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

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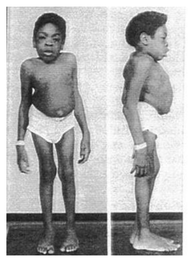
INTRODUCTION

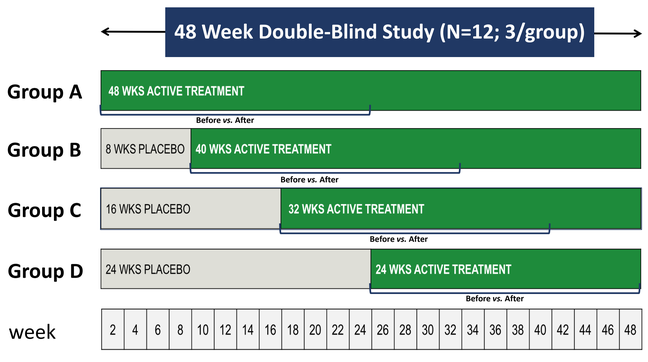
- MPS VII (Sly syndrome) is an ultra-rare, chronically debilitating, and life-threatening lysosomal disease caused by a deficiency of beta-glucuronidase enzyme activity leading to accumulation of dermatan (DS), heparan (HS), and chondroitin sulfate (CS) glycosoaminoglycans in a wide variety of tissues. No specific approved therapy exists.



- Key symptoms/prognosis of MPS VII
  - Large liver, 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[1] (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 rhGUS
- 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 LS 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)

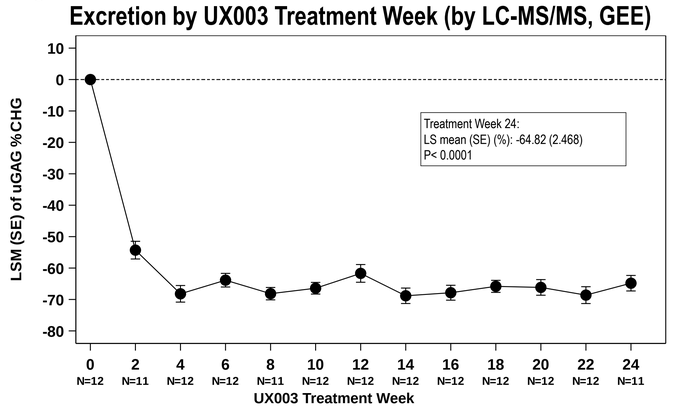


Figure 2: Percent Change from Baseline in uGAG (Chondroitin Sulfate) Excretion by UX003 Treatment Week (by LC-MS/MS, GEE)

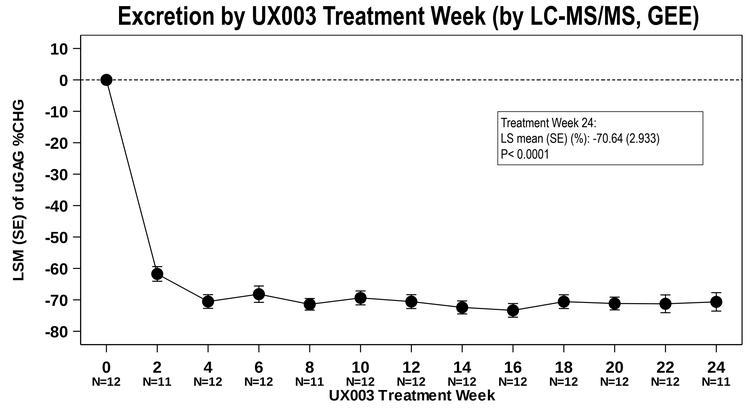


Figure 3: Percent Change from Baseline in uGAG (Dermatan Sulfate) Excretion by Visit and Subject (by LC-MS/MS)

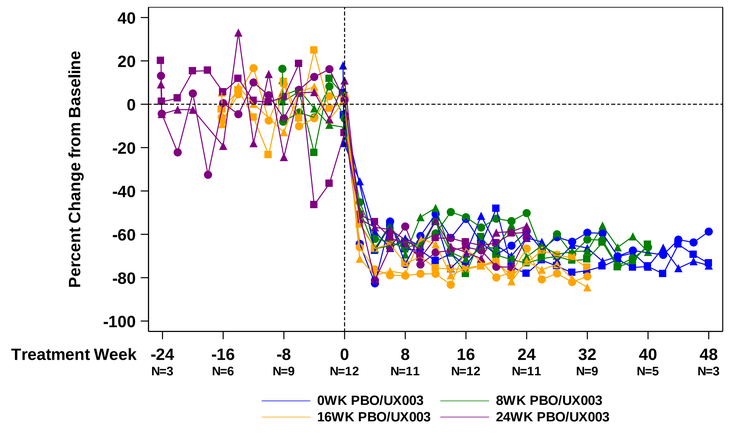
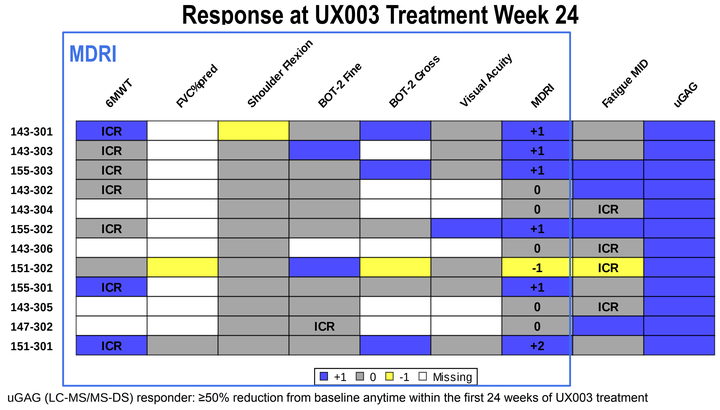


Figure 4: Endpoints Defined with MID or Response at UX003 Treatment Week 24



uGAG (LC-MS/MS-DS) responder: ≥50% reduction from baseline anytime within the first 24 weeks of UX003 treatment

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

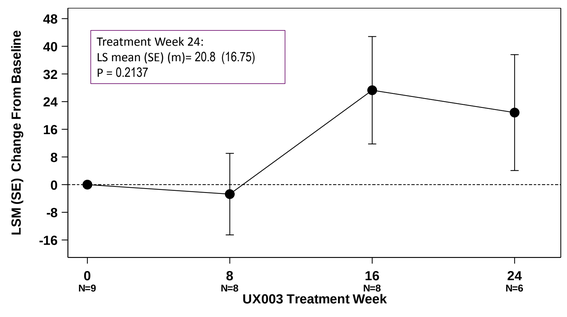


Figure 6: Fatigue Total Score (PedsQL) Results by Subject

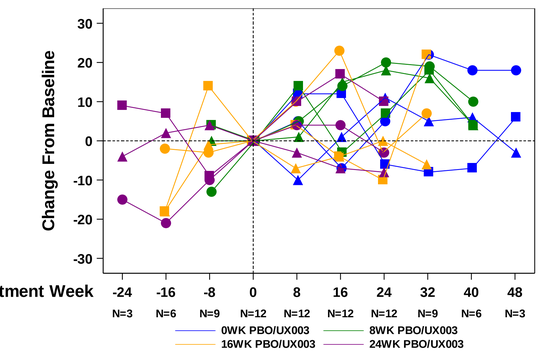


Table 1: Treatment Emergent Adverse Events by Preferred Term in Descending Frequency in >15% of UX003 Subjects

Preferred Term	Placebo (N = 9) n%	UX003 (N=12) n (%)
Upper respiratory tract infection	3 (33.3)	5 (41.7)
Pain in extremity	3 (33.3)	4 (33.3)
Infusion site extravasation	1 (11.1)	4 (33.3)
Cough	2 (22.2)	3 (25.0)
Vomiting	2 (22.2)	3 (25.0)
Rash	1 (11.1)	3 (25.0)
Diarrhoea	0	3 (25.0)
Anaphylactoid reaction	0	2 (16.7)

- AEs were mild to moderate in severity with one Grade 3 event
- 6 of 8 subjects with IARs on UX003 had events involving the IV catheter; two subjects had hypersensitivity-type IARs that did not recur with subsequent infusions
- No deaths or AEs leading to treatment discontinuation and no withdrawals from study
- 2 SAEs: One related anaphylactoid reaction due to infusion error; one unrelated SAE of "craniocerebral injury" due to a fall
- 7 of 12 subjects developed anti-rhGUS antibodies; not associated with IARs

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 (0.80) (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

1. Montano AM et al. Clinical course of Sly syndrome (mucopolysaccharidosis type VII). *J Med Genet* 2016;0:1-16