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Regular Article

# The long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis VII

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ABSTRACT

Vestronidase alfa (recombinant human beta-glucuronidase) is an enzyme replacement therapy (ERT) for Mucopolysaccharidosis (MPS) VII, a highly heterogeneous, ultra-rare disease. Twelve subjects, ages 8–25 years, completed a Phase 3, randomized, placebo-controlled, blind-start, single crossover study (UX003-CL301; NCT02377921), receiving 24–48 weeks of vestronidase alfa 4 mg/kg IV. All 12 subjects completed the blind-start study, which showed significantly reduced urinary glycosaminoglycans (GAG) and clinical improvement in a multi-domain responder index, and enrolled in a long-term, open-label, extension study (UX003-CL202; NCT02432144). Here, we report the final results of the extension study, up to an additional 144 weeks after completion of the blind-start study.

Three subjects (25%) completed all 144 weeks of study, eight subjects (67%) ended study participation before Week 144 to switch to commercially available vestronidase alfa, and one subject discontinued due to non-compliance after receiving one infusion of vestronidase alfa in the extension study. The safety profile of vestronidase alfa in the extension study was consistent with observations in the preceding blind-start study, with most adverse events mild to moderate in severity. There were no treatment or study discontinuations due to AEs and no noteworthy changes in a standard safety chemistry panel. Out of the eleven subjects who tested positive for anti-drug antibodies at any time during the blind-start or extension study, including the baseline assessment in the blind-start study, seven subjects tested positive for neutralizing antibodies and all seven continued to demonstrate a reduction in urinary GAG levels. There was no association between antibody formation and infusion associated reactions.

Subjects receiving continuous vestronidase alfa treatment showed a sustained urinary GAG reduction and clinical response evaluated using a multi-domain responder index that includes assessments in pulmonary function, motor function, range of motion, mobility, and visual acuity. Reduction in fatigue was also maintained in the overall population. As ERT is not expected to cross the blood brain barrier, limiting the impact on neu-

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rological signs of disease, and not all subjects presented with neurological symptoms, outcomes related to central nervous system pathology are not focused on in this report.

Results from this study show the long-term safety and durability of clinical efficacy in subjects with MPS VII with long-term vestronidase alfa treatment.

## 1. Introduction

Mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders caused by the absent or deficient activity of the enzymes involved in the degradation of glycosaminoglycans (GAGs) [1]. While all seven types of MPS are characterized by the excessive lysosomal storage of GAGs and most patients experience physical and/or mental decline, each type is categorized based on the deficiency of a specific enzyme [2]. MPS VII, also known as Sly syndrome, is an ultra-rare, chronically debilitating, life-threatening, autosomal recessive disorder caused by deficiency of the ß-glucuronidase enzyme [3,4]. Deficiency of the ß-glucuronidase enzyme leads to the accumulation of partially degraded GAGs, dermatan sulfate (DS), heparan sulfate (HS), and chondroitin sulfate (CS), in many tissues leading to cellular and organ dysfunction [3,4].

Clinical presentation may occur prenatally with hydrops fetalis, which can result in an early death in utero, or at birth [4]. Over 50 different pathogenic DNA variants in *GUSB,* the gene encoding β-glucuronidase, have been identified including missense/nonsense, splicing, regulatory mutation, small deletions, and gross deletion [5]. MPS VII presents across a wide spectrum of disease severity and its progression is highly heterogeneous; key symptoms include enlarged liver and spleen, cardiac and pulmonary involvement, joint and bone abnormalities, cognitive impairment, corneal clouding, and short stature [4,6]. Estimated prevalence worldwide is 0.01 in 100,000 live births, and most patients with MPS VII die before reaching age 20 or 30 due to progressive organ dysfunction [5]; though with increasing disease awareness that MPS VII can also present with more mild symptoms, it is likely that this number underestimates the prevalence.

Vestronidase alfa is a formulation of recombinant human ß-glucuronidase (rhGUS; UX003) intended as enzyme replacement therapy (ERT) [6]. Vestronidase alfa was approved in 2017 by the FDA to treat children and adults with MPS VII based on findings from multiple studies including non-interventional reviews of medical records, patient surveys, and clinical trials [6–9]. In 2018, the EMA also granted Marketing Authorization Application for the non-neurological manifestations of vestronidase alfa. In a previous Phase 3, randomized, placebo-controlled, blind-start study (NCT02230566; 2014–005638-71) in 12 subjects with MPS VII, vestronidase alfa 4 m/kg administered intravenously (IV) every other week (Q2W) significantly reduced urinary GAG levels and improved clinical outcomes specific to each patient's expression of the disease [9,10]. Here, we report the final results from the Phase 3, open-label, long-term extension study, in which subjects from the 48-week, Phase 3, blind-start study continued receiving vestronidase alfa for up to an additional 144 weeks.

## 2. Methods

UX003-CL202 is a Phase 3, open-label, multinational, long-term extension study investigating the efficacy and safety of vestronidase alfa 4 mg/kg IV Q2W for up to 144 weeks. Subjects with MPS VII who completed the 48-week, Phase 3, blind-start study were eligible to enroll in this long-term extension study; key inclusion and exclusion criteria are published in Harmatz et al. and Haller et al. [9,10]. In the novel, blind-start study, all subjects received at least 24 weeks of vestronidase alfa, but began active treatment at one of four pre-defined time points with pre-treatment placebo data serving as individual controls; therefore, out of 12 subjects, groups of three subjects received 48, 40, 32, and 24 weeks of vestronidase alfa respectively before enrolling into the extension study. To mitigate infusion site reactions, administration of prophylactic, non-sedating antihistamine prior to dosing and a slower initial infusion rate was allowed. More specifically, subjects received 2.5% of their dose in the first hour and the remaining dose over the course of the following three hours.

The primary objective was safety, summarized as the frequency and severity of adverse events that were new or worsened after completion of the Phase 3, blind-start study; changes in vital signs, weight, physical examination findings, echocardiogram, and clinical laboratory tests; concomitant medications; and anti-drug antibodies. The secondary objective was evaluation of sustained efficacy in reducing urinary GAG levels, measured as percentage change from baseline. A posthoc analysis was also included examining this endpoint in subjects whose baseline urinary GAG level was greater than the median level of the cohort (high excretors), and those less than the median level of the cohort (low excretors). The median baseline urinary GAG level of the study cohort was 24.69 times the age-adjusted upper limit of normal. Additional key efficacy assessments included mobility as assessed with the six-minute Walk Test (6MWT) [11], fatigue using the Pediatric Quality of Life (PedsQL) Multidimensional Fatigue Scale [12], presence and severity of hepatosplenomegaly, and a composite multi-domain responder index (MDRI). Outcomes were age specific where appropriate, and the full schedule of assessments is available in the supplemental appendix.

The MDRI includes 6 different domains: 6MWT distance walked, forced vital capacity (FVC) percentage of predicted [13–15], goniometer-quantified shoulder flexion, Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) Fine Motor Proficiency outcome [16], BOT-2 Gross Motor Function Outcome, and visual acuity using a standard eye chart. The BOT-2 Fine Motor Proficiency outcome consisted of two subtests: fine motor precision and manual dexterity. The BOT-2 Gross Motor Function outcome consisted of two subtests: balance and running speed and agility. These subtests were omitted if the subject was unable to complete the task. Higher BOT-2 scores indicate a greater level of functioning. The rubric used to assign BOT-2 scoring was dependent on age and sex.

The Minimal Important Difference (MID) was defined prior to enrollment in the blind-start study for each of these domains based on data from other related diseases. The MID was 23 m and 10% change from baseline for the 6MWT [17–24]; 5% absolute change or 10% relative change from baseline for FVC [21,23]; 20° change of passive shoulder range of motion for shoulder flexion [21,22,24,25]; 3 lines (corrected for both eyes) for visual acuity [26–28]; a change of 0.72 on the fine motor precision subtest and 1.47 on the manual dexterity subtest for BOT-2 Fine Motor [29]; and a change of 0.57 for the balance subtest and 0.59 for the running speed and agility subtest for the BOT-2 gross motor function [29]. Based on the MID, subjects were assigned a − 1 for decline, 0 for no change, or + 1 for improvement per domain. For example, a subject was assigned a + 1 for the 6MWT when there was change ≥23 m or 10% from baseline and a − 1 if the change was a decrease of 23 m or decrease of 10% from baseline. Total MDRI was the sum of these 6 domain scores. Though fatigue was not a component of the MDRI, a MID of ≥10 point change from baseline in total fatigue score was provided to help assess clinically meaningful changes in fatigue.

Each subject was assigned an individual clinical response (ICR) assessment by their investigator at the beginning of the blind-start study. The ICR was determined by what signs or symptoms impacted the subject's daily life the most and then the answers were mapped to the

appropriate clinical outcome.

Due to the rarity of MPS VII and the small number of subjects in this trial, individual patient data will not be shared in order to safeguard patient privacy.

## 3. Results

### 3.1. Disposition & baseline characteristics

All 12 subjects completed the Phase 3 blind-start study, enrolled in the long-term, open-label, extension study, and were included in the efficacy and safety analysis (Fig. 1). Two subjects enrolled in the long-term extension study following a 13-month delay (hiatus from vestronidase alfa) after completing the Phase 3, blind-start study. Three subjects (25%) completed all 144 weeks of the long-term extension study, eight subjects (67%) ended study participation before Week 144 to switch to commercially available vestronidase alfa as is typical when a drug under investigation receives regulatory approval, and one subject was non-compliant with study treatment after the first dose and discontinued vestronidase alfa treatment. The latter subject is still included in this study analysis. Of the eight subjects who switched to commercially available vestronidase alfa, two subjects had their last dose at Week 40, five subjects had their last dose between Weeks 102 and 114, and one subject had their last dose at Week 138.

The duration of exposure to vestronidase alfa in both the blind-start and extension study combined ranged from 49 to 185 weeks (Fig. 1). A total of 90% of the planned vestronidase alfa volumes were infused during the study. Five subjects missed more than two doses, but no subject missed more than four doses, except for the one subject who received only 1 dose of vestronidase alfa in the extension study and discontinued due to non-compliance.

Baseline characteristics from the primary Phase 3 study are reported in Harmatz et al. and Haller et al.; briefly, of the 12 enrolled subjects, a majority were female (8 subjects), white (9), and < 18 years-old at the start of the extension study (7) [9,10].

### 3.2. Safety

Overall, the safety profile of vestronidase alfa in the extension study was similar to previous observations in the blind-start study, with most

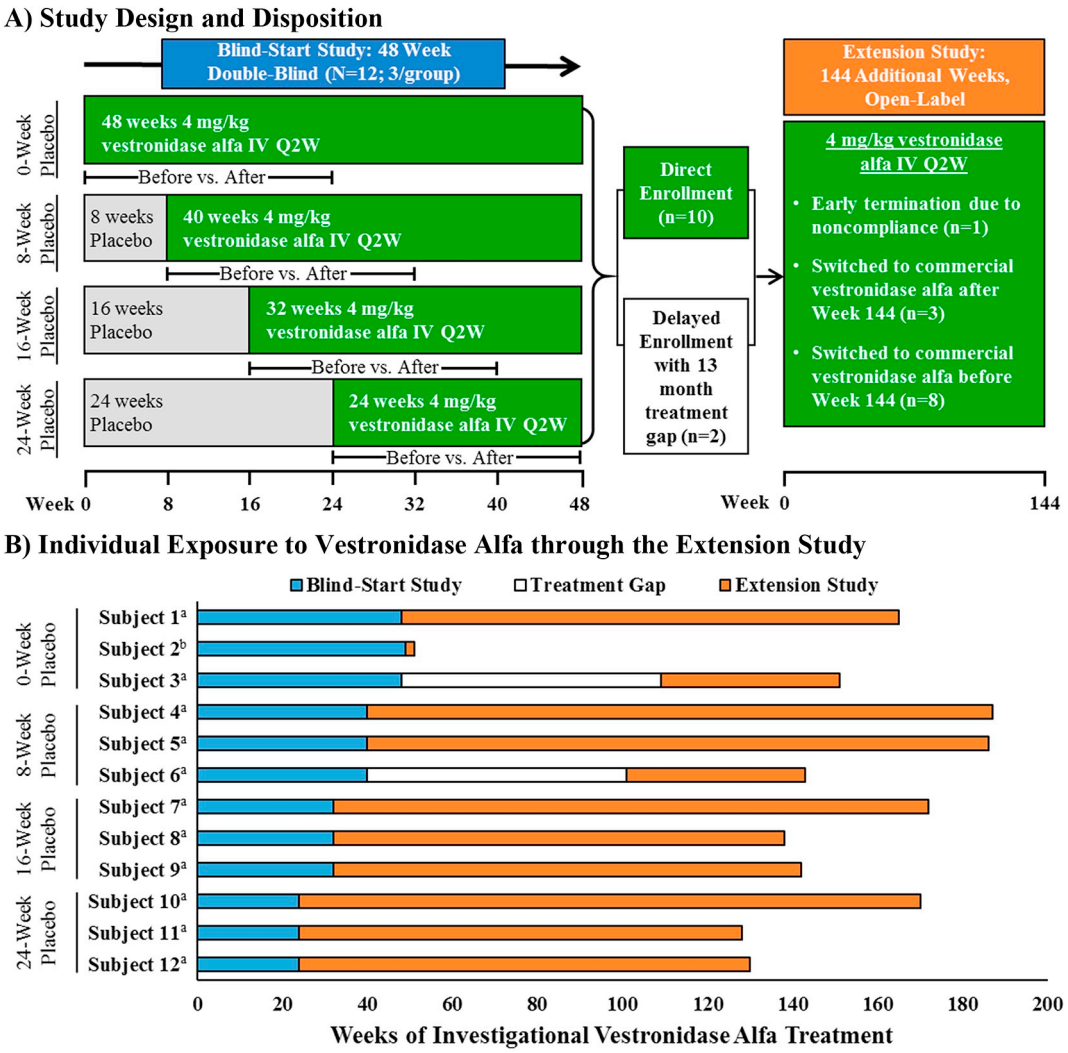


**Fig. 1.** Phase 3 blind-start study and extension study.
A) Study design and disposition.
B) Individual exposure to vestronidase alfa through the extension study.
[a]Switched to commercially available vestronidase alfa treatment. After receiving regulatory approval, it is common practice for clinical trials investigating the efficacy and safety of an investigational product to close and participants in the trial transition to the commercially available product. The sponsor continues to monitor the safety of the approved drug, as required by regulatory authorities, often through long-term observational studies. There is no difference in the manufacturing of vestronidase alfa used in the clinical trial and commercially available vestronidase alfa. [b]Discontinued due to non-compliance.

**Table 1**
Safety summary from extension study UX003-CL202.

| | Vestronidase alfa (***N*** = 12) n (%) |
|---|---|
| Number of subjects with AEs | 12 (100.0) |
| Number of subjects with serious AEs | 3 (25.0) |
| Number of subjects with treatment-related AEs | 9 (75.0) |
| Number of subjects with treatment-related serious AEs | 1 (8.3) |
| Number of subjects with grade 3 or 4 AE | 3 (25.0) |
| Number of subjects with AEs leading to treatment discontinuation | 0 (0.0) |
| Number of subjects with AEs leading to study discontinuation | 0 (0.0) |
| Number of subjects with AEs leading to death | 0 (0.0) |
| Most commonly reported AEs (> 1 subject) | |
| Upper respiratory tract infection | 7 (58.3) |
| Infusion site extravasation | 5 (41.7) |
| Urticaria | 5 (41.7) |
| Cough | 4 (33.3) |
| Vomiting | 4 (33.3) |
| Gastrooesophageal reflux disease | 3 (25.0) |
| Nasal congestion | 3 (25.0) |
| Rhinitis | 3 (25.0) |
| Arthralgia | 2 (16.7) |
| Bronchospasm | 2 (16.7) |
| Conjunctivitis allergic | 2 (16.7) |
| Diarrhoea | 2 (16.7) |
| Ear infection | 2 (16.7) |
| Ear pain | 2 (16.7) |
| Head injury | 2 (16.7) |
| Headache | 2 (16.7) |
| Infusion site swelling | 2 (16.7) |
| Lethargy | 2 (16.7) |
| Ligament sprain | 2 (16.7) |
| Nasopharyngitis | 2 (16.7) |
| Nausea | 2 (16.7) |
| Oedema peripheral | 2 (16.7) |
| Otitis media acute | 2 (16.7) |
| Pain in extremity | 2 (16.7) |
| Pollakiuria | 2 (16.7) |
| Pyrexia | 2 (16.7) |
| Rash | 2 (16.7) |
| Rash papular | 2 (16.7) |
| Rhinitis allergic | 2 (16.7) |
| Rhinorrhoea | 2 (16.7) |
| Skin abrasion | 2 (16.7) |
| Upper respiratory tract congestion | 2 (16.7) |

adverse events (AEs) mild (Grade 1) or moderate (Grade 2) in severity. All 12 subjects experienced an AE. The most commonly reported AE was upper respiratory tract infection, occurring in 7/12 (58%) subjects (Table 1).

Nine subjects had at least one AE considered related to treatment by the investigator: four subjects with an infusion site extravasation, three subjects with urticaria, and one subject each for erythema, macule, papule, rash maculo-papular, rash papular, rash pruritic, bronchospasm, eosinophilia, headache, infusion site swelling, joint swelling, sensory disturbance, and tooth loss. Infusion-associated reactions, defined as an AE occurring up to four hours following the end of an infusion, occurred in seven (58%) subjects and were mild to moderate in severity. All infusion-associated reactions resolved without intervention, except urticaria and bronchospasm that occurred in one subject who received medication for their symptoms.

No deaths, AEs categorized as life-threatening (Grade 4), or discontinuations due to AEs occurred. Four subjects experienced serious AEs: asthmatic crisis, bronchospasm, interstitial lung disease, gastroenteritis, head injury, headache, and urticaria. The serious AEs of bronchospasm and urticaria occurring in one subject were considered related to treatment by the investigator; these events resolved within 24 h and did not impact the administration of vestronidase alfa.

There were no clinically meaningful changes in vital signs and the safety laboratory panels – hematology, chemistry, and urinalysis. At baseline in the blind-start study, six (50%) subjects tested positive for anti-drug antibodies; of these six, three tested positive (i.e. expressed a titer greater than what they had at baseline) at a post-baseline assessment during the combined blind-start and extension study. Of the six (50%) subjects who were negative for anti-drug antibodies at baseline in the blind-start study, one subject remained negative and five tested positive at least once during the combined blind-start and extension studies. Out of the eleven subjects who tested positive at any point during the blind-start or extension study, including the baseline assessment, seven subjects tested positive for neutralizing antibodies; these seven subjects still demonstrated a sustained decrease in urinary GAG excretion with vestronidase alfa.

### 3.3. Efficacy

Reductions in urinary GAG levels observed in the 48-week, Phase 3, Blind-start study were sustained in subjects receiving vestronidase alfa in this long-term extension study (Fig. 2). In this extension study, mean ± SD urinary GAG DS level, including the two subjects who were off treatment for 13 months, was 1.55 ± 0.41 g GAG/g creatinine at blind-start study baseline ($N$ = 12), 0.57 ± 0.23 g GAG/g creatinine at extension study Week 0 ($N$ = 10), 0.68 ± 0.41 g GAG/g creatinine at extension study Week 48 ($N$ = 10), 0.25 ± 0.12 g GAG/g creatinine at extension study Week 96 ($N$ = 8), and 0.14 ± 0.04 g GAG/g creatinine at extension study Week 144 ($N$ = 4). The least squares (LS) mean ± SE percentage change in urinary GAG DS from the blind-start study baseline was −62% ± 5% ($N$ = 12) at Week 0 of the extension study and − 58% ± 7% ($N$ = 10) at Week 48 of the extension study. For the high urinary DS GAG excretor subgroup, the mean ± SD percentage change from baseline of urinary GAG DS level was −59% ± 21% at extension study Week 0 ($N$ = 6) and − 58% ± 19% at Week 48 ($N$ = 4). For low urinary DS GAG excretor subgroup, the mean ± SD percentage change from baseline of urinary GAG DS level was −65% ± 10% at extension study Week 0 (N = 6) and − 56% ± 28% at Week 48 (N = 6).

In this extension study, treatment with vestronidase alfa also resulted in sustained reduction of urinary GAG CS and HS levels. Mean ± SD urinary GAG CS level was 0.65 ± 0.25 g GAG/g creatinine at blind-start study baseline ($N$ = 12), 0.23 ± 0.16 g GAG/g creatinine at extension study Week 0 (N = 12), 0.27 ± 0.18 g GAG/g creatinine at extension study Week 48 ($N$ = 10), 0.19 ± 0.10 g GAG/g creatinine at extension study Week 96 ($N$ = 8), and 0.26 ± 0.08 g GAG/g creatinine at extension study Week 144 ($N$ = 4). The LS mean ± SE percentage change in urinary GAG CS from the blind-start study baseline was −62% ± 8% (N = 12) at Week 0 of the extension study and − 61% ± 5% (N = 10) at Week 48 of the extension study.

Mean ± SD urinary GAG HS level was 0.0098 ± 0.0042 ± g GAG/g creatinine at blind-start study baseline (N = 12), 0.0044 ± 0.0023 g GAG/g creatinine at extension study Week 0 (N = 12), 0.0075 ± 0.0039 g GAG/g creatinine at extension study Week 48 (N = 10), 0.0038 ± 0.0056 g GAG/g creatinine at extension study Week 96 (N = 8), and 0.0117 ± 0.0042 g/g at Week 144 (N = 4). The LS mean ± SE percentage change in urinary GAG HS from the baseline value in blind-start study was −51% ± 6% (N = 12) at Week 0 of the extension study and − 20% ± 10% (N = 10) at Week 48 of the extension study.

The mean ± SD MDRI score at the beginning of this extension study was +0.3 ± 0.8, reflecting improvement from the baseline in the Phase 3, blind-start study (Fig. 3). Sustained benefits in mean ± SD MDRI were observed in the extension study at Week 24 (+0.7 ± 1.0) and Week 48 (+0.9 ± 1.3). Only one subject showed a decline in one of the domains at Week 48 in the extension study, a reduction in the 6MWT which may have been due to challenges with comprehension as this subject had development delay and showed variable improvement in the 6MWT throughout the study. After Week 48, the MDRI score

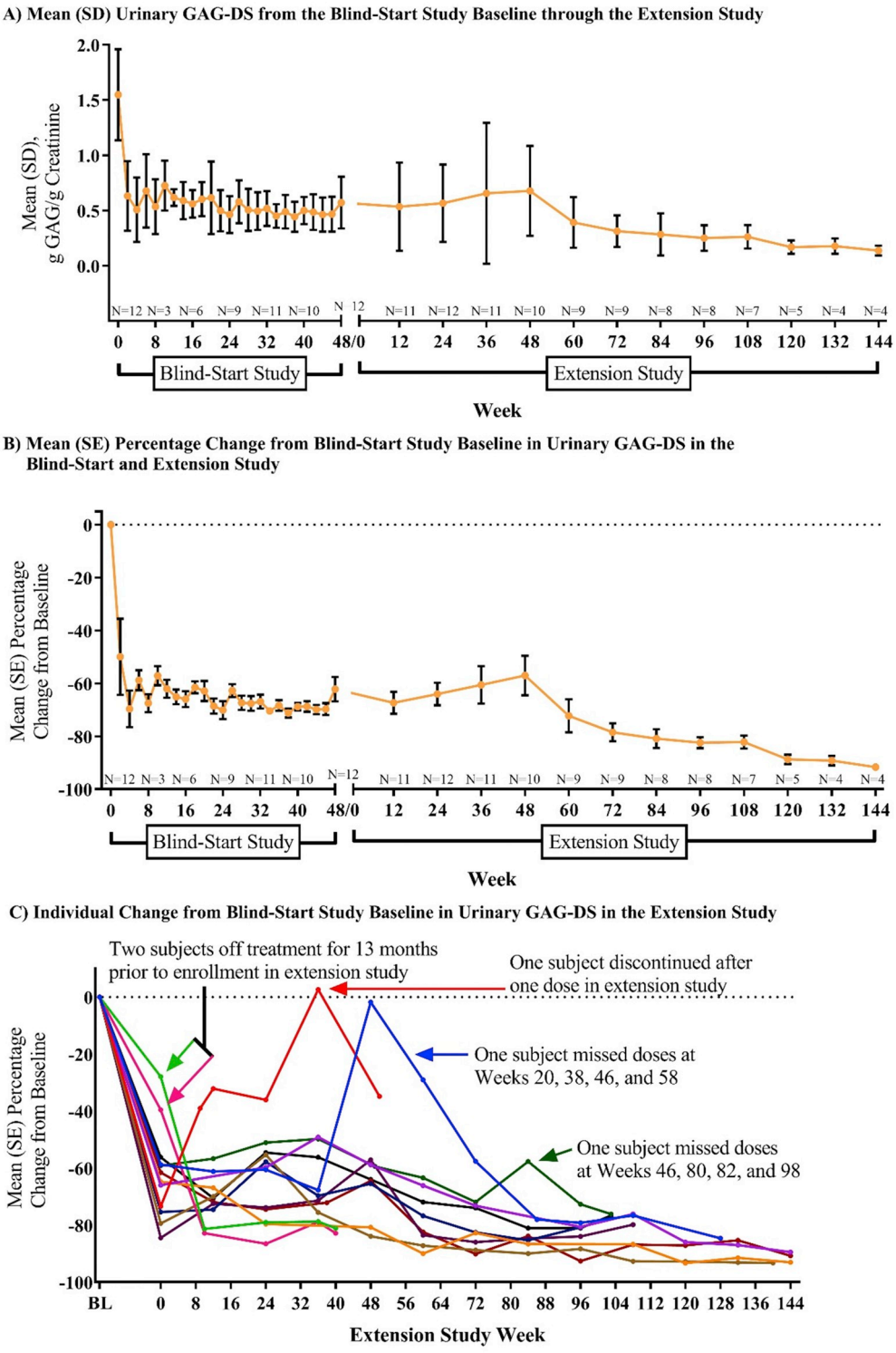


**Fig. 2.** Reduction in urinary GAG DS with vestronidase alfa.

included 4/6 assessments, as the BOT-2 assessments were not required beyond Week 48. Mean ± SD MDRI score was +0.5 ± 0.9 at Week 96 in eight subjects and + 0.3 ± 0.6 at Week 144 in 3 subjects.

Within the MDRI, only two subjects completed pulmonary function testing, both of whom showed little change from baseline in the blind-start study (blind-start study baseline: 88.0% and 81.0%; Week 104: 86% and 84%; Fig. 3). Shoulder flexion, which is more impaired in other types of MPS [21,22,24,25], showed no appreciable worsening (Fig. 3). Mean ± SD maximum range of motion was 138.7 ± 13.9° at baseline in the blind-start study ($N$ = 12), 139.7 ± 12.0° at Week 0 in the extension study (N = 12), 139.6 ± 16.1 at Week 48 in the extension study ($N$ = 11), 134.0 ± 19.1 at Week 96 in the extension study ($N$ = 8), and 126.7 ± 7.6 at Week 144 in the extension study ($N$ = 3).

BOT-2 scale scores for fine motor or gross motor skills remained stable (Fig. 3). The mean ± SE change from blind-start study baseline to Week 48 in the extension study for each scale score was 0.3 ± 0.47 for fine motor precision ($N$ = 7), −0.8 ± 0.53 for manual dexterity

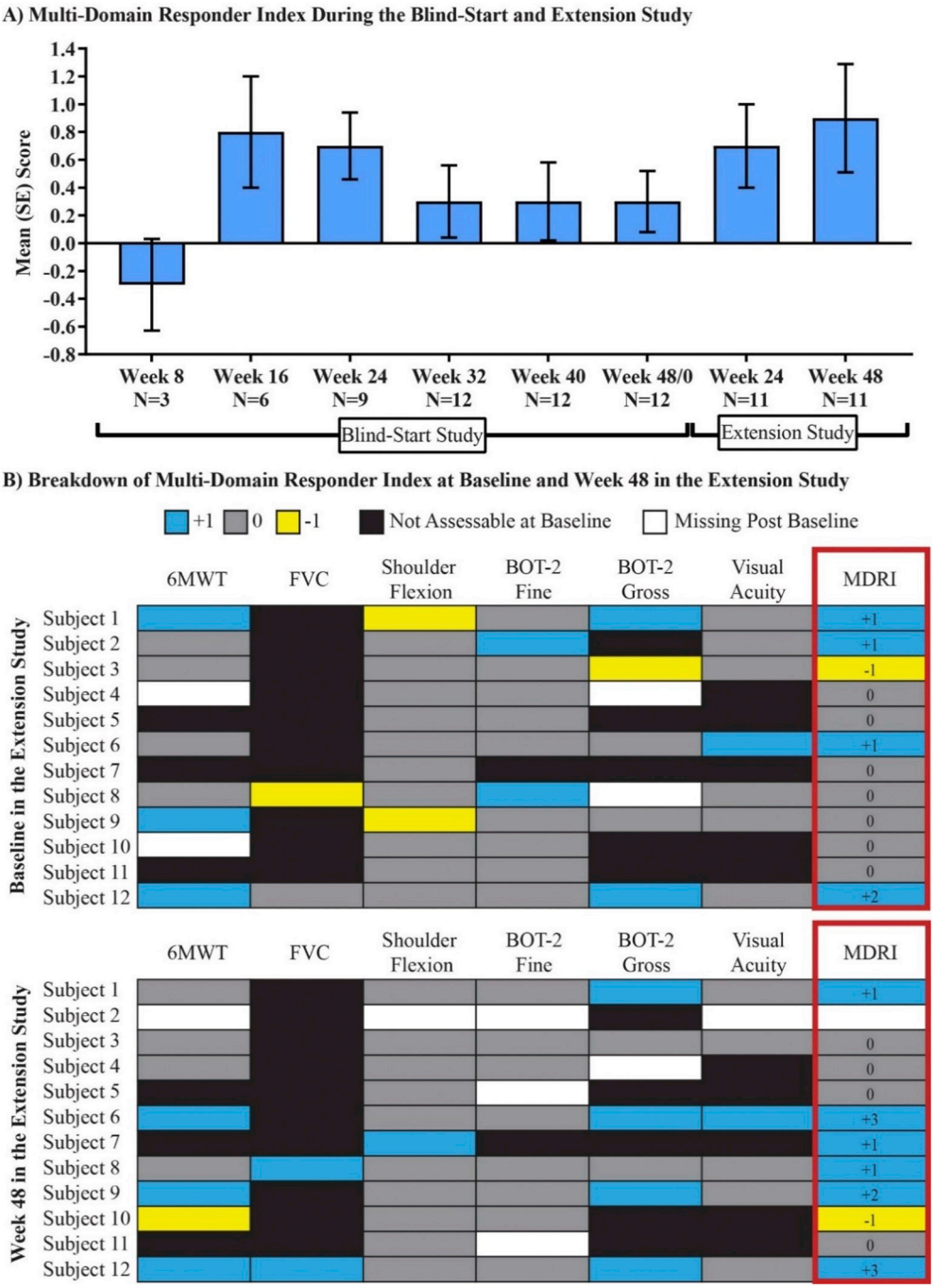


**Fig. 3.** Improvement in the MDRI with vestronidase alfa in the phase 3, blind-start and extension studies
6MWT, 6-min walk test; FVC, percent predicted forced vital capacity, BOT-2, Bruininks-Oseretsky Test of Motor Proficiency; MDRI, multi-domain responder index.

(N = 8), 0.2 ± 0.48 for balance (*N* = 6), and 0.3 ± 0.21 for running speed and agility (N = 6). For the one subject whose ICR assessment was the BOT-2 Fine Motor outcome, there was no change at baseline in the extension study and no data was collected for subsequent time points.

Visual acuity also remained stable with continuous vestronidase alfa treatment (Fig. 3). The mean ± SE change from blind-start study baseline to Week 48 in the extension study in the number of lines subjects were able to read on a standard eye chart, with letters on the first line being the biggest and the following lines showing increasingly smaller numbers, was 1.3 ± 0.76 lines for the left eye (uncorrected) and 1.2 ± 0.83 lines for the right eye (uncorrected).

Mean ± SD distance walked in the 6MWT was 259 ± 186 m (or 38% ± 25% predicted distance walked for age and sex) at baseline in the blind-start study (*N* = 9); 319 ± 202 m (45% ± 28%) at Week 0 in the extension study (*N* = 7); 308 ± 174 m (44% ± 23%) at Week 48 in the extension study (*N* = 8); and 349 ± 168 m at (50% ± 22%) Week 96 in the extension study (*N* = 5) (Fig. 4). 6MWT was the ICR assessment for seven out of 12 subjects. Four of these seven subjects achieved a clinically meaningful difference in the 6MWT at Week 24, Week 48 or both time points in the extension study; for the remaining three subjects, there was either no change or the evaluation was not conducted (Fig. 3).

Fatigue scores increased (improved) from baseline in the blind-start study, and improvements were sustained through the extension study (Table 2). Fatigue was the ICR assessment for four out of 12 subjects.

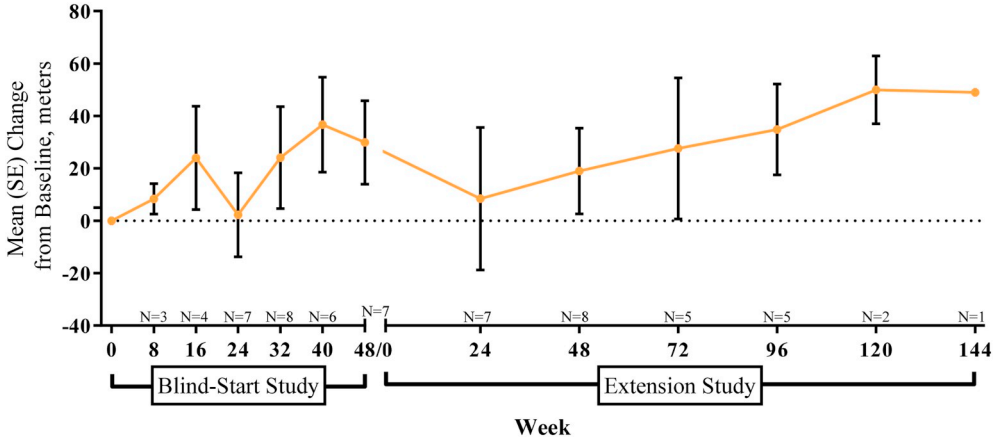


**Fig. 4.** Increases in distance walked in the 6MWT with vestronidase alfa in the phase 3 blind-start and extension studies.

During the extension study, out of these four subjects, two subjects achieved a clinically meaningful improvement in total fatigue score at Week 48; one subject achieved a clinically meaningful improvement at Week 24, but also showed decline at Week 48; and one subject achieved a clinically meaningful improvement at extension study Week 0 and no change at Week 24 and Week 48.

Liver and spleen size assessed via MRI or ultrasound was only assessed in seven of the 12 subjects in the blind-start study, showing no significant change during the course of the study. Only three of the eight subjects who had hepatosplenomegaly assessed by physical examination in the extension study also had blind-start study baseline assessments. Two of these subjects showed complete resolution. The remaining subject showed a reduction in liver size from 5 cm below the right costal margin at baseline in blind-start study to 1 cm at Week 144 in the extension study.

## 4. Discussion

All subjects in the Phase 3, blind-start, 48-week study showed a decrease in urinary GAG levels with minimal safety concerns and enrolled in the long-term extension study. The safety profile of long-term treatment with vestronidase alfa for up to 144 weeks in this extension study was consistent with the safety profile observed in the preceding, blind-start study. There were no treatment or study discontinuations due to AEs, and no new clinically significant safety findings occurred. There was no association between antibody formation and infusion associated reactions, and all three subjects who tested positive for neutralizing antibodies demonstrated a sustained reduction in urinary GAG level. Long-term treatment with vestronidase alfa resulted in sustained improvement in urinary GAG excretion, fatigue, and MDRI score which includes assessments for pulmonary function, motor function, range of motion, mobility, and visual acuity.

A few studies have evaluated the long-term ERT in MPS I, II, and VI [30–33]. In a 15-year continuation study, 104 subjects with MPS VI treated with long-term galsulfase ERT showed a lower mortality rate compared to 14 treatment naïve subjects (24% vs 57%) [33]. Similar results were obtained from the same population at the 10-year follow-up assessment, with a mortality rate of 17% in 103 subjects treated with ERT and 50% in 14 treatment naïve subjects. At follow-up, subjects with MPS VI receiving long-term ERT also showed a sustained decrease in urinary GAG level and increases in the walking ability, pulmonary function, and height (mostly in subjects under the age of 19 years) [31]. In a 10-year follow-up study in 35 subjects with MPS I, long-term treatment with laronidase ERT resulted in a sustained decrease in urinary GAG levels and maintenance in pulmonary function, walking ability, height, corneal clouding, and cardiac function [30]. Subjects that initiated treatment at younger ages (≤ 10 years) were able to sustain these clinical outcomes at levels closer to age-associated norms. Finally, in a retrospective chart review of 22 subjects with MPS II, all subjects demonstrated symptomatic improvement with two years of treatment with idursulfase ERT, including decreases in liver or spleen size, reduction in frequency of respiratory infections, and improvements in hair and/or skin texture. Several subjects showed improvement in joint range of motion and stabilization in skeletal and cardiac disease. Our findings are consistent with these studies suggesting that long-term ERT is associated with a sustained reduction in urinary GAG level and maintenance or improvement in disease-specific clinical manifestations.

While ERT has been shown to have benefits for MPS I, II, IV, VI and VII, it does not appear to have the ability to halt central nervous system (CNS) decline present in many MPS subtypes due to inefficient transport of lysosomal enzymes across the blood brain barrier [34]. At present, different approaches are explored for the treatment of neurodegeneration, including intrathecal ERT, gene therapy, enzyme-fusion proteins, translational read-through facilitated by small molecules, and others [35]. So far, no treatments have shown promise in modifying CNS manifestations and neurodegeneration remains an elusive target [36].

Neurological involvement in MPSs varies widely in frequency and severity of disease, with intellectual impairment more prominent in

**Table 2**
Improvement in fatigue scores with vestronidase alfa in the phase 3 blind-start and extension studies.

| Fatigue category | Blind-start study | Extension study | | | | |
|---|---|---|---|---|---|---|
| | Baseline (N = 12) | Week 0 (N = 12) | Week 24 | Week 48 (N = 11) | Week 96 (N = 9) | Week 144 (N = 4) |
| Cognitive | 55.8 (22.5) | 66.7 (21.6) | 63.6 (16.6) | 63.9 (20.8) | 69.4 (17.4) | 50.0 (35.5) |
| General | 65.4 (20.8) | 68.9 (20.0) | 72.8 (16.0) | 70.6 (22.0) | 74.8 (17.1) | 78.3 (22.5) |
| Sleep/rest | 72.0 (25.4) | 76.5 (20.8) | 79.0 (21.1) | 76.6 (23.3) | 71.8 (31.3) | 86.5 (11.6) |
| Total | 64.5 (15.9) | 71.3 (15.1) | 72.1 (14.2) | 70.9 (19.7) | 72.0 (16.8) | 71.5 (11.2) |

Data is presented as mean (SD). Increases in fatigue scores indicate a reduction in fatigue. The MID is a change from baseline in Total fatigue score ≥ 10 points.

MPS III and some cases of MPS I, II, and VII [37–39]. The most common neurological symptoms in MPS VII are limited vocabulary (94%) and mental retardation (86%) [4]. At baseline in the blind-start study, 83% of subjects in this study presented with history of a nervous system disorder. Cognitive disability, assessed by investigators without the requirement of age-relevant cognitive tests, ranged from mild to severe. This study did not focus on neurological symptoms, as ERT was not expected to cross the blood brain barrier and impact neurological symptoms. Addressing neurological symptoms remains an unmet medical need, even with ERT, for patients with MPS manifesting such impairments.

The effects of discontinuing ERT or missing a few doses in this study were observed in one and five subjects, respectively. For the subject that discontinued after their first dose of vestronidase alfa, the increase in urinary GAG level started immediately and reached pre-treatment levels before 40 weeks off-treatment. Similarly, there was a swift rise in urinary GAG level in the two subjects who missed four doses of treatment, even when these missed doses were non-consecutive. Additionally, the two subjects who enrolled 13 months late in the extension study from the blind-start study described wanting to re-start treatment in the extension study due to increased fatigue while off-treatment. These findings are consistent with observations of ERT discontinuation in other MPS types [40,41]. Out of five subjects with MPS II who discontinued idursulfase ERT for a median of three months, 80% had recurrent respiratory infections, 60% had difficulty walking/standing, and 40% had joint stiffness, decreased hematological parameters, and renal insufficiency; similar results were reported in a study of one MPS II subject and four MPS VI subjects. Symptoms increased with longer duration off-treatment. Together, such findings encourage stable use of ERT for the treatment of lysosomal storage diseases.

MPS VII is a rare disorder with high variability in disease manifestation and progression [10]. Due to the nature of this disease, this study is limited by the small number of subjects included, as well as the heterogeneity of disease manifestations and age of these subjects. Additionally, due to the variability in the presentation of symptoms, not all subjects could perform each assessment. Developmental delay, present in majority of patients, could have also interfered with comprehension required to complete some of the assessments. Nevertheless, data from the phase 3 blind-start and extension study represent the largest data for a randomized controlled clinical trial in MPS VII to date. Despite the heterogenous nature of MPS VII, sustained improvement in the MDRI and clinical outcomes suggest that subjects with MPS VII benefit from long-term treatment with vestronidase alfa. While not all subjects completed 144 weeks of the study, sustained improvement was observed for each subject's study duration overall.

## 5. Conclusions

Clinical assessments showed sustained improvement over time with continuation of vestronidase alfa treatment, despite significant baseline variability in disease severity and functional ability. Vestronidase alfa's safety profile in this extension study was consistent with previous observations in the blind-start study, with no fatal or life-threatening adverse events.

## Disclosures

RYW, JFdSF, JL-V, EM, VRS, CBW, and PH served as principal investigators for this study sponsored by Ultragenyx Pharmaceutical Inc. PH has been a consultant for BioMarin, Shire, Genzyme, Chiesi, Inventiva, Paradigm, Ultragenyx, SOBI, JCR, Denali, Orphazyme, RegenXbio, Aeglea, and Sangamo, he receive grants from BioMarin, payments (lectures, speakerships, honoraria) from BioMarin, Chiesi, Ultragenyx, and Orphazyme and travel, accommodations, and/or payments for meeting expenses from BioMarin, Shire, Genzyme, Chiesi, Inventiva, Ultragenyx, SOBI, and RegenXbio. LZ, TC, DM, and AJ are employees and shareholders of Ultragenyx Pharmaceutical Inc.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2020.01.003.

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# Update


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Corrigendum

# Corrigendum to "The long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis VII" [*Mol Genet Metab* 2020 Mar;129(3):219–227]

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We would like to correct the clinicaltrials.gov study registration number mentioned in the manuscript in several areas:

In the abstract, the NCT number mentioned and linked (NCT02377921) is incorrect. The sentence that reads "… completed a Phase 3, randomized, placebo-controlled, blind-start, single crossover study (UX003-CL301; NCT02377921) …" should instead read, "… completed a Phase 3, randomized, placebo-controlled, blind-start, single crossover study (UX003-CL301; NCT02230566) …

The link to the corrected NCT number should point to: https://clinicaltrials.gov/ct2/show/NCT02230566

The authors would like to apologize for any inconvenience caused.

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