A Novel, Randomized, Placebo-Controlled, Blind-Start, Single-Crossover Phase 3 Study to Assess the Efficacy and Safety of UX003 (rhGUS) Enzyme Replacement Therapy in Patients with MPS VII

Harmatz P1, Whitley CB2, Wang RY3, Bauer M4, Song W5, Chesler S5, Schwartz E5, Haller C5, Kakkis E5
1UCSF Benioff Children’s Hospital Oakland, Oakland, CA, 2University of Minnesota, Minneapolis, MN, 3Children’s Hospital of Orange County, Orange, CA, 4Miami Children’s Hospital, Miami FL, 5Ultragenyx Pharmaceutical Inc., Novato, CA

INTRODUCTION

- MPS VII (Sly syndrome) is an ultra-rare, chronically debilitating, and life-threatening lysosomal disease caused by a deficiency of beta-glucuronidase enzyme activity leading to accumulation of dermatan (DS), heparan (HS), and chondroitin sulfate (CS) glycosaminoglycans in a wide variety of tissues. No specific approved therapy exists.
- Key symptoms/prognosis of MPS VII
  - Large lver, large spleen, cardiac/ pulmonary disease, severe joint and bone abnormalities, cognitive impairment, corneal clouding, infections, short stature
  - Severity spectrum but death often in teens-30s
  - Approximately 40% of patients with history of non-immune hydrops fetalis [NIHF], i.e., total body fluid retention, high mortality rate

METHODS

- Phase III, multicenter, randomized, placebo-controlled, blind-start, single crossover study
- Assess the safety and efficacy of UX003
- 48-week duration
- 12 subjects with MPS VII aged 5 to 35 years
- During active treatment, subjects received IV infusions of 4 mg/kg rhGUS every other week through Week 46, with all subjects receiving at least 24 weeks of active treatment
- Subjects blindly randomized 1:1:1:1 to one of 4 treatment sequence groups
  - Group A, B, C, or D; (3 subjects per group) to start treatment with rhGUS (Group A) or placebo (Groups B, C, and D)
  - Placebo-initiated groups crossed over to treatment with rhGUS at 8, 16 or 24 weeks for Groups B, C, and D, respectively

uGAG Primary Analysis

- Primary efficacy endpoint (in EU): Percentage change from baseline in urinary GAG (LC-MS/MS-DS) excretion after 24 weeks of treatment
  - In US, primary efficacy assessed on totality of clinical data on a per subject basis; uGAG secondary efficacy endpoint
- Primary efficacy analysis: mean percent change in uGAG over 24 weeks of treatment for significant reduction from the pre-treatment baseline (average of all assessments prior to beginning rhGUS treatment) using GEE modeling
- Statistical significance assessed at the two-sided 5% level of Type I error

Other Efficacy and Safety Variables

- The Subject-specific Multi-Domain Responder Index (MDRI) score
  - Consisting of the six-minute walk test (6MWT), forced vital capacity (FVC), shoulder flexion, visual acuity, and the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) fine motor and gross motor function
  - Treatment week 24 MDRI score compared with no change (0) using a t-test. Missing week 24 domain scores were imputed by available week 32 or 16 domain scores
- Individual Clinical Response (ICR) (most impactful clinical problem(s) reported by the caregiver), fatigue by PedsQL multi-dimensional fatigue scale
- Safety (treatment-emergent adverse event [AE] and serious AE [SAE]; infusion-associated reactions [IAR] anti-drug antibodies)

BASELINE CHARACTERISTICS

- Twelve subjects were enrolled and completed the study in the US
  - 4 male; 8 female
  - Subjects enrolled in the study were 8-25 years of age
  - From 4 countries (US, Mexico, Brazil, Portugal)

RESULTS

Marked Reduction in Urinary GAG of 64.8% (p<0.0001) at Treatment Week 24

- uGAG primary analysis of change from baseline showed a dramatic reduction for dermatan sulfate (DS) (Fig 1 and 3; -64.8%, p<0.0001) and chondroitin sulfate (CS) (Fig 2; -70.6%, p<0.0001)

Improvement in Clinical Disease Observed

- MDRI Week 24 treatment response as assessed by MDRI was positive with a mean score improvement of +0.5 domains (p=0.0527); 6 of 12 subjects had a MDRI score of +1 or more. Five subjects had score of 0 (no change), indicative of no worsening in progressive disease (Figure 4). One subject with -1 MDRI score had acute viral illness on (blinded) treatment week 24 visit
- Fatigue: Majority of subjects improved over baseline in fatigue at some point during study (Figure 6)
- Individual clinical response (ICR) endpoint met by 3 of 12 subjects at 24 week treatment assessment (all 6MWT), others were unchanged except one who worsened due to viral illness
- 6MWT: Change from baseline in (m) at treatment week 24 increased with L5 mean (SE) of 20.8 (16.75) (p=0.2137) in subjects able to complete assessment (Figure 5)

Figure 1: Percent Change from Baseline in uGAG (Dermatan Sulfate) Excretion by UX003 Treatment Week (by LC-MS/MS, GEE)

Figure 2: Percent Change from Baseline in uGAG (Chondroitin Sulfate) Excretion by UX003 Treatment Week (by LC-MS/MS, GEE)

Figure 3: Percent Change from Baseline in uGAG (Dermatan Sulfate) Excretion by Visit and Subject (by LC-MS/MS)

Figure 4: Endpoints Defined with MID or Response at UX003 Treatment Week 24

Figure 5: Change from Baseline in 6 Minute Walk Test (m) (GEE)

Table 1: Treatment Emergent Adverse Events by Preferred Term in Descending Frequency in >15% of UX003 Subjects

Table 6: Fatigue Total Score (PedsQL) Results by Subject

CONCLUSIONS

- Primary Endpoint met with highly significant 64.8% reduction in urinary GAG excretion after 24 weeks of treatment (p<0.0001)
- Clinical results indicate improvements in certain domains for some subjects including 6MWT, fatigue and visual acuity as well as patient and clinician assessments of change
- Majority of subjects improved on active treatment in at least one domain; some assessments were hindered by cognitive and physical impairments
- MDRI showed overall improvement with mean score (SD) of +0.5 domains (0.82) (p=0.0527)
- ICR met in 25% of subjects at treatment week 24
- Acceptable safety profile with only 2 hypersensitivity-type IARs (including 1 treatment-related SAE), no discontinuations or missed infusions due to AEs
- 7 of 12 subjects developed anti-rhGUS antibodies; not associated with hypersensitivity AEs

REFERENCES