RGX-111 Gene Therapy for the Treatment of Severe Mucopolysaccharidosis Type I: Interim Analysis of the First in Human Study and a Single Patient IND

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### MPS I is a Systemic Disease Representing a Wide Spectrum of Severity

#### Severity of Disease Manifestations Correlates with Degree of alpha-L-iduronidase (IDUA) Deficiency

<table>
<thead>
<tr>
<th></th>
<th>Hurler (60%)</th>
<th>Hurler-Scheie (23%)</th>
<th>Scheie (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Onset</strong></td>
<td>0.5 y</td>
<td>3.0 y</td>
<td>7.8 y</td>
</tr>
<tr>
<td><strong>Age of diagnosis</strong></td>
<td>0.8 y</td>
<td>3.9 y</td>
<td>9.3 y</td>
</tr>
<tr>
<td><strong>Cognitive</strong></td>
<td>100% Regression</td>
<td>35% IQ &lt; 85</td>
<td>Usually normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14% IQ &lt; 70</td>
<td></td>
</tr>
<tr>
<td><strong>Somatic</strong></td>
<td>Most manifestations and most severe</td>
<td>Intermediate number and severity</td>
<td>Fewest manifestations, least severe</td>
</tr>
<tr>
<td></td>
<td>Coarse facial features, organomegaly, dysostosis multiplex, carpal tunnel syndrome, stiff joints, hydrocephalus, cord compression, cardiac valvular disease, recurrent upper airway infections, OAD/ sleep apnea, corneal clouding, hearing loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Life expectancy</strong></td>
<td>Rapid progression; &lt; 10 y</td>
<td>Slower progression; 30 – 40 y</td>
<td>Slow progression; &gt; 40 y</td>
</tr>
<tr>
<td><strong>SoC</strong></td>
<td>HSCT</td>
<td>Systemic ERT</td>
<td>Systemic ERT</td>
</tr>
<tr>
<td><strong>Unmet needs with SoC</strong></td>
<td>Musculoskeletal/orthopedic Cardiac valve disease Corneal clouding Neurocognitive – improved but often not normal</td>
<td>Musculoskeletal/orthopedic Cardiac valve disease Corneal clouding Neurocognitive – milder dysfunction</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Beck et al. (2014) Genet Med
Shapiro et al. (2015) Mol Genet Metab
**RGX-111: MPS I Phase 1/2 Clinical Study Summary**

NCT03580083 on ClinicalTrials.gov

**Participants**

Enrollment up to 11 MPS I participants with CNS involvement or severe MPS I (≥ 4 months of age)

May be on Standard of Care IV ERT or ERT Naïve

**Cohorts (dose levels)**

Cohort 1: 1.0 x 10^{10}
Cohort 2: 5.0 x 10^{10}

RGX-111 AAV9 + IDS

**Data**

Primary Endpoint is Safety

Secondary & Exploratory Endpoints Include:

- CSF Biomarkers (Heparan Sulfate)
- Neurodevelopmental Assessments (Bayley / WASI)
- Caregiver reported outcomes (Vineland)
- Systemic Biomarkers (urine & plasma)

**Screening**

Single Direct to CNS Injection of RGX-111

**Immunosuppression Therapy**

Option to discontinue after week 28

**Treatment Evaluation**

(48 weeks)

**Long-term Follow up Study**

(104 weeks)
### RGX-111 Phase 1/2 Trial and Single Patient Investigator-Initiated IND

- 6 participants dosed as of December 20, 2021, 5 in Phase 1/2 trial and 1 in single patient IND
- Ages at dosing from 4 months to 13 years in Phase 1/2 trial and 20 months in single patient IND
- *IDUA* Mutations among Phase 1/2 trial and single patient IND participants include nonsense/frameshift, nonsense/null variant splice site, and missense
- No SAEs related to study drug as of December 20, 2021
- Immunosuppression discontinued per protocol in one trial participant and single patient IND participant

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Dose (GC/g Brain Mass)</th>
<th>Follow-Up (Weeks)</th>
<th>Prior / Treatment at Dosing</th>
<th>Immunosuppression Regimen Status</th>
<th>ERT (IV) Status†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>2</td>
<td>1.0 x 10^{10}</td>
<td>40-56 wks</td>
<td>1 prior HSCT + ERT^1 ERT</td>
<td>1 completed 1 active</td>
<td>1 not on ERT 1 weekly</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>3</td>
<td>5.0 x 10^{10}</td>
<td>3-32 wks*</td>
<td>1 HSCT + ERT 1 ERT</td>
<td>3 active</td>
<td>2 weekly 1 ERT naïve</td>
</tr>
<tr>
<td>Single Patient IND</td>
<td>1</td>
<td>1.0 x 10^{10}**</td>
<td>87 wks</td>
<td>ERT</td>
<td>completed</td>
<td>weekly</td>
</tr>
</tbody>
</table>

† Per protocol, participants may discontinue ERT after week 28
^ Participant had <1 month of exposure to ERT
* 2 participants recently dosed. Data for Cohort 2 will only include 1 or 2 participants depending on data availability
** Previously reported as 1.3 x 10^{10} from initial calculations for brain mass
Cerebrospinal Fluid (CSF) Biomarker
Heparan Sulfate (HS)

- Decreased CSF heparan sulfate in all participants through last time point available
- Measurable CSF IDUA enzyme activity* in 3 of 4 participants in the Phase 1/2 trial and the single patient IND participant

Note: Normative data are based on 29 normal samples. Age ranges from 1 mo. to 21 years of age

* Data not shown

Data cut December 20, 2021
Neurodevelopmental Assessments

Age and developmentally appropriate validated instruments for neurodevelopmental testing were used to evaluate all participants

$n = 4^*$

Bayley Scale of Infant and Toddler Development, Third Edition (BSID-III) for chronological or developmental ages 0 to 42 months

$n = 3$
- 2 Phase 1/2 trial participants
- 1 single patient IND participant

Wechsler Abbreviated Scale of Intelligence (WASI-II) for chronological and development age > 6 years

Vineland Adaptive Behavior Scale, Third Edition (VABS-III)

$n = 1$
- 1 Phase 1/2 trial participant

* With at least one post-baseline assessment
All participants showed continued skill acquisition within 2 SD of normative mean on the cognition, expressive language and fine motor subtests at last assessment.

Data cut December 20, 2021
Cognitive function remains within 2 SD of normative range at the last assessment, 20 months after RGX-111 administration.

BSID cognition in participant approaching 42 months of age demonstrated higher age equivalent scores than available natural history data.

* Natural history data (Shapiro et al., 2018) gathered using BSID-II; RGX-111 single patient IND data gathered using BSID-III.
**Neurodevelopmental Function: WASI-II and VABS-III**

13 year-old Phase 1/2 Trial Participant

<table>
<thead>
<tr>
<th>WASI-II Full Scale Composite</th>
<th>Baseline Chronologic Age 13y</th>
<th>Week 52 Chronologic Age 14y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 100 (SD 15)</td>
<td>43</td>
<td>47</td>
</tr>
</tbody>
</table>

**VABS-III Age Equivalent Scores (year:month)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline Chronological Age 13y</th>
<th>Week 52 Chronological Age 14y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal (dressing, feeding, toileting, and washing/hygiene)</td>
<td>4:1</td>
<td>7:10</td>
</tr>
<tr>
<td>Domestic</td>
<td>7:7</td>
<td>6:7</td>
</tr>
<tr>
<td>Community</td>
<td>7:4</td>
<td>6:10</td>
</tr>
<tr>
<td>Interpersonal Relationships</td>
<td>5:10</td>
<td>7:4</td>
</tr>
<tr>
<td>Play and Leisure</td>
<td>8:1</td>
<td>8:1</td>
</tr>
<tr>
<td>Coping Skill</td>
<td>3:4</td>
<td>9:10</td>
</tr>
<tr>
<td>Adaptive Behavior</td>
<td>6:3</td>
<td>7:10</td>
</tr>
<tr>
<td>Fine Motor</td>
<td>5:7</td>
<td>6:4</td>
</tr>
<tr>
<td>Gross Motor</td>
<td>4:0</td>
<td>4:6</td>
</tr>
</tbody>
</table>

13 yr old Phase 1/2 trial participant demonstrated improvements in WASI composite and the majority of components of the VABS 52 weeks after RGX-111 administration
Systemic Effects: Plasma I0S6

I0S6 is a non-reducing end (NRE) disaccharide of glycosaminoglycans shown to be elevated in plasma, urine and CSF of MPS I patients\textsuperscript{1,2,3,4,5}

Participants with elevated I0S6 at baseline showed a decrease in I0S6 following RGX-111 administration.
Systemic Effects: Urine Total GAGs

Total urinary GAGs remained below 30 g/mol in all participants at last time point available
RGX-111 Phase 1/2 Trial and Single Patient IND
Summary of Results

Safety: RGX-111 appeared to be well tolerated

- A total of 6 participants dosed with RGX-111 with no SAEs related to study drug

CNS: Biomarker and neurodevelopmental assessments indicate encouraging RGX-111 CNS profile

- Biomarker:
  - CSF HS reduction and IDUA enzyme activity indicate CNS biological activity
  - Neurodevelopment:
    - Participants showed continued skill acquisition within 2 SD of normative mean on the cognition, expressive language and fine motor subtests at last assessment
    - Single patient IND participant at 42 months of age demonstrated higher age equivalent scores than available natural history data 20 months after RGX-111 administration

Emerging evidence of systemic biomarker activity after CNS administration of RGX-111

- Plasma I0S6 reductions observed following RGX-111 administration
- Low levels of urinary GAGs maintained in all participants

Data cut December 20, 2021
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