Enzyme replacement therapy (ERT) for mucopolysaccharidosis VII (MPS VII; Sly’s Syndrome) reduces lysosomal storage in a 36-week Phase 1/2 clinical study

Emil D. Kakkis, M.D., Ph.D, Simon A. Jones, M.D., Arunabha Ghosh, M.D., Catherine Breen, M.D., and Wiliam S. Sly, M.D.

1Manchester Centre for Genomic Medicine, St Mary's Hospital, CMFT, University of Manchester, UK; 2Ultragenyx Pharmaceutical Inc., Novato, CA; 3Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, St. Louis, MO

WORLDSymposium, Orlando, FL; Feb 12, 2015
I have the following financial relationships to disclose:
   Employee and Stockholder of Ultragenyx Pharmaceutical Inc.

   - and -

I will discuss the following off label use and/or investigational use in my presentation:

UX003 (recombinant human beta-glucuronidase; rhGUS) for MPS VII
rhGUS for MPS VII Clinical Development Plan

Phase 1/2 open-label study
Assessing the safety, efficacy and dose of UX003
*Ongoing*

Phase 3 Pivotal Study
Randomized, Placebo-controlled, blind-start, single-crossover study to assess the safety and efficacy of UX003
*Enrolling*

Under 5 and Infant Study
Open-label in patients < 5 years of age, including those with Hydrops Fetalis
*Planned for 2015*

Long-term efficacy and safety study
All subjects on UX003 (Extension study)
*Planned*
Phase 1/2 Study rhGUS Objectives

• Primary objectives
  1) Safety and tolerability
  2) Evaluate impact on lysosomal storage
  3) Establish the dose for rhGUS

• Secondary objectives
  – Pulmonary function
  – Shoulder range of motion
  – Physical function including walking and stair climbing capacity
  – Patient reported outcomes
  – Height and weight growth velocity

• Key other objectives
  – Liver and spleen size
  – Pharmacokinetics (PK)

Study is not powered to assess clinical endpoints
rhGUS Phase 1/2 Study Overview

- **N = 3**
  - Confirmed Dx (enzyme assay/genetic test)
  - 5 – 30 years old inclusive
  - uGAG excretion >2-fold over normal
  - No history of successful BMT
- **Dosing every 2 weeks (QOW)**
- **Single central site in Manchester, UK**
rhGUS Phase 1/2 Study Status

• Study started with FPI in Dec 2013
• 3 subjects enrolled and enrolment ended
• All subjects received 19 infusions
  – No missed infusions
• Key data available
  – Clinical, Safety, PK/PD up to 36 weeks
• All subjects currently in Continuation Phase
  – 2 mg/kg QOW
## Phase 1/2 Subject Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Subject:</th>
<th>111-201</th>
<th>111-202</th>
<th>111-203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>History of Hydrops Fetalis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>1.1 yrs</td>
<td>&lt; 1 mos</td>
<td>5.5 yrs</td>
</tr>
<tr>
<td>Age at start of ERT (years)</td>
<td>5.5</td>
<td>9.4</td>
<td>25.1</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>White</td>
<td>Asian</td>
</tr>
<tr>
<td>Standing height (cm)</td>
<td>102.5</td>
<td>123.9</td>
<td>157.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.6</td>
<td>34.6</td>
<td>78.8</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Leukocyte enzyme activity</td>
<td>Leukocyte enzyme activity</td>
<td>Leukocyte enzyme activity</td>
</tr>
</tbody>
</table>
Key Findings: Safety and Tolerability
rhGUS infusions appear safe and well tolerated

• No SAEs up to 36 wks
• No drug-related or hypersensitivity infusion associated reactions (IARs)
• Complement levels normal at week 12
• All AEs were Grade 1 (mild) except one Grade 2 (moderate) event of hip arthralgia (unrelated)
• AEs consistent with symptoms of MPS VII or related to IV catheterization
  – Most Common AEs: Respiratory disorders, infections, arthralgia, infusion site extravasation
• No AEs were considered to be drug-related
PK: Subject Profiles Show Dose-Dependence

- [rhGUS] is well above $K_{\text{uptake}}$ for 7 hours+
- PK is dose-dependent, non-linear from 2 to 4 mg/kg dose
Rapid and Sustained Dose-Dependent Reduction in uGAG: 4 > 2 > 1 mg/kg

Time course of uGAG reduction

Mean uGAG reduction at end of each dosing interval
Progressive Reduction in Serum GAG
Significant Reduction in Enlarged Liver Size

-24% ULTRASOUND

-53% ULTRASOUND

*Baseline scan was not determined (ND); subjectively radiologist reports no change at BL vs. week 12

*Baseline scan was not determined (ND); subjectively radiologist reports no change at BL vs. week 12
Clinical Evaluations: Pulmonary Function

- Only 1 subject (203) was able to perform the tests
- Subject 203 had improved pulmonary function
  - **FVC increased 13.4%** from baseline at week 30
  - **MVV1 increased 14.9%** from baseline at week 30
  - FEV was comparable to screening

<table>
<thead>
<tr>
<th>203 Assessments</th>
<th>dose</th>
<th>FVC (L)</th>
<th>FEV1</th>
<th>MVV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td>2.91</td>
<td>2.26</td>
<td>77.13</td>
</tr>
<tr>
<td>Week 6</td>
<td>2 mg/kg</td>
<td>3.04</td>
<td>2.07</td>
<td>87.1</td>
</tr>
<tr>
<td>Week 12</td>
<td>2 mg/kg</td>
<td>2.99</td>
<td>2.04</td>
<td>85.68</td>
</tr>
<tr>
<td>Week 22</td>
<td>1 mg/kg</td>
<td>2.78</td>
<td>2.07</td>
<td>86.88</td>
</tr>
<tr>
<td><strong>Week 30</strong></td>
<td>4 mg/kg</td>
<td><strong>3.3</strong></td>
<td>2.31</td>
<td><strong>88.61</strong></td>
</tr>
<tr>
<td>Week 36</td>
<td>2 mg/kg</td>
<td>3.21</td>
<td>2.24</td>
<td>84.08</td>
</tr>
</tbody>
</table>
Shoulder Flexion and Motor Abilities

• Goniometry: shoulder range of motion
  – Normal shoulder flexion (n=2) and extension (n=3) measures at baseline
  – 1 subject with limited passive ROM in shoulder flexion at screening AND baseline resolved at Week 6 and maintained within normal range at subsequent visits

• BOT-2: assesses fine and gross motor abilities
  – 2 subjects could not complete all assessments: age or cognitive ability
  – Subject 111-203 was cooperative and attentive
    – Gross motor tests difficult to assess due to persistent hip pain
    – Manual dexterity results suggest improved function following treatment, no change in fine motor precision

• 6MWT/Stair Climb: difficult to interpret
  – Variable due to cooperation of 5 and 9 year olds & hip pain in adult
    – 201 showed fluctuations up and down in 6MWT; 202 had high baseline 6MWT and modest changes
Other Clinical Assessments

- 2 of 3 subjects showed substantial weight gain
  - 1 physician assessment of improved appetite
- No significant improvement in standing height
- MPS health assessment questionnaire (HAQ) and physician global impression of change (PGIC) indicate subjective improvements in the patients
  - All 3 subjects showed improvement in fatigue/ lack of energy on PGIC
  - MPS HAQ Caregiver and Mobility scores, but not Self Care score improved for 2 of 3 subjects
- Not a blinded study
Summary of Phase 1/2 Key Findings

• Safety of every other week infusions of rhGUS
  • rhGUS appears safe and well tolerated and no SAE’s
  • No infusion associated reactions in 57 infusions

• Lysosomal storage is substantially reduced
  – Rapid reduction in uGAG and in liver size

• Clinical Evaluation is still preliminary
  – Heterogeneous subjects and only 3 total
  – Some evidence of clinical benefit
    • Increased PFT’s in one patient, HAQ and PGIC scores

• Dose data supports 4 mg/kg QOW dosing
  – rhGUS is 4x MW of other MPS enzymes
Acknowledgements

• All patients and families who contributed time and effort for traveling and assessments
• UK MPS Society
• The Willink team
• Manchester NIHR Wellcome Trust Clinical Research facility
• Joanne Guest, study lead
• Pauline Hensman, physiotherapist
• Ultragenyx Pharmaceutical Inc.