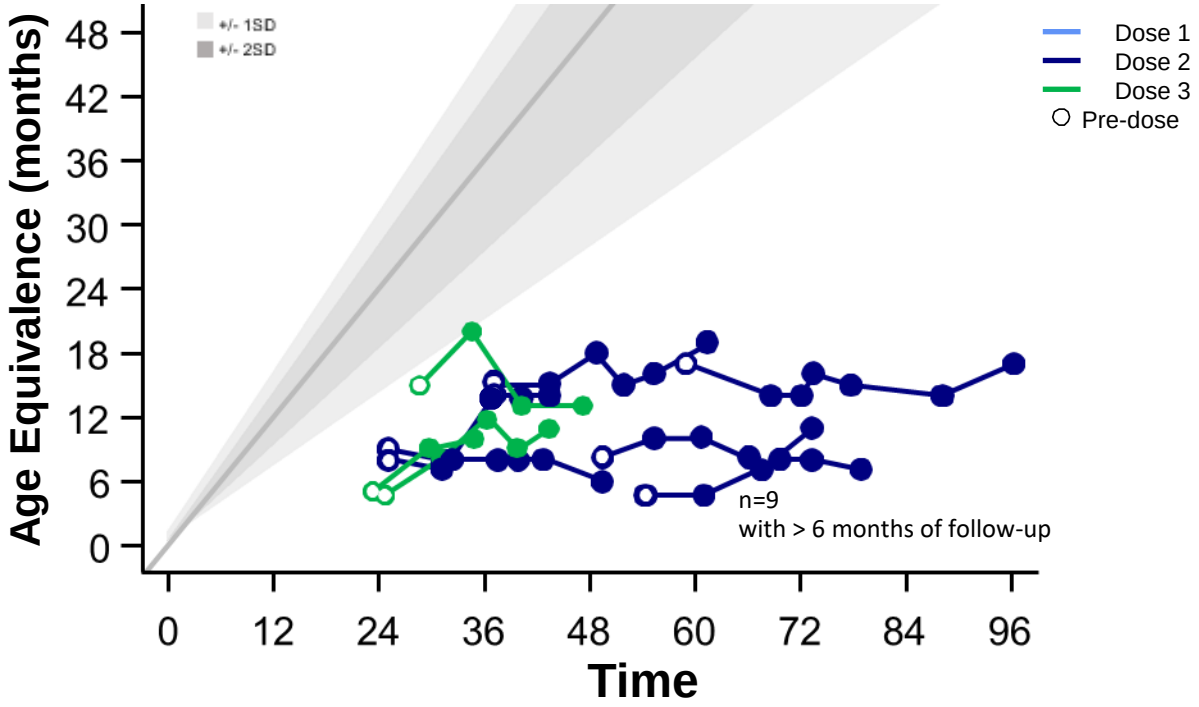
Majority of Participants Continued to Gain Skills

Baseline BSID-III Cognitive Function > -2SD



Majority of Participants Gained at Least 3 Months of Skills in AEq or Stabilized

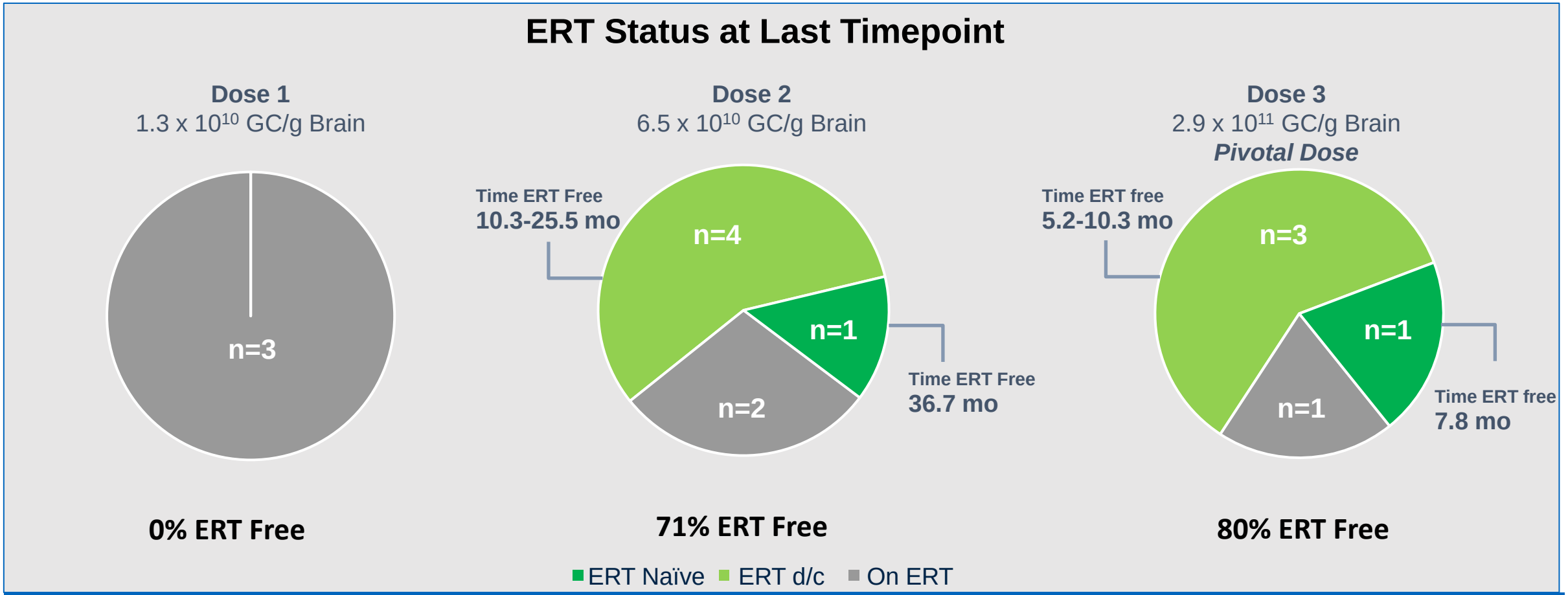
Baseline BSID-III Cognitive Function < -2SD



Treatment response appeared to be dependent on the extent of neurologic deficits at baseline

Cognitive function measured via the Bayley Scale of Infant and Toddler Development, 3rd Edition (BSID-III) Cognitive Subtest

Investigators are Choosing to Discontinue ERT or Allow Participants to Remain ERT Naive



ERT free status supports systemic activity of RGX-121

ERT Free = discontinued from ERT or remained ERT Naïve
Decision to discontinue ERT was at the clinical judgement of the PI and agreed to with the sponsor
Option to discontinue ERT was changed from 52 to 24 weeks in May 2022 via protocol update

RGX-121 CAMPSIITE Part 1, Dose-Finding

Summary of Interim Results

RGX-121 was well tolerated in 15 participants across 3 dose levels

CSF D2S6 levels were reduced to attenuated levels, approached normal levels at pivotal dose

Developmental skill acquisition was observed up to 4 years after RGX-121 administration

Investigators are choosing to discontinue ERT or allow participants to remain ERT naïve, supporting systemic activity of RGX-121

Data cut June 20, 2023 for Part 1 Participants

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

Topline Pivotal Data
CAMPSIITE Part 2, Pivotal

RGX-121 CAMPSIITE Part 2, Pivotal

Participants

10 Neuronopathic MPS II participants dosed
(Age range 4 months to 56 months)

May be on Standard of Care IV ERT or ERT Naïve

Pivotal Dose

RGX-121
AAV9 + *IDS*

2.9×10^{11}
Genome copies/g brain

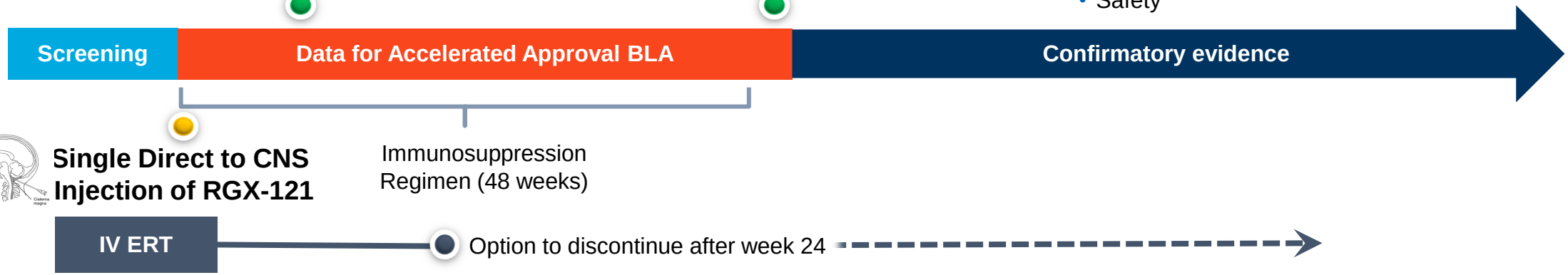
Data

Primary Endpoint:
Proportion of patients with CSF D2S6 below maximum attenuated level at W16

Secondary Endpoints:
- Neurodevelopmental Assessments (Bayley, Mullen)
- Caregiver Reported Outcomes (VABS)
- Systemic Biomarkers (I2S, GAGs)
- MRI
- Safety

CSF D2S6
16 weeks

Safety
1 year



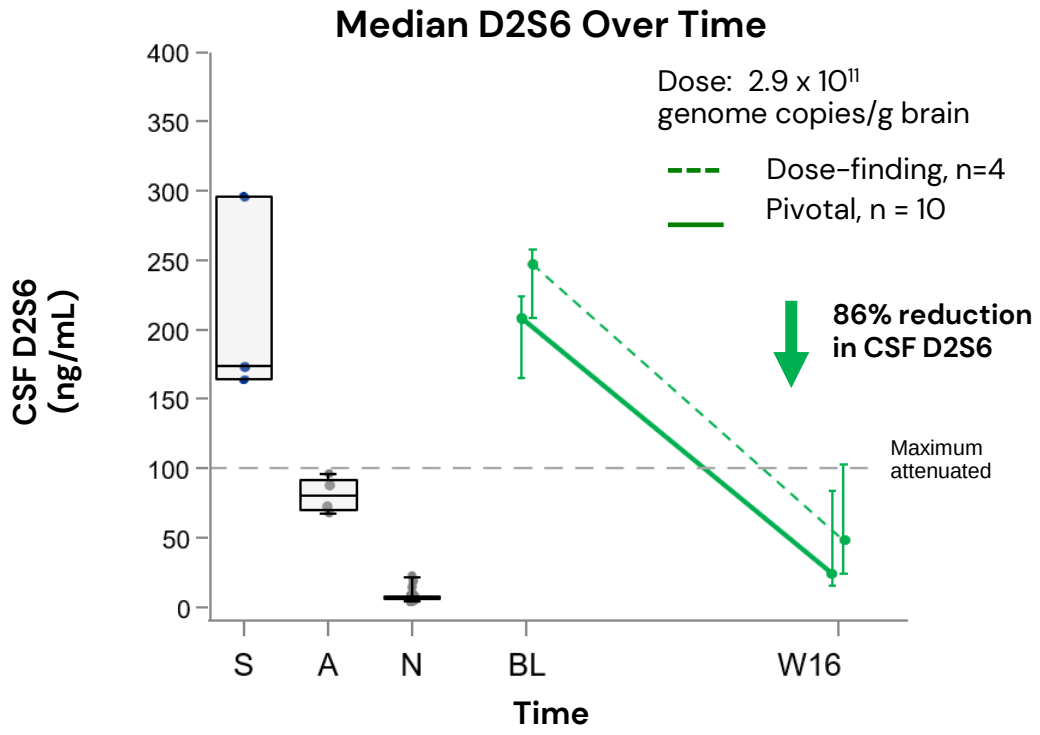
- **RGX-121 has been well tolerated as of January 3, 2024**
- **One SAE possibly related to RGX-121, elevated liver enzymes, resolved with steroid treatment**

NCT03566043 on ClinicalTrials.gov
If MPS II phenotype was unknown, serial neurodevelopmental assessments were performed for up to 12 Months prior to screening for intervention
Dose is the same as Cohort 3 in CAMPSIITE Part 1 Dose-Finding
VABS: Vineland Adaptive Behavior Scales

Pivotal primary endpoint achieved with robust reduction in CSF D2S6

Primary Endpoint:
Proportion of Patients with CSF D2S6 below maximum attenuated level at W16

- Primary endpoint reached with statistical significance (p = 0.00016)*
  - 8 of 10 pivotal patients demonstrated reductions in CSF D2S6 to below maximum attenuated levels
  - Other 2 pivotal patients also exhibited robust reductions in CSF D2S6 (55%, 85%)



Meaningful reductions in CSF D2S6

10 participants dosed as of July 31, 2023
* Response rate was compared to the margin of 20% (two-sided p value of 0.00016)
Median CSF D2S6 concentration +/- Q1 and Q3 per cohort.
Normative data are based on 29 normal samples (N). Attenuated (A) defined as IQ > 70. The ages of 4 attenuated samples range from 11 years to 29 years old. Severe (S) defined as IQ < 70. The ages of 3 severe samples range from 4 years 8 months to 10 years old.
Data cut January 3, 2024

Summary of CAMPSIITE Pivotal Topline Results

RGX-121 was well tolerated in 10 patients

Pivotal phase met primary endpoint

CSF D2S6 surrogate endpoint reasonably likely to predict clinical benefit

Results support plans to file BLA in 2024 utilizing the Accelerated Approval pathway

10 participants dosed as of July 31, 2023
Data cut as of January 3, 2024

Acknowledgements

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* RGX-121 is an investigational therapy and has not been approved by any regulatory authority.