



Short Communication

Open-label phase 1/2 study of vestronidase alfa for mucopolysaccharidosis VII

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ABSTRACT

Vestronidase alfa is an enzyme replacement therapy for mucopolysaccharidosis VII (MPS VII). In this open-label, phase 1/2 study, three subjects with MPS VII received intravenous vestronidase alfa administered every other week (QOW) for 14 weeks (2 mg/kg), followed by 24-week forced-dose titration (1, 4, and 2 mg/kg QOW; 8 weeks each), 36-week continuation (2 mg/kg), and long-term extension (4 mg/kg). Vestronidase alfa was well tolerated and led to dose-responsive, sustained reductions in urinary glycosaminoglycan excretion.

1. Introduction

Mucopolysaccharidosis type VII (MPS VII) is an ultra-rare, life-threatening, autosomal recessive lysosomal storage disorder caused by deficiency of β -glucuronidase that results in accumulation of glycosaminoglycans (GAGs) and tissue and organ dysfunction [1,2]. MPS VII is clinically heterogeneous, often presenting with hydrops fetalis, which may be fatal [3,4].

Vestronidase alfa (recombinant human β -glucuronidase) is an enzyme replacement therapy approved in the United States for the treatment of MPS VII in children and adults, in Europe for non-neurological manifestations of MPS VII, and in Brazil [5–7]. In a randomized, placebo-controlled, phase 3 study (N = 12), vestronidase alfa 4 mg/kg administered intravenously every other week (QOW) for 24 weeks significantly reduced urinary GAG (uGAG) excretion, and most subjects with MPS VII exhibited improvement in other clinical and patient-reported outcomes [8,9]. In the open-label, long-term extension, reductions in uGAG excretion were sustained, and treatment was well tolerated [10]. In the open-label, phase 1/2 first-in-human study, vestronidase alfa 1–4 mg/kg for the initial 38 weeks of treatment led to reduction in uGAG excretion in subjects with MPS VII [11]. We report the safety, optimal dose, and efficacy of vestronidase alfa through the long-term extension of the first-in-human study in subjects with MPS

VII.

2. Materials and Methods

UX003-CL201 (NCT01856218) was an open-label, phase 1/2 first-in-human study with a novel, ascending dose design to assess the safety, optimal dose, and efficacy of vestronidase alfa in subjects with MPS VII [11]. The study was conducted at three sites: Ege University Faculty of Medicine Children's Hospital, Bornova-Izmir, Turkey; Hospital Universitario Virgen del Rocío, Sevilla, Spain; and The NIHR/Wellcome Trust Clinical Research Facility, Manchester, UK. The inclusion criteria for subjects were aged 5–30 years with MPS VII confirmed by leukocyte or fibroblast glucuronidase enzyme assay or by genetic testing, elevated uGAG excretion ≥ 2 -fold greater than mean normal and provided written, and informed consent or consent by a legal representative before enrollment. Institutional review board approval was obtained for all study procedures. This work was performed in accordance with the Declaration of Helsinki.

The planned duration of intravenous vestronidase alfa treatment was 242 weeks. Phase 1 of the study consisted of a 14-week initial treatment period (2 mg/kg QOW), a 24-week forced-dose titration period (8 weeks each at 1, 4, and then 2 mg/kg QOW), and a 36-week continuation period (2 mg/kg QOW). These doses were selected to evaluate the

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Table 1
Summary of adverse events.

	Total (N = 3)
Subjects with any treatment-emergent AE, n (%)	3 (100)
Subjects with any treatment-related AE, n (%)	2 (67)
Subjects with any serious treatment-emergent AE, n (%)	2 (67)
Subjects with grade 3 or 4 treatment-emergent AEs, n (%)	2 (67)
Arthralgia (grade 3)	1 (33)
Cerebral ventricle dilatation (grade 3)	1 (33)
Spinal cord compression (grade 4)	1 (33)
Osteoarthritis (grade 3)	1 (33)
Subjects with grade 1 or 2 treatment-emergent AEs, n (%)	3 (100)
Allergic rhinitis	2 (67)
Cough	2 (67)
Diarrhea	2 (67)
Otitis media	2 (67)
Peripheral edema	2 (67)
Pharyngitis	2 (67)
Upper respiratory tract infection	2 (67)
Vomiting	2 (67)
Weight increased	2 (67)
Acute sinusitis	1 (33)
Anemia	1 (33)
Body temperature increased	1 (33)
Bronchospasm	1 (33)
Constipation	1 (33)
Decubitus ulcer	1 (33)
Dermatitis infected	1 (33)
Discomfort	1 (33)
Dizziness	1 (33)
Ear infection	1 (33)
Erythema	1 (33)
Gait disturbance	1 (33)
Generalized edema	1 (33)
Groin pain	1 (33)
Incarcerated inguinal hernia	1 (33)
Increased appetite	1 (33)
Increased viscosity of bronchial secretion	1 (33)
Infusion site extravasation	1 (33)
Inguinal hernia repair	1 (33)
Ligament sprain	1 (33)
Molluscum contagiosum	1 (33)
Musculoskeletal pain	1 (33)
Musculoskeletal stiffness	1 (33)
Myalgia	1 (33)
Nasal congestion	1 (33)
Nasopharyngitis	1 (33)
Nosocomial infection	1 (33)
Nystagmus	1 (33)
Oral mucosa erythema	1 (33)
Oropharyngeal pain	1 (33)
Papilloma	1 (33)
Pruritus	1 (33)
Pyrexia	1 (33)
Rash	1 (33)
Rash macular	1 (33)
Reflexes abnormal	1 (33)
Respiratory failure	1 (33)
Respiratory tract infection	1 (33)
Rhinorrhea	1 (33)
Seborrheic dermatitis	1 (33)
Skin abrasion	1 (33)
Tonsillitis	1 (33)
Tooth abscess	1 (33)
Toothache	1 (33)
Urinary tract infection	1 (33)
Viral rash	1 (33)
Visual field defect	1 (33)

AE, adverse event.

differences in treatment response (ie, change in uGAG excretion). The forced-dose titration was performed after the initial treatment period to allow stabilization of any immune response during the first 14 weeks of exposure. In the phase 2 portion (the long-term extension), subjects could continue for up to 168 weeks (4 mg/kg QOW).

Primary objectives were the incidence and severity of adverse events

Table 2
Summary of Vestronidase Alfa Pharmacokinetic Parameters at Week 28.

	C_{max} ($\mu\text{g}/\text{mL}$)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC_{0-inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	CL (L/h/kg)	V_{ss} (L/kg)
Subject 1	10.7	4.08	1.41	30.5	33.5	0.119	0.262
Subject 2	11.3	4.23	1.52	37.9	40.6	0.099	0.179
Subject 3	18.0	4.27	1.03	55.3	57.8	0.069	0.116
Mean	13.3	4.19	1.32	41.3	44.0	0.096	0.186
SD	4.05	0.10	0.26	12.7	12.5	0.025	0.073
Geometric mean	13.0	4.19	1.30	40.0	42.8	0.093	0.176
CV%	29.1	2.3	20.9	30.8	28.2	28.2	42.6

AUC_{0-inf} , area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t} , area under the plasma concentration-time curve from time zero to the time of last measurable concentration; CL, clearance; C_{max} , maximum plasma concentration; CV, coefficient of variation; SD, standard deviation; t_{max} , time to maximum plasma concentration; $t_{1/2}$, elimination half-life; V_{ss} , apparent volume of distribution at steady-state.

(AEs) and serious AEs per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and uGAG excretion normalized to urinary creatinine concentration by LC-MS/MS (Greenwood Genetic Center, Greenwood, SC) and nonreducing ends (NRE) method (ARUP Laboratories, Salt Lake City, UT). Pharmacokinetics of vestronidase alfa QOW was an additional objective.

3. Results

Between November 2013 and February 2014, three subjects aged 5.5 years (male), 9.4 years (female), and 25.1 years (male) were enrolled; all received vestronidase alfa [11]. The two pediatric subjects were diagnosed as infants; the adult subject was diagnosed at 5 years of age. All subjects completed the study through week 38 and continued in long-term follow-up through weeks 118, 132, and 124, respectively. Treatment compliance across the study was 89% (60 infusions), 91% (67 infusions), and 96% (63 infusions), respectively.

All three subjects experienced mostly mild to moderate treatment-emergent AEs considered unrelated to treatment (Table 1). Two (67%) subjects experienced grade ≥ 3 treatment-emergent AEs (grade 3, $n = 3$; grade 4, $n = 1$). The 5.5-year-old male experienced grade 3 arthralgia from weeks 38 to 72, grade 3 cerebral ventricle dilatation from weeks 86 to 92, and grade 4 spinal cord compression from weeks 84 to 91. The 25.1-year-old male experienced grade 3 osteoarthritis from weeks 59 to 85. Two (67%) subjects each experienced one treatment-related AE. The 9.4-year-old female experienced treatment-related grade 1 weight increase from week 28 to end of study, and the 25.1-year-old male experienced treatment-related grade 1 pruritus during week 22.

Two subjects experienced a total of eleven serious AEs during the study (Table 1). The serious AEs experienced by the 5.5-year-old male were unrelated grade 2 spinal cord compression (week 60) that resolved, unrelated grade 1 peripheral edema (weeks 77–80) that resolved, four occurrences of unrelated grade 1 incarcerated inguinal hernia (weeks 78, 80, and 81) that were resolved, unrelated grade 1 inguinal hernia repair (week 84), unrelated grade 4 spinal cord compression (weeks 84–96) that resolved with sequelae, and unrelated grade 3 cerebral ventricular dilatation (week 86–91) that resolved. The grade 4 spinal cord compression, which occurred during the long-term extension and resolved after spinal cord decompression surgery, was the only AE causing treatment interruption during the study. The serious AEs experienced by the 25.1-year-old male were unrelated grade 2 osteoarthritis (weeks 45–85) and unrelated grade 3 left coxarthrosis (weeks 59–85), both of which resolved. There were no study discontinuations or deaths due to AEs.

Intrasubject and intersubject pharmacokinetic parameters varied due to the small sample size (Table 2). Vestronidase alfa was detectable in serum at the earliest assessed timepoint after the beginning of the

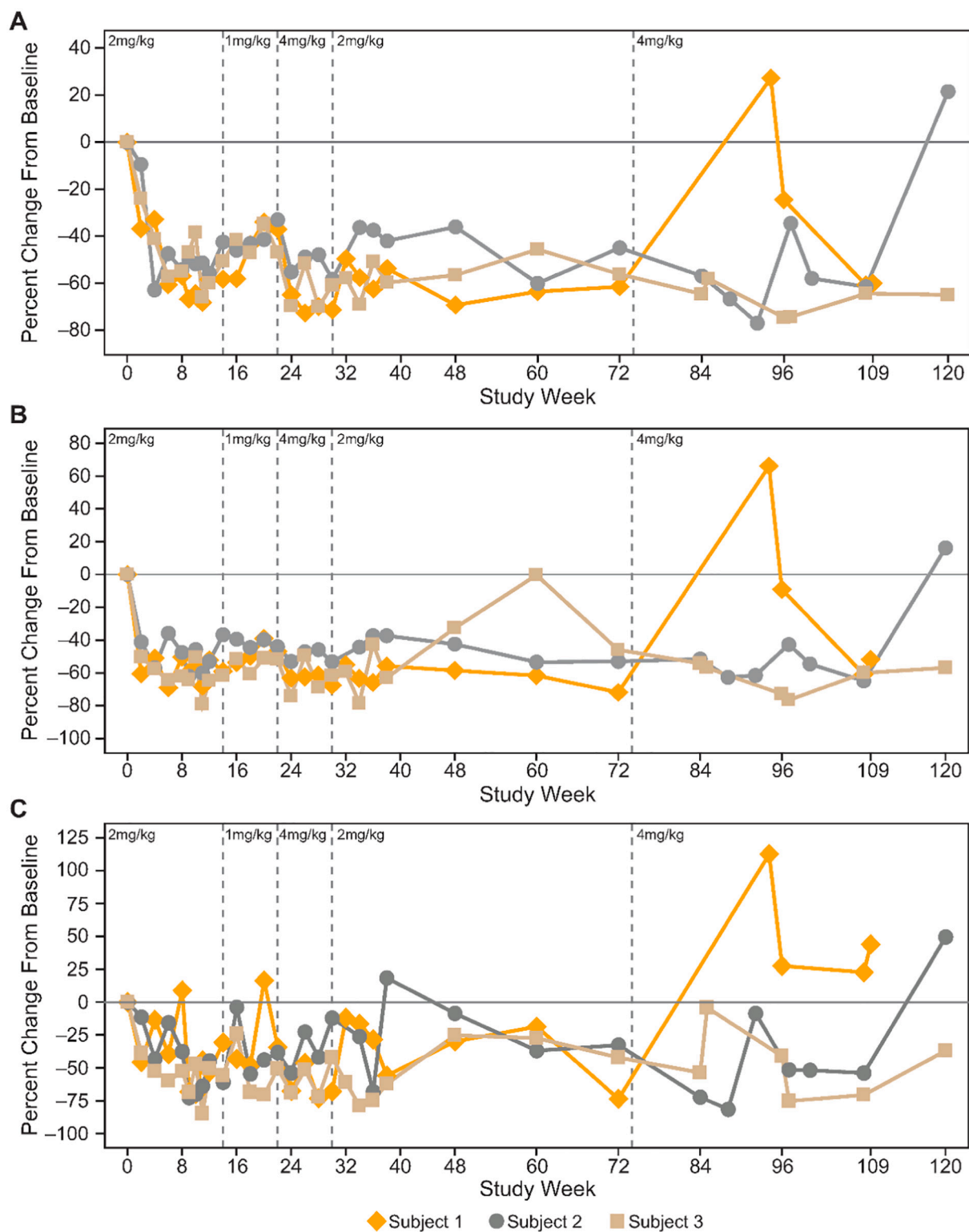


Fig. 1. Percentage change from baseline to week 120 in uGAG dermatan sulfate (A), chondroitin sulfate (B), and heparan sulfate (C) excretion by LC-MS/MS. Brief increases in uGAG excretion may have resulted from missed doses of vestronidase alfa, which occurred at weeks 88, 90, and 92 for Subject 1 (due to surgery), at weeks 74, 96, 188, and 122 for Subject 2 (reasons not given), and at weeks 112 and 116 in Subject 3 (reasons not given). Data through week 40 were previously reported by Cadaoas J, et al. *Mol Genet Metab.* 2020;130:65–76 [11]. uGAG, urinary glycosaminoglycan.

infusion (1 h) and reached maximum concentrations by approximately the end of the infusion (4 h). Following infusion, vestronidase alfa concentrations declined multi-exponentially. All pre-dose concentrations were below the limit of quantitation, indicating no accumulation with repeated QOW dosing. The mean half-life of vestronidase alfa

ranged from 1.3 to 1.9 h, mean clearance ranged from 0.10 to 0.25 L/h/kg, and the estimated volume of distribution ranged from 0.19 to 0.75 L/kg.

During the initial 38 weeks of treatment, reduction of uGAG excretion was rapid and sustained (Fig. 1), including during the 24-week

forced-dose titration period, where reduction in uGAG excretion was dose-responsive [11]. Mean reductions in dermatan sulfate (DS) and chondroitin sulfate (CS) were 42.2% and 47.7%, respectively, at 1 mg/kg QOW, 61.8% and 59.0% at 4 mg/kg QOW, and 52.4% and 54.8% at 2 mg/kg QOW [11]. During the 36-week continuation period (2 mg/kg), mean reductions of 54.8% and 46.7% in uGAG DS and CS, respectively, were maintained (Fig. 1). Excretion reduction was also maintained during the long-term extension except for brief increases corresponding with missed or interrupted dosing followed by re-treatment. Heparan sulfate (HS) was similarly reduced during treatment but to a lesser extent due, in part, to HS within the normal range at baseline. Results were consistent using the NRE method.

4. Discussion

In this open-label phase 1/2 study, intravenous vestronidase alfa QOW was generally well tolerated up to the maximum tested dose of 4 mg/kg, with most AEs being of mild or moderate severity. All three subjects received treatment in the long-term follow-up. No deaths or study discontinuations were attributed to AEs, and there was one interruption of treatment due to an AE unrelated to treatment. Vestronidase alfa concentrations declined multi-exponentially following infusion, and there was no evidence of accumulation with QOW dosing. A pharmacokinetic-pharmacodynamic modelling study that included subjects in this study supported the vestronidase alfa dosing regimen of 4 mg/kg QOW [5,6,8,9,12].

Treatment with vestronidase alfa QOW led to rapid reductions in uGAG excretion of up to 61.8% of DS and 59.0% of CS in the forced-dose titration period [11]. Reductions in uGAG excretion were maintained in the 36-week continuation period and into the 168-week long-term extension. Mean reductions in DS and CS in the continuation period were 54.8% and 46.7%, respectively. Although interpretation of the safety and efficacy data in this study are limited by the heterogeneity, small sample size ($n = 3$), and change over time in clinical symptoms, these results were confirmed in a phase 3 study in which treatment with vestronidase alfa at 24 weeks led to significant decreases in uGAG excretion that were maintained for up to an additional 144 weeks [9,10].

5. Conclusions

In this open-label phase 1/2 study, intravenous vestronidase alfa administered QOW was well tolerated up to 4 mg/kg and led to reductions in uGAG excretion that were dose-responsive and sustained into the long-term extension phase in subjects with MPS VII. This study demonstrates the ability to achieve translatable results from small populations in an ultra-rare disease, and may therefore serve as a useful model for the assessment of therapies in other ultra-rare diseases.

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Declaration of Competing Interest

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