RGX-121 Gene Therapy for Severe Mucopolysaccharidosis Type II (MPS II):
Interim Results of an Ongoing First in Human Trial

11 February 2021

Marie-Laure Névoret, MD
Senior Clinical Development Lead - REGENXBIO
Disclosures

Marie-Laure Névoret is an employee of REGENXBIO
Objectives

Mucopolysaccharidosis Type II (MPS II) and RGX-121 as a therapeutic candidate

Overview of RGX-121-101 First in Human Study

Biochemical and Clinical Interim Analysis

Conclusions and Program Outlook of Gene Therapy for MPS II
Mucopolysaccharidosis Type II (MPS II)

MPS II is also known as Hunter syndrome

Rare X-linked recessive genetic disease (predominantly occurs in males)

Caused by a deficiency of iduronate-2-sulfatase (I2S), an enzyme required for the degradation of the glycosaminoglycans (GAGs)

GAG build-up causes:
- Systemic Symptoms
- Frequent Neurodegeneration
- Early Death

Standard of care includes IV enzyme replacement therapy (ERT), which does not address CNS disease involvement

Incidence

1 in 100,000 to 1 in 170,000

Prevalence

Attenuated MPS II ~25%

Severe MPS II ~75%
RGX-121-101: MPS II Phase 1/2 Clinical Study Summary
NCT03566043 on ClinicalTrials.gov

Patients
Approximately 12 MPS II patients
(≥ 4 months to < 5 years of age)

Cohorts (dose levels)
Genome copies/g brain mass
Cohort 1: 1.3 x 10^{10}
Cohort 2: 6.5 x 10^{10}
Cohort 3: 2.0 x 10^{11}

Data
Primary endpoint is safety; secondary endpoints include signs of efficacy

Primary Safety Endpoint (24 weeks)
Screening
Single Intracisternal Injection of RGX-121
Immunosuppression Therapy
(48 weeks)
Treatment Evaluation
Long-term Follow-up
(104 weeks)
**RGX-121-101: Patient overview**

- No SAEs related to study drug as of 04 January 2021
- Immunosuppression discontinued per protocol in first 4 patients
- 8 patients dosed to date
- Ages at dosing: 5 months to 59 months
- Mutations among patients: 3 missense, 2 gene inversions, 3 frameshifts

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (GC/g brain mass)</th>
<th>Follow-Up (weeks)</th>
<th>Immunosuppression Regimen Status</th>
<th>ERT (IV) status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3 x 10^{10}</td>
<td>104</td>
<td>Complete</td>
<td>Weekly</td>
</tr>
<tr>
<td>2</td>
<td>1.3 x 10^{10}</td>
<td>78</td>
<td>Complete</td>
<td><strong>Discontinued</strong></td>
</tr>
<tr>
<td>3</td>
<td>1.3 x 10^{10}</td>
<td>64</td>
<td>Complete</td>
<td><strong>Discontinued</strong></td>
</tr>
<tr>
<td>4</td>
<td>6.5 x 10^{10}</td>
<td>56</td>
<td>Complete</td>
<td>Weekly</td>
</tr>
<tr>
<td>5</td>
<td>6.5 x 10^{10}</td>
<td>32</td>
<td>Tapering</td>
<td>Weekly</td>
</tr>
<tr>
<td>6</td>
<td>6.5 x 10^{10}</td>
<td>24</td>
<td>Tapering</td>
<td><strong>Naïve</strong></td>
</tr>
<tr>
<td>7*</td>
<td>6.5 x 10^{10}</td>
<td>8</td>
<td>Active</td>
<td>Weekly</td>
</tr>
<tr>
<td>8*</td>
<td>6.5 x 10^{10}</td>
<td>4</td>
<td>Active</td>
<td><strong>Naïve</strong></td>
</tr>
</tbody>
</table>

* Limited data available for Patients 7 and 8
† Protocol allows ERT discontinuation only after Week 52
Cerebral spinal fluid (CSF) Biomarker: Heparan Sulfate (HS)

Consistent Heparan Sulfate decrease in the CSF after RGX-121 dosing

- The median change from baseline at week 8 (N=6) is -30.3% and p-value is 0.03*
- The median change from baseline at the last available timepoint (N=6) is -35.8% and p-value is 0.03*
- Measurable CSF I2S enzyme concentration in cohort 2 after RGX-121 administration (range 1170-1940 pg/mL)

* p-values are from Wilcoxon signed rank test
HS Digestion with Heparinase

- I2S enzyme cleaves sulfates from HS in the lysosome
- Absence of I2S causes long chains of fully sulfated D2S6 to accumulate in HS
- Quantitative measurement of D2S6 is reflective of I2S enzyme activity level

I2S6 and D2S6 are products of heparinase digestion

CSF Biomarker: HS D2S6 Disaccharide

- HS sulfation has been correlated with pathogenesis in neurodegenerative disorders\(^1\)-\(^3\)

**Consistent decrease in CSF D2S6, a correlate of neuropathology phenotype in severe MPS II\(^4\)-\(^6\)**

- The median change from baseline at week 8 (N=6) is -44.2% and p-value is 0.03*
- The median change from baseline at the last available timepoint (N=6) is -39.2% and p-value is 0.03*

* p-values are from Wilcoxon signed rank test

---

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

- Patients 1, 3 and 5 demonstrate continued cognitive development within a normal range
- Patients 2 and 4 presented with significant cognitive delay at baseline
  - Patient 2 has continued cognitive development
  - Patient 4 acquired expressive and receptive language skills (see next slide)

Continued cognitive development in 4 of 5 patients with > 6 months of follow-up
Neurodevelopment Function: Language and Motor Domains
BSID-III

Continued language and/or motor skills acquisition in patients with > 6 months of follow-up
**Systemic Efficacy:** Urine Total GAGs
ERT-Treated Patients

Sustained decrease in urine GAG levels across all patients receiving ERT
Rapid decrease in urine GAGs in ERT-naïve patients after RGX-121 administration; absence of urine GAG rebound post ERT withdrawal
Systemic Efficacy: Plasma I2S Enzyme Concentration

General increase in plasma I2S enzyme levels in 5 out of 6 patients after RGX-121 administration
Systemic Efficacy: Liver and Spleen Ultrasounds
ERT Naïve Patient

- Hepatosplenomegaly occurs almost universally in untreated MPS II

- Patient 6, who never received ERT, demonstrated clear reduction in liver and spleen dimensions 24 weeks after receiving RGX-121

<table>
<thead>
<tr>
<th>Patient</th>
<th>Follow-Up (weeks)</th>
<th>Liver Diameter (cm)</th>
<th>Spleen Length (cm)</th>
<th>Spleen Height (cm)</th>
<th>Spleen Width (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Screening</td>
<td>12.0</td>
<td>9.0</td>
<td>6.0</td>
<td>7.2</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td>10.8</td>
<td>7.6</td>
<td>4.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Decreased liver and spleen dimensions in ERT-naïve patient 24 weeks after RGX-121 administration

RGX-121-101: Summary of Results

RGX-121 appeared to be well tolerated

- 8 patients dosed with no SAEs related to study drug (as of 04January2021)
- Immunosuppression discontinued in first 4 patients according to protocol

Biomarker and neurodevelopmental function indicate encouraging RGX-121 CNS activity

- Consistent reductions in HS in the CSF up to 2 years
- CSF I2S enzyme concentration measurable in all cohort 2 patients
- Continued cognitive development in 4 of 5 patients with > 6 months of follow-up
- Continued language and/or motor skills acquisition in patients with > 6 months of follow-up
- Continued acquisition of cognitive and/or language skills in patients with cognitive delay prior to dosing

Emerging evidence of systemic enzyme expression and biomarker activity of RGX-121

- Plasma I2S enzyme levels increased in 5 of 6 patients
- Rapid urine GAG reduction in ERT naïve patients
- Decreased liver and spleen dimensions in ERT naïve patient
- Absence of urine GAG rebound in the 2 patients who have discontinued ERT
The study principal investigators:

- Dr Maria Escolar, University of Pittsburgh, USA
- Dr Can Ficicioglu, Children’s Hospital of Philadelphia, USA
- Dr Roberto Giugliani, Hospital de Clínicas de Porto Alegre, Brazil
- Dr Paul Harmatz, University of California San Francisco, USA

MPS II Program:
RGX-121-101: NCT03566043
Age 5-18 years: NCT04571970
Observational: NCT04591834

MPS I Program:
First in human: NCT03580083

REGENXBIO, the sponsor of the RGX-121-101 trial