First-in-human Intracisternal Dosing of RGX-111
(Adeno-associated Virus 9 / Human Alpha-l-Iduronidase) for a 20-Month-old Child with Mucopolysaccharidosis Type I (MPSI): 1 Year Follow-up

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Introduction

MPS I is a lysosomal storage disorder caused by mutations in the IDUA gene and resultant deficiency of lysosomal α-L-iduronidase (IDUA) enzyme(1).

Patients with severe MPS I have mutations encoding completely inactive IDUA enzyme and have early-onset developmental delay and cognitive regression in addition to multisystemic manifestations(2).

Treatment for severe MPS I involves intravenous recombinant human IDUA (rhIDUA) enzyme infusions followed by stem cell transplant (SCT). However, SCT carries risks of engraftment syndrome, graft failure, graft-versus-host disease, death, and occasionally incomplete correction of neurodevelopmental manifestations(3).

RGX-111, an investigational gene therapy, was administered intracisternally to a 20-month-old child with severe MPS I (Hurler) under a single-patient investigator-initiated IND.

RGX-111

RGX-111 (AAV9.CB7.hIDUA) is a recombinant AAV9 capsid containing a hIDUA expression cassette. Preclinical studies in feline and canine models indicated RGX-111 can increase IDUA protein expression in a robust and rapid manner, resulting in near-complete correction of biochemical changes resulting from IDUA deficiency(4,5).

Intracisternal administration in canines and non-human primates was well-tolerated and resulted in efficient transduction of RGX-111 with sustained expression for nearly 4 years(5,6).

References

3. Aldenhoven et al. 2015, Blood. 125(13):2164-2172
Patient History, Treatment, and Post RGX-111 Evaluations to Date

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**2 Months**
- **First Evaluation at CHOC**
- Family History: Patient is 5th of 5 siblings. Three prior siblings diagnosed with MPS I. One is still alive but did not receive ERT. Two siblings died of ERT-related complications.
- **Biochemical & Molecular Testing**
  - OPA p.R628*;R632* known pathogenic mutation
- **Biomarkers**
  - Elevated uric total GAGs
  - Elevated urinary heparan and dermatan sulfate GAGs
  - Deficient L-Iduronidase enzyme
- **Diagnostic evaluations**
  - IAM autopsy constellation
  - Hepatosplenomegaly
- **ERT started at 6 months of age (standard dose 0.58mg/kg/week)**
- **Plan is to continue ERT throughout 2-year RGX-111 study follow-up**
- **Successful bilateral inguinal herniorrhaphy**
- **Walking unsupported, able to feed himself, has 3 words**
- **No developmental regression noted**
- **Demonstrates normal growth (length 20th percentile, weight 90th percentile, head circumference 90th percentile)**
- **Macrocephaly and physical examination findings are consistent with symptoms of MPS I that current ERT treatment is unable to fully mitigate**

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**20 Months**
- **Gene Therapy Administered**
- **Biomarkers (CSF Heparan sulfate and IDUA activity) previously reported**
- **Vector: RGX-111 (AAV9 + IDUA)**
- **(7 days before administration) Screening MRI to determine IC administration feasibility. 8-brain mass for gene therapy dose calculation**
- **Dose: 1.3 x 10¹⁰GCs/kg brain mass**
- **Route of Administration: Image-guided intracranial injection**
- **Immune-suppression Regimen**
  - Methylprednisolone one-time prior to RGX-111 administration
  - Prednisone was gradually tapered to discontinuation by 12 weeks post RGX-111 administration
  - Tacrolimus was gradually tapered over 8 weeks to discontinuation by 32 weeks post RGX-111 administration
  - Graft was discontinued at 48 weeks post RGX-111 administration

**23 Months**
- (12 Weeks Post RGX-111 Administration)

**29 Months**
- (32 & 33 Weeks Post RGX-111 Administration)
- **Biomarkers (CSF heparan sulfate and neurodevelopment assessment) previously reported**
- **Safety: No AEs related to administration of study drug (December 27, 2020)**
- **CNS Biomarker: Heparan sulfate concentration, IDUA activity**
- **Neurodevelopment: (BEDI-78) cognitive, language & motor domains**
- **Systemic Biomarker: urine GAGs**
- **Biochemical Investigation: normal at week 52 follow-up**
**Results**

**Safety**

RGX-111 is reported to be well-tolerated in this patient with no administration or study-drug related SAEs (as of December 27, 2020)

**Biochemistry**

- There was a durable reduction in CSF heparan sulfate up to 59 weeks after RGX-111 administration
- CSF IDUA activity was below the limit of detection at baseline and week 59; detectable at week 12. (data not shown)

Overall sustained decrease in total urine GAG levels

**Neurodevelopment Function**

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

Patient demonstrated continued cognitive development within a normal range

**Language and Motor Domains**

Patient demonstrated continued language and motor skills acquisition 60 weeks post RGX-111 dosing (~35 months of age).
### Conclusions

RGX-111 delivered via intracisternal administration has been well-tolerated with no administration or study-drug related SAEs (December 27, 2020).

CSF HS demonstrated a durable reduction up to 59 weeks post RGX-111 administration in this patient.

Urine total GAGs demonstrated an overall sustained decrease post RGX-111 administration in the patient.

Cognitive development continued within a normal range as measured using the BSID-III at 60 weeks post RGX-111 administration (~35 months of age). Language and motor skill acquisition also continued through 60 weeks post RGX-111 administration.