# CAMPSIITE® Phase I/II/III: Interim Clinical Update of RGX-121, an Investigational Gene Therapy for Treatment of Neuronopathic Mucopolysaccharidosis Type II (MPS II)


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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

*D2S6 is a trisulfated disaccharide component of heparan sulfate.

**RGX-121 May Provide Meaningful Advantages Over Standard of Care**

### Potential of RGX-121 for MPS II

**AAV9 Vector + *IDS* Transgene**

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

## 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**

**Dose 1** n = 3 → Safety Review → **Dose 2** n = 7 → Safety Review → **Dose 3** n = 5

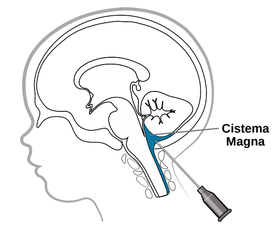
**Dose 3 Chosen for Pivotal** → **Pivotal Dose** n = 10

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

| 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

### IC Administration Results in Widespread Distribution in the Brain




## 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)

**Primary Safety Endpoint (24 weeks)**

Screening | Treatment Evaluation | Long-term Follow Up Study Yearly Assessments

**Single Direct to CNS Injection of RGX-121**

Immunosuppression Regimen (48 weeks)

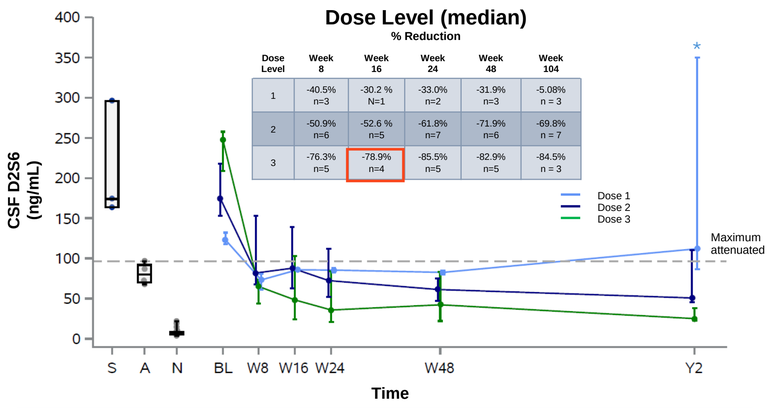
**(104 weeks)**

IV ERT → Option to discontinue after week 52*

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

### Dose-Dependent Decreases in CSF D2S6

**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.
* 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

Data cut January 5, 2024

### 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 x $10^{10}$ | 3.0-4.0 yrs | n = 3 / 0 |
| Dose 2 | 7 | 6.5 x $10^{10}$ | 1.5-3.2 yrs | n = 7 / 0 |
| Dose 3 / Pivotal[2] | 5 | 2.9 x $10^{11}$ | 0.5-2.0 yrs | n = 4 / 1 |

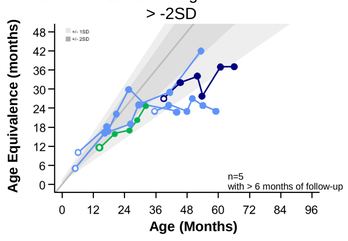
1. Intracerebroventricular (ICV) administration is alternate route of administration if IC administration is not possible
2 Cohort 3 / pivotal dose participants received RGX-121 produced by a proprietary bioreactor platform process

Data cut January 5, 2024

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

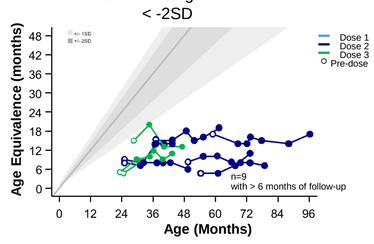
**Majority of Participants Continued to Gain Skills**

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

Data cut June 20, 2023

### CAMPSIITE Part 1, Dose-Finding Interim Safety Summary

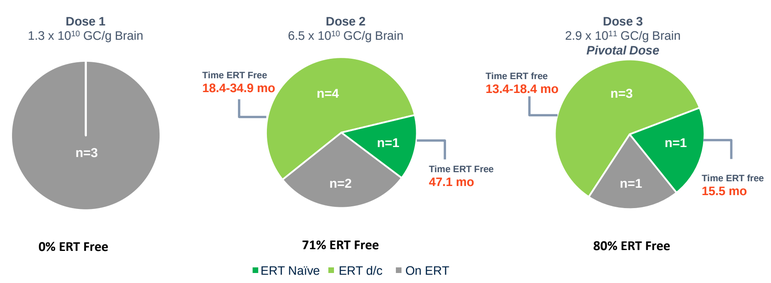
- 17 SAEs; no SAEs related to RGX-121 or administration procedure, and no SAEs occurring within one week of dosing
- No TEAEs leading to study discontinuation
- No TEAEs of central and peripheral neurotoxicity
- The most common TEAEs were vomiting in 11 (73.3%) participants, followed by pyrexia, cough, and gastroenteritis in 9 (60.0)% participants. The majority of TEAEs were mild-moderate in severity.
- No single AE was experienced by all participants, and no clear dose-response relationship (increased incidence of AEs with increasing dose) could be discerned

**RGX-121 has been well tolerated at all dose levels**

Data cut January 5, 2024

### Investigators are Choosing to Discontinue ERT or Allow Participants to Remain ERT Naïve on Dose Levels 2 and 3

**ERT Status at Last Timepoint**




**ERT free status supports systemic activity of RGX-121**

Data cut: January 5, 2024

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, and approached normal levels at pivotal dose for up to 2 years[1]**

**Developmental skill acquisition was observed up to 4 years after RGX-121 administration[2]**

**Investigators are choosing to discontinue ERT or allow participants to remain ERT naïve, supporting systemic activity of RGX-121 at dose levels 2 and 3[1]**

1. Data cut January 5, 2024
2. Data cut June 20, 2023

## Topline Pivotal Data CAMPSIITE Part 2, Pivotal

### CAMPSIITE Part 2, Pivotal Study Design

**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 x $10^{11}$**
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**

Screening | Data for Accelerated Approval BLA | Confirmatory Evidence

**Single Direct to CNS Injection of RGX-121**

Immunosuppression Regimen (48 weeks)

IV ERT → Option to discontinue after week 24

- **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**

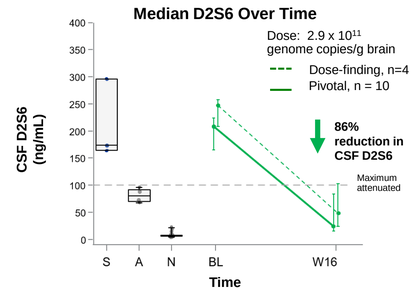
NCT03566043 on ClinicalTrials.gov
If MPS II phenotype was unknown, serial neurodevelopmental assessments were performed for up to 12 Months prior to screening for intervention
Dose is the same as Cohort 3 in CAMPSIITE Part 1 Dose-Finding
VABS: Vineland Adaptive Behavior Scales

### 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%)

**Median D2S6 Over Time**




**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

### RGX-121 CAMPSIITE Study Interim Summary

**RGX-121 was well tolerated across 25 patients in all phases of CAMPSIITE [1,2]**

**RGX-121 pivotal dose reduced CSF D2S6 to attenuated levels for up to 2 years for dose-finding participants [1]**

**Primary CSF D2S6 endpoint was met in pivotal [2]**

**RGX-121 may treat both neuronopathic and systemic aspects MPS II**

**REGENXBIO expects to initiate submission of a rolling BLA in the third quarter of 2024 to pursue Accelerated Approval for RGX-121 using CSF D2S6 as a surrogate endpoint reasonably likely to predict clinical benefit**

1. Dose-finding data cut January 5, 2024
2. Pivotal 10 patients dosed as of July 31, 2023; data cut January 3, 2024


### Acknowledgements

**The MPS II Patients and their Families**

**The Study Coordinators**
(Diana Juica Aguinaga, Dawn Kolar, Ryan Kuehl, Matt Thura, and Marina Zambrano)
**Research Assistants, and Study Teams at the Clinical Study Sites**


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