CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761047Orig1s000

CLINICAL REVIEW(S)

UNIFIED CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761,047
Priority or Standard	Priority
Submit Date(s)	March 16, 2017
Received Date(s)	March 16, 2017
PDUFA Goal Date	November 16, 2017
Division/Office	ODEIII/DGIEP
Review Completion Date	November 16, 2017
Medical Officer	Dina Zand, M.D.
Cross Discipline Team Leader	Kathleen Donohue, M.D.
Deputy Division Director	Dragos Roman, M.D.
Director of the Office of Drug Evaluation III	Julie Beitz, M.D.
Established Name	UX003/rhGUS
(Proposed) Trade Name	Mepsevii (vestronidase alfa)
Applicant	Ultragenyx
Formulation(s)	IV
Dosing Regimen	4 mg/kg by IV every other week
Applicant Proposed Indication(s)/Population(s)	Sly Syndrome
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Patients with a confirmed diagnosis of Mucopolysaccharidosis type 7 (MPS VII)

Table of Contents

Table of Tables

Table of Figures

Glossary

6MWT	Six-minute walk test
12MWT	Twelve-minute walk test
3MSCT	Three-minute stair climb test
3MWT	Three-minute walk test
AE	adverse event
BLA	biologics license application
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCRP	Division of Cardiovascular and Renal Products
DMC	data monitoring committee
DTOP	Division of Transplant and Ophthalmology Products
ECG	electrocardiogram
EMA	European Medicines Agency
ERT	enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FEV	forced expiratory volume
FVC	forced vital capacity
GAG	glycosaminoglycan
GCP	good clinical practice
GUSB	beta-glucuronidase gene
ICH	International Conference on Harmonization
ICR	Individualized clinical response
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LVMI	left ventricular mass index
M6P	mannose-6-phosphate
MDRI	multi-domain responder index

MedDRA	medical Dictionary for Regulatory Activities
MPS	mucopolysaccharidosis
MPS I	mucopolysaccharidosis type I
MPS II	mucopolysaccharidosis type II
MPS IVA	mucopolysaccharidosis type IVA
MPS VI	mucopolysaccharidosis type VI
MPS VII	mucopolysaccharidosis type VII
MPS-HAQ	MPS Health Assessment Questionnaire
MVV	maximum voluntary ventilation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NIHF	non-immune hydrops fetalis
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFT	pulmonary function test
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
QOW	Every other week
QW	Every week
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	standard of care
TEAE	treatment emergent adverse event
US	United States

1 Executive Summary

1.1. Product Introduction

Vestronidase alfa is an enzyme replacement therapy (ERT) for mucopolysaccharidosis type 7 (MPS VII), also known as Sly disease. Patients diagnosed with MPS VII are deficient in human beta-glucuronidase (GUS) activity. Vestronidase alfa is an engineered human beta-glucuronidase identical in amino acid sequence to endogenous GUS. The proposed proprietary name for vestronidase alfa is Mepsevii (previous names earlier in development: rhGUS or UX003). Consistent with FDA's naming convention for biologic products, vestronidase alfa will be the core name and vjbk will be the FDA-designated suffix. The Applicant proposes chronic administration of Mepsevii in patients with MPS VII. Vestronidase alfa is a new biologic and is produced by recombinant DNA technology in a Chinese hamster ovary cell line.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted clinical efficacy data on 17 patients with MPS VII, including 12 patients enrolled in a randomized start trial (Study 301), 3 patients in an open-label dose-ranging trial (Study 201), and 2 patients treated with vestronidase alfa on an expanded access protocol.

The demonstration of effectiveness of vestronidase alfa is based on several lines of evidence and data streams that incorporate pharmacological, biochemical, and clinical data. As such, it includes the following:

1. The current understanding of the etiology and pathophysiology of MPS VII.
2. The demonstrated identity of vestronidase (same structure as the missing endogenous enzyme).
3. The confirmation of pharmacological activity *in vivo.* Specifically, administration of vestronidase alfa was associated with substrate reduction (i.e., reduction in urinary GAGs) in 23 patients evaluated to date.
4. The identification of a dosing regimen that was associated with durable clinical

5. responses (ranging from 78 to 164 weeks) in 5 of 17 patients exposed. Given the current understanding of the clinical course of MPS VII, such changes are not expected to occur by chance alone.
6. The prior demonstration that ERTs in several other MPS disorders are effective therapies.

Several limitations were noted in the clinical development program of vestronidase alfa. The number of exposed patients was small due to the rarity of the disease and limited patient availability. Thus, it was not feasible to conduct a traditional, parallel group, placebo-controlled clinical trial. No formal developmental assessments were performed; however, there is evidence that all patients have a sufficient degree of cognitive impairment such that some clinical assessments were either infeasible or could be completed only sporadically, despite being specified in the protocol. Finally, there was insufficient information to assess if there is any relation between genotype and the development of immunogenicity in MPS VII patients.

The decrease in urinary glycosaminoglycan (uGAG) levels in all patients treated with vestronidase alfa establishes that the selected dose is pharmacologically active and provides supportive evidence for the observed clinical effects.

Because systematic natural history data have not been obtained for MPS VII, formal comparisons to a historical cohort were not feasible; however, the clinical course of the disease is progressive and improvements are not anticipated to occur spontaneously. While clinical efficacy study data are consistently available only for a period of 12 months, evidence of durability of response was also substantiated by two patients treated in Study 201 and in an expanded access protocol, respectively. One adult enrolled in the phase ½ Study who received vestronidase alfa for 120 weeks and underwent bilateral hip replacement demonstrated clinically significant improvement in % predicted FVC (21%) and 6MWT (105 meters). Importantly, another patient with impending respiratory failure received vestronidase alpha via expanded access and had reduced need for mechanical ventilation after 164 weeks of treatment.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Vestronidase alfa, a recombinant human β-glucuronidase (GUS), has been evaluated as a new enzyme replacement therapy (ERT) for the treatment of Mucopolysaccharidosis type VII (Sly disease), a rare autosomal recessive lysosomal storage disorder caused by mutations in the GUSB gene. MPS VII is a slowly progressive disease that is universally fatal. Vestronidase alfa is infused intravenously and binds to mannose-6-phosphate receptor and subsequently is internalized to the lysosomes to act as a hydrolytic lysosomal glycosaminoglycan-specific enzyme that catalyzes the hydrolysis of beta-D-glucuronic acid residues.

There have been less than 150 reports of MPS VII worldwide. Clinical manifestations can present *in utero* as non-immune hydrops fetalis (NIHF) and progress to features like those noted in other mucopolysaccharidoses such as skeletal dysplasia (dysostosis multiplex), cardiac pathology and respiratory compromise related to tracheal dysplasia, airway obstruction and pulmonary insufficiency. Almost all patients with MPS VII have moderate to severe cognitive disability. Children diagnosed with NIHF may die within the first year of life. Others can live until the third decade. There is no approved disease-modifying therapeutic agent for MPS VII and current disease management is supportive only.

Given the rarity of MPS VII, the clinical program for MEPSEVII included 23 patients with MPS VII, 17 of whom were evaluable for efficacy, 20 for safety, and 23 for immunogenicity. Patients were enrolled in clinical trials and expanded access protocols receiving treatment at doses up to 4 mg/kg once every two weeks for up to 164 weeks. The patients ranged in age from 5 months to 25 years. Sixteen patients were younger than 18 years of age. Treatment duration ranged from 24-48 weeks in Study 301, to 142-164 weeks for the patients treated in expanded access INDs (eINDs).

The Division of Gastroenterology and Inborn Errors Products recommends approval of vestronidase alfa for patients diagnosed with MPS VII, based on the following clinical and biochemical considerations: 1) the current understanding of the pathophysiology of MPS VII, 2) the mechanism of action of the drug, 3) the finding of durable clinical responses (ranging from 78 to 164 weeks) in 5 of 17 patients evaluated, 4) evidence of substrate reduction as measured by reduction in urinary GAGs in all patients, and in liver and spleen size in some, consistent with the known mechanism of action of vestronidase alfa, 5) the prior demonstration that ERTs can be effective as replacement therapy in other MPS disorders, and 6) manageable toxicity that appears similar to other ERTs. The effects on clinical improvement and substrate reduction would not be anticipated in the absence of treatment. The Office of Drug Evaluation III concurs with this recommendation. The recommended dosage is 4 mg/kg vestronidase alfa administered as an intravenous infusion over 4 hours every other week.

An FDA Advisory Committee Meeting was not held to discuss this application.

The most compelling evidence of a treatment effect was observed in 4 of the 17 patients exposed to vestronidase alfa, and the treatment effect appeared to be related to duration of exposure. The treatment response observed in these four subjects is described below; patients are listed in the order from the longest to shortest duration of treatment:

- Reduced need for mechanical ventilation in a 12-year-old male patient who initiated treatment under eIND for impending respiratory failure (164 weeks exposure).
- Improvement in 6-minute walk test (6MWT) of 105 meters (*285 meters to 390 meters*) from baseline to week 120 in a 25-year-old male patient that also experienced an improved 21 % predicted FVC (Study 201; Patient A3; 120 weeks' exposure).
- Improvement in 6MWT of 83 meters (*300 meters to 383 meters*) in a 15-year-old female patient with the Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT-2) gross motor assessments that were qualitatively supportive (Study 301, Patient C1; 120 weeks' exposure)
- Improvement in 6MWT of 65 meters (*455 meters to 520 meters*) and in BOT-2 gross motor performance in a 25-year-old male patient that were qualitatively supportive (Study 301, Patient C8; 80 weeks exposure).

A fifth patient may have also demonstrated a treatment effect. This 17-year-old female patient was unable to complete baseline testing. However, she could complete two 6MWT evaluations after 8 weeks and 80 weeks exposure to vestronidase alfa and increased her distance by 73 meters (*96 meters to169 meters*) over this period during Studies 301/202 (Patient C6). A longer duration of exposure may be needed to determine if this effect is sustained in this patient.

With the caveat that this is a very small clinical program, the patients who responded best to treatment tended to be older and female. Duration of observation of the clinical response ranged from 24 to 164 weeks. As patients were still receiving treatment as of the data cut-off date, one cannot assess whether patients could improve further or whether they reached the maximum clinical response under the current treatment. The magnitude of improvement in 6MWT observed in these patients was similar to that demonstrated with ERTs for other MPS disorders. The improvements in 6MWT and BOT-2 gross motor performance should be considered in the context of disease-related cognitive disability which was present in all patients. Cognitive disability significantly impacted each patient's ability to comply with other efficacy measures, e.g., tests of forced vital

capacity.

The safety dataset included a total of 20 pediatric and adult MPS VII patients treated with vestronidase alfa in the clinical development program. Nineteen of the patients evaluated in the safety dataset received vestronidase for at least 12 months, and four of those patients received it for at least 24 months, all at a dose of 4 mg/kg dose. The data evaluable from Study 301 and open label extension Study 202 ranged from 48 weeks to 120 weeks of exposure to vestronidase alfa. Data evaluable from Study 201 was up to 120 weeks exposure and expanded access INDs offered evaluable data up to 164 weeks of exposure to vestronidase alfa.

Similar to other approved ERTs for mucopolysaccharidoses, anaphylaxis emerged as an important safety signal. Otherwise, treatment with vestronidase alfa was well tolerated by patients with MPS VII. The most commonly reported adverse events were infusion site extravasation, diarrhea, emesis, rash, extremity pain or arthralgia and pyrexia. Other adverse events included rhinorrhea, edema, pruritus, abdominal pain and urticaria.

The safety risks associated with vestronidase alfa in patients with MPS VII can be adequately communicated through appropriate product labeling and further monitored via routine postmarketing pharmacovigilance. Prescribers of vestronidase alfa will likely be practitioners with expertise or experience in the management of lysosomal storage diseases such as MPS VII. As an enzyme replacement therapy, infusion of vestronidase alfa was associated with both hypersensitivity reactions (40% of subjects) and anaphylaxis (10% of subjects). Therefore, infusions will be administered in hospital settings that can monitor for and treat anaphylaxis.

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for vestronidase alfa. A required postmarketing safety study will 1) evaluate the long term immunogenic potential of vestronidase alfa, including the development of anti-drug antibodies (including any potential correlation between antibody formation, response to treatment, and the rate of adverse events, specifically hypersensitivity adverse events), and 2) assess the relationship between of genotype and the occurrence of anaphylaxis in patients followed for a minimum of 3 years. A nonclinical study to assess the effects of vestronidase alfa on pre- and post-natal development in rats will also be required.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MPS VII, also called beta-glucuronidase deficiency or Sly syndrome, is a rare and progressive lysosomal storage disease for which there is no current therapy. Clinical presentation can begin in utero with non-immune hydrops fetalis (NIHF). Those patients who survive the neonatal period develop multiple clinical manifestations such as coarsened facial feature, joint stiffness, dysostosis multiplex, short stature, moderate to severe neurocognitive disability, pulmonary disease, cardiomyopathy and valvular disease. While the natural history of disease is not sufficiently documented, most patients die before the second or third decade of life due to cardiorespiratory compromise.	• MPS VII is a rare, progressive disease associated with significant morbidity and early death. • While there are some similarities in clinical features to other mucopolysaccharidoses such as bone and tracheal dysplasia, there are also significant differences. The degree of cognitive disability in patients with MPS VII who were studied appears to be more significant than initially appreciated.
Current Treatment Options	• Currently, there are no approved therapies for patients with MPS VII. Treatment is symptomatic and supportive.	• There is a substantial unmet need for effective and safe therapies for patients with MPS VII.
Benefit	• Due to the rarity of MPSVII, only seventeen patients were evaluable for efficacy in the vestronidase alfa development program. • Patients who received intravenously administered vestronidase alfa and who could complete a	• Intravenously administered ERT can improve systemic manifestations of MPS VII in some patients ranging from 78 to 164 weeks. As patients continued to respond as of the cutoff date for this application, it is not known whether these patients would have continued

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	6MWT demonstrated a mean improvement of 18 meters after 24 weeks. Improvement in balance appeared to coincide with improvement on the 6MWT in some patients. • Assessment of other clinical measures, such as forced vital capacity, could only be sporadically performed due to the patients' disease-related cognitive disability and inability to perform the assessments. • Intravenously administered enzyme replacement therapy (ERT) can result in substrate reduction. Reduced excretion of urinary GAGs was noted in all 17 patients exposed; some patients were also noted to have reduced liver and spleen size. Sufficient evidence to support the conclusion that uGAG reduction alone predicts clinical benefit in this population is lacking at this time.	to improve on treatment. Longer follow-up of these patients is needed. • Intravenously administered ERT can result in substrate reduction, consistent with the mechanism of action of the drug. This observation supports the selected dosing regimen as being pharmacologically active. • The effects on systemic manifestations of disease and substrate reduction would not be anticipated in the absence of ERT.
Risk	• Due to the rarity of MPS VII, only twenty patients were evaluable for safety in the vestronidase alfa development program. • Anaphylaxis was observed in at least 10% • Infusion associated reactions (IAR) were observed	• The risks for IAR and anaphylaxis are within the reported spectrum of approved ERTs for other mucopolysaccharidoses. • A safety PMR will be required to further assess the product's long-term safety and determine the contribution of genotype and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in at least 40% • Intravenously administered ERT does not easily cross the blood brain barrier and therefore is not expected to affect neurologic manifestations of disease.	immunogenicity on the rates of anaphylaxis and hypersensitivity reactions.
Risk Management	• The identified risks associated with vestronidase alfa treatment can be handled through routine labeling.	• Vestronidase alfa is not suitable for home administration due to the risk of anaphylaxis. Labeling (including a Boxed Warning) will be sufficient to address the identified concerns.

2 Therapeutic Context

2.1. Analysis of Condition

Mucopolysaccharidosis type VII is a rare genetic disorder caused by autosomal recessive mutations in the β-glucuronidase gene (GUSB). The corresponding enzyme, β-glucuronidase, is a lysosomal hydrolase involved in the stepwise degradation of glucuronic acid-containing glycosaminoglycans. As assessed by the literature and the Applicant, an estimated 150 patients have been diagnosed with MPV VII since the initial report was published by Sly et al. (Sly, Quinton et al. 1973) Systemic deficiency of β-glucuronidase, as occurs in patients with MPS VII, results in the deposition of heparan sulfate, chondroitin 4-, 6-sulfate and dermatan sulfate, predominantly in connective tissues. Patients with MPS VII can present clinically *in utero* with non-immune hydrops fetalis (NIHF). Those patients who survive the neonatal period will usually present for diagnosis with clinical phenotypes similar to other mucopolysaccharidoses such as MPS I (Hurler syndrome) and MPS II (Hunter syndrome). Not all patients develop NIHF; however, the incidence of NIHF may also be underreported as patients with NIHF may not be ultimately diagnosed with MPS VII. There is a reported variability to the common findings on clinical exam (**Table 1**), but any combination of these clinical features may lead to a diagnosis of MPS VII in combination with molecular and biochemical testing.

Table 1: Common Clinical Findings in MPS VII

Feature	Description
Short stature	Skeletal dysplasia Dysostosis multiplex
Joint contractures	Restriction of movement Joint pain
Facial dysmorphia	Coarse facial features Macrocephaly Prominent forehead Short neck Broad nose Thickened lips
Respiratory insufficiency	Adenotonsillar hypertrophy Obstructive sleep apnea Tracheal dysplasia
Cardiac pathology	GAG deposition in valvular tissue, coronary arteries and arterioles
Abdominal features	Hepatosplenomegaly Umbilical or inguinal hernias
Ophthalmologic	Corneal clouding and cataracts
Audiologic	Sensorineural hearing loss
Development	Progressive motor and cognitive disabilities

Sources: Modified from https://rarediseases.org/rare-diseases/sly-syndrome/ Montano AM et al., J Med Genet. 2016 Jun; 53(6): 403–418.

Patient quality of life is impacted by limitations in movement due to contractures of small and large joints, spinal deformities and spinal stenosis. While not well studied, the pulmonary manifestations of MPS VII appear to be similar to MPS I and MPS II (Muhlebach MS, Wooten W et al. 2011). Upper airway obstruction can manifest as abnormal vocal cord shape, laryngomalacia, enlarged tonsils and adenotonsillar hypertrophy. Lower airway obstruction manifests as tracheomalacia, endobronchial lesions or infiltration of the submucosa and tracheal cartilage with both GAG deposition and inflammatory component. Restrictive lung volumes due to scoliosis and rib cage abnormalities can also be present. In addition, patients with MPS VII often have obstructive sleep apnea related to GAG deposition in adenoid and tonsillar tissues. Cardiac involvement occurs because of due to GAG deposition in both cardiac valves and muscle. The exact cause of fatigue in these subjects is not clear and may be a manifestation of pulmonary, cardiac or additional pathology related to GAG deposition. Moderate to severe cognitive disability presenting as delayed milestones and variable loss of acquired skills may be present in patients with MPS VII and can directly impact learning and

functional independence (Montano AM, Lock-Hock N et al. 2016).

Similar to other mucopolysaccharidoses, urinary analysis of patients with MPS VII demonstrates increased levels of the mucopolysaccharides dermatan sulfate, chondroitin sulfate and heparan sulfate. Confirmatory diagnostic testing via enzymatic evaluation of β-glucuronidase activity in leukocytes or fibroblasts and molecular analysis for mutations in the GUSB gene is pursued when clinical features are present.

MPS VII appears to affect all ethnicities. Currently there is insufficient information available to attempt genotype/phenotype correlation and there is no known founder effect for any ethnicity. The Applicant stated that of the mutations currently identified in the GUSB gene, the majority are missense mutations. The Applicant reviewed molecular analysis of 7 of 15 subjects with a MPS VII phenotype enrolled in their program. Eight of 15 subjects were reported to have biochemical analysis for residual enzymatic activity, and 6 of 15 were evaluated both molecularly and biochemically.[1] However, the biochemical results were not easily comparable as the testing was completed in different laboratories over a time span of at least 15 years. Subjects who participated in the vestronidase alfa development program did not require repeat diagnostic testing upon enrollment.

In review of a clinician based survey of patients from 11 countries, about 40% of subjects diagnosed with MPS VII presented with non-immune hydrops fetalis during pregnancy (Montano AM, Lock-Hock N et al. 2016). Of those patients with a known history of NIHF, 40% did not survive past infancy (**Figure 1**). Of the 46 patients with MPS VII, with or without a history of NIHF, who lived past infancy their post-natal clinical course appeared to be heterogeneous and slowly progressive. Life expectancy depends upon presentation, but patients with milder disease die by 20 or 30 years of age. Death is most frequently related to cardiopulmonary compromise.

Figure 1: Natural History of MPS VII

Source: Derived from Montano et al. Clinical course of Sly syndrome (mucopolysaccharidosis type VII). J Med Genet. 2016 June;53(6):403-18. PMID 26908836. Figure by DJ Zand.

[1] DARRTS, initial IND 123788 submission; October 10, 2014

2.2. Analysis of Current Treatment Options

Currently, there are no approved disease-specific treatment options for patients with MPS VII. Treatment is primarily supportive. Patients are typically followed by multiple pediatric specialists and often receive physical therapy, occupational therapy, and special education services. Despite diffuse skeletal involvement, some children can be independently mobile. There is a single report in the literature of a child who received hematopoietic stem cell transplant that resulted in improved motor function and activities of daily living, but there was no improvement in cognitive function (Yamada Y, Kato K et al. 1998). A study of allogeneic hematopoietic cell transplantation in patients with inherited metabolic disorders including mucopolysaccharidoses currently is enrolling, but this type of therapy poses great risk of mortality and is not specific to MPS VII pathology.[2]

As noted in **Table 2**, currently there are four approved enzyme replacement therapies (ERTs) for the treatment of other mucopolysaccharidoses: MPS I, MPS II, MPS IVA and MPS VI. All four of these approvals were based upon patient demonstrated improvement in either the six-minute walk test (6MWT) or twelve-minute walk test (12MWT). Evidence of improvement in the percent prediction of forced vital capacity (FVC) also supported ERT approval in patients with MPS I. In addition, patient improvement in three-minute stair climb testing (3MSCT) was additional evidence for approval of the ERT for MPS VI.

Table 2: Approved Drugs to Treat Mucopolysaccharidoses

Disease/Drug Approval Date	Dosage	Efficacy
MPS I Laronidase (Aldurazyme) 30 Apr 2003	0.58 mg/kg QW	Approved based upon results of placebo controlled trial with 45 patients aged 6 to 43 years with baseline percent predicted FVC ≤77%. This pivotal study was 26 weeks duration with improvement in 6MWT and FVC. <u>6MWT:</u> Mean ± SD: 319± 131m drug vs. 367± 114m placebo Mean ± SD at 26 Weeks: 339± 127m drug vs. 348± 129m placebo Difference in Change: 38m (observed) <u>FVC (% predicted)</u> Mean ± SD: 48±15 drug vs. 54±16 placebo Mean ± SD at 26 Weeks: 50±17 drug vs. 51±13 placebo) Difference in Change: 4 (observed) • Age < 6 months: unknown • Age 6 months to 5 years: unknown • Age ≤ 5 years: unknown; decrease in spleen and liver size • Age ≥5 years: Approved based upon results of 6MWT FVC

[2] https://clinicaltrials.gov/ct2/show/NCT02171104?term=MPS+VII&rank=10

Disease/Drug Approval Date	Dosage	Efficacy
MPS II Idursulfase (Elaprase) 24 Jul 2006	0.5 mg/kg QW	Approved based upon results of a randomized, placebo controlled trial with 96 patients ≥ 5 years three treatment groups, of 53 weeks duration and statistically significant results in the 6MWT but not FVC. <u>6MWT:</u> Mean± SD: 392±108 m drug vs. 393±106 m placebo Mean ± SD at 53 Weeks: 436±138 m drug vs. 400±106 m placebo Difference in Change: 37±16 m (observed) <u>FVC (% predicted)</u> Mean ± SD: 55.3±15.9 drug vs. 55.6±12.3 placebo Mean ± SD at 53 Weeks: 58.7±19.3 drug vs. 56.3±15.7 placebo Difference in Change: 2.7±2.5 (observed) • Age < 16 months: unknown • Age 16 months to 5 years: unknown; approval based on decrease in spleen size in 27 patients, confirmatory trial ongoing • Age ≥5 years: Approved based upon results of 6MWT FVC
MPS IVA Elosulfase alfa (Vimizim) 14 Feb 2014	2mg/kg QW	Approved based upon results of placebo controlled trial with 176 patients ages 5 to 57 years for 24 weeks duration. At baseline, all enrolled patients could walk more than 30 m but less than 325 m in six minutes. Approval was based upon improvement in 6MWT. No further improvement was seen after extension trial of 48 weeks duration. <u>6MWT:</u> Mean ± SD: 204±76 m drug vs. 212±70 m placebo Mean ± SD at 24 Weeks: 243±84 m drug vs. 225±83 m placebo Difference in Change: 23 m (observed) • Age < 6 months: unknown • Age 6 months to5 years: unknown • Age ≥5 years: Approved based upon results of 6MWT
MPS VI Galsulfase (Naglazyme) 31 May 2005	1mg/kg QW	Approved based upon results of placebo controlled trial with 39 patients aged 5-29 years with baseline 12- minute walk of 5-400 m. This pivotal study was 24 weeks duration with improvement in 12MWT and 3-minute stair climb (3MSC) <u>12MWT:</u> Mean ± SD: 227± 170 m drug vs. 381± 202 m placebo Mean ± SD at 24 Weeks: 336 ± 227m drug vs. 399± 217 m placebo Difference in Change: 83 ± 42 m (observed) <u>3MSC(stairs/minute)</u> Mean± SD: 19.4 ± 12.9 drug vs. 31.0 ± 18.1 placebo Mean ± SD at 24 Weeks: 26.9 ± 16.8 drug vs. 32.6 ± 19.6 placebo Difference in Change: 4.7 ± 2.8 (observed) • Age < 5 years: unknown • Age ≥5 years: Approved based upon results of 6MWT and 3MSC

Source: Drugs@FDA.com; Aldurazyme label, Elaprase label, Vimizim label, Naglazyme label.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Vestronidase alfa is a new biologic, currently not marketed in the United States or elsewhere. Vestronidase alfa is being developed solely for the treatment of patients diagnosed with MPS VII.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development program for vestronidase alfa was initiated (b) (4) Clinical investigations of vestronidase alfa in the US commenced under IND 123788, submitted on October 10, 2014. The pivotal phase 3 study (UX003-CL301) was submitted after discussion with the Agency (July 29, 2014). Agreement regarding the design of study UX003-CL301 was reached prior to submission of IND 123788 and took into account the extremely rare incidence of MPS VII. The Agency agreed there would be no pre-specified primary endpoint and that review of this pivotal trial would be based upon the totality of evidence provided by a unique staggered start study design using a multi-domain responder index (MDRI) of the following clinical endpoints:

- Six-minute walk test (6MWT)
- Shoulder flexion as a measure of joint range of motion (ROM)
- Forced vital capacity (FVC) from pulmonary function testing (PFT)
- Visual acuity
- Fine motor testing
- Gross motor testing

Additional endpoints evaluating fatigue, cardiac function, uGAGs and clinician/caregiver reported outcomes were also included in the study design.

The Applicant submitted a Proposed Pediatric Study Request (PPSR) for vestronidase alfa on January 23, 2015 and a response to an information request on May 20, 2015. In reference to these submissions, (b) (4)

(b) (4)

To address the need to evaluate the long-term effects of vestronidase alfa in patients with MPS VII, the Applicant submitted protocol UX003-CL401[3] under IND 123788 on August 5, 2016. The study is described as a MPS VII disease monitoring program/longitudinal cohort study (MPS VII DMP-LCS). (b) (4) The Agency responded to the Applicant on October 13, 2016, stating that the information from Study UX003-CL401 may not be comparable to other studies from IND 123788, (b) (4). On May 9, 2017, the Applicant responded with a proposal to require yearly clinical evaluations that would rely upon (b) (4). This open label extension study has not been initiated.

Vestronidase alfa received US Orphan Drug designation (#11-3598) on February 16, 2012. The Applicant also received Fast Track designation (FT) on July 15, 2015, for the investigation of enzyme replacement therapy (ERT) for the treatment of MPS VII. A regulatory summary is provided in Table 3.

Table 3: Summary of Regulatory Meetings in INDs Related to BLA 761047

Date	Type of Meeting	Key Discussion
(b) (4)		

[3] At the time of submission, no NCT available on ClinicalTrials.gov

(b) (4)

10 Oct 2014	IND 123788	**IND submission**

(b) (4)

24 Aug 2016	IND 123788 Type C	**Concerns Expressed by the FDA** CMC only – refer to meeting minutes
5 Oct 2016	IND 123788 Type B, Pre-BLA	**Concerns Expressed by the FDA** 1. The Agency expressed reservations that the Phase 3 study will contain sufficient data to support a definitive conclusion of efficacy at the currently proposed dosage of 4 mg/kg/QOW in the absence of rigorously collected natural history data. 2. The Agency reiterated that the lack of clinical deterioration cannot be interpreted as "disease stabilization" without reliable natural history data. 3. The briefing package did not contain sufficient descriptive information regarding individual patient history. 4. The Agency reiterated concerns that missing data might affect the evaluation for efficacy. 5. The immunogenicity data provided would need to be complete for BLA review. 6. The Agency requested that the Applicant provide comprehensive medical histories including information on disease progression (with developmental milestones) at and after diagnoses were made and prior to treatment with study drug. 7. There was agreement with the proposed plan for the BLA 120-day safety update. 8. A pre-and postnatal development study will be required post-marketing. 9. There was insufficient information to determine: a. if a REMS will be required. b. if an advisory committee meeting will be needed 10. In-clinic assessments are optional in the protocol for the longitudinal observational study, protocol UX003-401. Therefore, the lack of salient information (liver and spleen size, standardized growth assessments, physical examination, cardiac 2D-echo) may not be fully informative or comparable to the Phase 3 study outcomes. **Other Topics Discussed** Nonclinical, Clinical Pharmacology, Regulatory, Biostatistics, **Other Teams Present:** Office of Biotechnology Products Office of New Drugs

		Division of Pediatric and Maternal Health Office of Surveillance and Epidemiology Clinical Outcome Assessment

Source: IND 123788 briefing package 10-2016, Table 2.6.1.1 page 17 of 212.

3.3. Foreign Regulatory Actions and Marketing History

The Applicant received Orphan Drug designation from the European Union (EU) ODD (#EU/3/12/973) on January 11, 2012. However, vestronidase alfa is not currently marketed in any country. The Applicant submitted marketing application to the EU in March 2017 which relies on the same pivotal study submitted in the United States (US) marketing application. The EU's regulatory decision is expected after the FDA's decision on this BLA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI) and the Office of Study Integrity and Surveillance (OSIS)

An OSI inspection of two clinical sites for Study 301 was performed. The sites chosen included the largest enrolling site for study UX003-CL301. Site (b) (6) enrolled six patients with MPS VII. Site (b) (6) enrolled two patients with MPS VII and was chosen for inspection as it had most reported protocol violations per subject. (Refer to **Figure 8**)

The FDA comparison of source documents submitted with the line listings determined the following:

- All identified errors involved information entered into individual case report forms.
- While there were some point differences in raw data, most of these errors did not change the point score, and therefore did not result in a point score error.
- A total of 17 transcription errors occurred in the raw data but only one resulted in a point error for the BOT-2 gross motor subdomains.
    - Subject (b) (6) was reported to have 12 points for the BOT-2 Balance subtest (study week 24), but this should have been reported as 13 points.

The discrepancies cited in the two site inspections were not considered to have an impact on data integrity, but the issues identified suggested that the administration and scoring of the BOT-2 gross motor assessment may be prone to error and therefore, may not be reliable. The changes identified were communicated to the statistical analysis team and incorporated into

their review. For additional information, please refer to the OSI review by Dr. Susan Leibenhaut.

Due to the use of different uGAG analytical methodologies during the development program, OSIS conducted inspections at the two biochemical genetics laboratories completing uGAG analyses in Study 301; the (b) (4) and the (b) (4). Both inspections identified inconsistent documentation for both method validation and quality control of uGAG assessments via both methodologies. Refer to the OSIS reports for additional detail.

Medical Officer's comment: The issues identified for the BOT-2 scoring and the validation and quality control of the uGAG analyses were concerning for both the overall study organization and consistency. These findings suggest that the scoring of the BOT-2 testing was complex and prone to human error and brings the reliability of results with this score into question. While the discrepancies in the raw data did not change the overall interpretation of scoring and efficacy results, it is not clear to this reviewer how reliable it will be to correlate the BOT-2 findings to other endpoint results. At best, improvements in BOT-2 gross motor scoring may be viewed as qualitatively supportive in a patient with a demonstrated improvement in the 6 MWT.

In the final analysis, the laboratory audits did not reveal any deficiencies that would preclude approval.

4.2. Product Quality

The CMC review team (Drs. Rukman De Silva, Jacek Cieslak, Cristina Ausin and Bo Chi) recommend approval of this application. They concluded that the data submitted in this BLA support the conclusion that the manufacture of vestronidase alfa is adequately controlled and yields a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the manufacturing parameters recommended by the FDA. The methodologies used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. Therefore, the CMC reviewers recommend that vestronidase alfa be approved for human use under the conditions specified in the package insert.

The CMC team found the existing manufacturing process acceptable. Additional validation will be required post approval. This concurrent validation approach to support approval is being used due to the rarity of the disease population.

Refer to the CMC reviews by Jacek Cieslak and Bo Chi for additional details.

4.3. Clinical Microbiology

The Clinical Microbiology review team (Dr. Max Van Tassell) recommends approval of this application. The vestronidase alfa drug product is a sterile, preservative-free 2mg/ml solution for infusion. The drug product is manufactured via (b) (4) single-use vials.

4.4. Nonclinical Pharmacology/Toxicology

Non-clinical studies were completed in mice (MPS VII/E540A^{TG} and gus^{mps}/ gus^{mps}), Sprague-Dawley rats and cynomolgus monkeys.

Placebo-controlled single-dose toxicity studies (UX003-PC002 and UX003-PC004) were completed in Sprague-Dawley Rats at dosages of 6 mg/kg and 20 mg/kg for evaluation of central nervous system and respiratory toxicology. The MPS VII/E540A^{TG} mice were also evaluated in the placebo-controlled study UX003-PC001 via weekly infusions for 8 weeks at doses of 0.1 mg/kg, 0.25 mg/kg, 1 mg/kg, 4 mg/kg and 20 mg/kg.

A 26-week placebo controlled cardiovascular toxicity study (UX003-PC003) was completed in cynomolgus monkeys at doses of 2 mg/kg, 6 mg/kg and 20 m/kg.

By the applicant's report, the 20 mg/kg infusions were associated with lethargy but no other signs of toxicity were seen in the female rats, while male rats did not gain weight as efficiently at this dosage. In addition, a chronic toxicology study in cynomolgus juvenile monkeys also assessed every other week infusions at doses of 0, 2, 6 and 20 mg/kg for 26 weeks. No target organs identified microscopic or macroscopic findings at any dosage. Based upon these evaluations, the no-observed adverse event level (NOAEL) for reproductive toxicity and developmental toxicity was determined to be 20 mg/kg/day in the monkeys. The human dosage equivalent of the 20 mg/kg NOAEL in cynomolgus juvenile monkeys is 1.6 mg/kg.

The nonclinical reviewer did not identify issues that would preclude approval and recommended approval for its proposed use as indicated in the labeling. Refer to the non-clinical review by Dr. Yolanda Branch for details.

Medical Officer's Comment: The human dose finding study was limited to doses of 1 mg/kg, 2 mg/kg and 4 mg/kg. As the nonclinical studies did not demonstrate clinical toxicities, additional higher doses could have been explored for assessment of maximal clinical impact.

4.5. Clinical Pharmacology

There are no clinical pharmacology deficiencies that preclude approval. Refer to the clinical pharmacology review by Dr. Christine Hon for additional details.

The selected dose and dosing regimens for patients with MPS VII were based upon trials conducted across pediatric and adult age groups. Study 201 evaluated three doses of vestronidase alfa (1 mg/kg, 2 mg/kg and 4 mg/kg) for the percent change in uGAG excretion in three patients. The largest percent increase in uGAG excretion occurred at the 4mg/kg dosage. As this dose was tolerated by all three subjects, it was used for the pivotal Study 301.

4.5.1. Mechanism of Action

Vestronidase alfa is a recombinant human beta-glucuronidase (rhGUS) enzyme, purified from a genetically engineered stable Chinese hamster ovary (CHO) cell line and has the same amino acid sequence as the native human enzyme. Vestronidase alfa contains mannose-6-phosphate (M6P) residues on the oligosaccharide chains, which facilitate cell surface receptor binding and subsequent internalization and lysosomal targeting. In the lysosome, rhGUS catalyzes the hydrolysis of beta-D-glucuronic acid residues from the non-reducing end of the glycosaminoglycans (GAGs) dermatan sulfate, chondroitin 6-sulfate and heparan sulfate. In patients with MPS VII, vestronidase alfa accomplishes the same function and is administered with the goal of decreasing the multi-tissue accumulation of uGAGs in the lysosomes.

4.5.2. Pharmacodynamics

Vestronidase alfa is an enzyme replacement therapy that reduces the amount of urinary glycosaminoglycans (GAGs) in patients with MPS VII.

When injected into the MPS VII/E540A^{TG} mice, vestronidase alfa accumulated in tissues in dose-dependent levels, with the highest presence in the liver, spleen and adrenal glands. The lowest levels were noted in cerebral tissue. The dose effect appeared to plateau above 1 mg/kg and was relatively unchanged between 4 mg/kg and 20 mg/kg dosages as graded by pathologic assessment of cytoplasmic vacuolization in murine tissue. Based upon these studies, 4 mg/kg dosing was selected for further testing. *In vitro* studies with human MPS VII fibroblasts noted that the half- life of vestronidase alfa is approximately 40 days. This half-life is longer in duration by about 8-fold compared to other enzyme replacement therapies to treat other mucopolysaccharidoses and is the basis for the selection of every other week dosing.

The Applicant proposes a single dosage of at 4 mg/kg of vestronidase alfa every other week via intravenous (IV) infusion for both pediatric and adult patients. The Applicant proposes a 1:1 dilution with an equal volume of 0.9% Sodium Chloride Injection, USP for intravenous infusion to be administered using an infusion set equipped with an in-line, low-protein binding 0.2 µm filter, over approximately 4 hours duration.

Percent changes from baseline in urinary glycosaminoglycan (uGAG) excretion were evaluated in an early dose-exploration study (Study 201) at doses of 1 mg/kg, 2 mg/kg and 4 mg/kg vestronidase alfa. The highest mean percent reduction was demonstrated at 4 mg/kg. In general, urinary dermatan sulfate and urine chondroitin sulfate levels were consistently elevated relative to urinary heparan sulfate levels in MPS VII subjects. Therefore, the total uGAG changes reported by the Applicant mostly represented changes in urinary dermatan sulfate and urinary chondroitin sulfate levels.

At the time of approval of this application, the impact of anti-drug antibodies (ADA) on safety and efficacy is inconclusive. The Division is recommending that the Applicant conduct a post-marketing longitudinal study to further inform these relationships. Refer to the discussion of PMR1 and PMC3for additional details.

4.5.3. Pharmacokinetics

The pharmacokinetics of vestronidase alfa was evaluated in 19 patients diagnosed with MPS VII. These patients were enrolled in three clinical trials and included 15 patients ≤ 18 years of age and 4 patients > 18 years.

The AUC_{last} appeared to increase more than proportionally from 1 mg/kg to 4 mg/kg every other week dosing.

APPEARS THIS WAY ON ORIGINAL

Table 4 demonstrates that the pharmacokinetics of vestronidase alfa appeared to be time independent with repeat dosing. The serum half-life ($T_{1/2}$) was estimated at 2.5 hours in Study 301, 1.3 hours in Study 201 and the intracellular half-life ($T_{1/2}$) was estimated at 40 hours in cultured human MPS VII fibroblasts as noted previously.

Table 4: Vestronidase Alfa Parameters following Multiple 4 mg/kg QOW Dosing in MPS VII Subjects

Study	UX003-CL201	UX003-CL203	UX003-CL301
No. of Subjects	3	4	12
Age (year)	9.4	3.0	14.1
Weight (kg)	34.6	12.3	52.5
PK Parameters			
Cmax (µg/mL)	13.0 (29.1%)	14.3 (98.9%)	19.0 (56.8%)
Tmax (h)	4.2 (4.1 – 4.3)	4.7 (4.1 – 5.5)	4.0 (3.9 – 4.2)
t1/2 (h)	1.3 (21%)	NE	2.5 (36%)
AUC0-t (µg*h/mL)	40.0 (30.8%)	60.6 (96.1%)	52.0 (54.7%)
AUC0-∞ (µg*h/mL)	42.8 (28.2%)	NE	56.7 (55.8%)
CL (L/h/kg)	0.0934 (28.2%)	NE	0.0706 (55.8%)
Vss (L/kg)	0.176 (42.6%)	NE	0.234 (56.7%)

Baseline age, baseline body weight and Tmax are median (min-max) values; all other PK parameters are reported as geometric mean (%CV). NE = not evaluated due to sparse sampling.

Source: BLA 761047; Section 2.7.2 Summary of Clinical Pharmacology Studies, Table 2.7.2.3.1.1 (page 24 of 41)

Serum clearance of vestronidase alfa (CL) was estimated at 0.07 L/hr/kg and was reported by the Applicant as similar to that labeled for laronidase, idursulfase and galsulfase. There were no apparent differences based upon race, gender or age.

Specific studies evaluating PK and PD of vestronidase alfa in subjects with either hepatic or renal impairment were not completed during this development program.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 5 summarizes the studies provided by the Applicant that are relevant to the evaluation of efficacy and safety of vestronidase alfa. No other studies were submitted with this application and all studies submitted were performed by the Applicant. After **Table 5**, all studies will be referred to by their number only (i.e., 201, 301 and 203).

Table 5: Listing of Clinical Studies for BLA 761047 using vestronidase alfa

Trial	Trial Design Clinical Trials.gov ID	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Studies and Expanded Access to Support Efficacy and Safety and Dose Selection (total of 17 unique subjects)							
UX003-CL201	Phase 1/2 Study: Open-label, uncontrolled study to evaluate safety, efficacy and dose exploration NCT01856218	Vestronidase alfa QOW by IV at the following doses: 2 mg/kg: 14 wks (Wk 0-12) 1 mg/kg: 8 wks (Wk 14-20); 4 mg/kg: 8 wks (Wk 22-28); 2 mg/kg: 44 wks (Wk 30-72); 4 mg/kg: up to 168 wks (Wk 74-240)	Safety Tolerability Reduction in uGAG excretion	Up to 240 weeks	3	Patients diagnosed with MPS VII (5-35 years of age, inclusive) 3 subjects	3 centers in three countries (UK, (b) (6))
UX003-CL301	Phase 3 Study: A multicenter, randomized, placebo-controlled, delayed start design NCT02230566	Vestronidase alfa QOW 4 mg/kg by IV	MDRI[a] ICR[b] uGAGs[c] Clinician and Patient reported outcomes	24-28 weeks	12	Patients diagnosed with MPS VII (5-35 years of age, inclusive) 12 subjects	4 centers in the United States
UX003-CL202	A long-term, open-label, extension study for subjects enrolled in Study UX003-CL301 NCT02432144	Vestronidase alfa QOW 4 mg/kg by IV	MDRI[a] uGAGs[c] Clinician and Patient reported outcomes	Up to 144 weeks	12	All subjects previously enrolled in Study UX003-CL301	Up to 12 sites four countries
IND 119935 (Expanded Access)		Initiated at 2 mg/kg QOW then increased to 4 mg/kg QOW	N/A	164 weeks	1	MPS VII	1 center in US
IND 123764 (Expanded Access)		Initiated at 2 mg/kg QOW then increased to 4 mg/kg QOW	N/A	125 weeks total under EA and study protocol	1	MPS VII	1 center in US Subject transitioned to study UX003-CL203 on November 3 2015
Additional studies only used to Support Safety (total of 4 unique subjects)							
UX003-CL203	Phase 2 Study: Open label,	Vestronidase alfa QOW 4 mg/kg by IV	Growth velocity Hepatosplenomegaly	Up to 240 weeks	4	Patients diagnosed with MPS VII	3 centers in 3 countries (US, (b) (6))

Trial	Trial Design Clinical Trials.gov ID	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	uncontrolled study to evaluate safety and efficacy NCT02418455					(<5 years of age)	
Other studies pertinent to the vestronidase program							
UX003-CL001	Retrospective, non-interventional review of medical records	N/A	Impact of ERT on uGAG excretion and clinical outcomes Relationship between uGAG excretion and clinical outcomes	N/A	50	MPS I: 18 subjects MPS II: 23 subjects MPS VI: 9 subjects	1 center in the UK
UX003-CL002	Non-interventional patient survey	N/A	Identify the type and severity of clinical symptoms in MPS VII impact of symptoms on functional status inform endpoint selection for clinical studies	N/A	10	Patients diagnosed with MPS VII All ages	Telephone interview from the US

Source: BLA 761047, Section 5.2, Table 5.2.1, Listing of UX003 Clinical Studies
[a] MDRI – multiple domain responder index
[b] ICR – individualized clinical response
[c] uGAGs – urinary glycosaminoglycans

5.2. Review Strategy

The efficacy analysis evaluated data on patients enrolled in studies 201, 301 and the expanded access INDs 119935 and (b) (4) for a total of 17 patients. Data from the published literature further informs the analysis of whether the results from study 301 represent a departure from the natural history of MPS VII.

The safety analysis is based upon data from studies 201, 203, 301 and expanded access INDs 119935 and (b) (4) for a total of 20 unique patients.

This review includes original analyses performed by the primary medical officer, Dina Zand, M.D., and a critical assessment of the analyses conducted and submitted by the Applicant.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 201

6.1.1. Study Design

Overview and Objective

Study 201 was a Phase 1/2 first-in-human, single-arm, open-label, multi-national dose exploration study of vestronidase alfa in patients with MPS VII.

There were two primary objectives of this study. The first was to assess the safety and tolerability of vestronidase alfa in patients with MPS VII. The second was to determine the efficacy of vestronidase alfa as evaluated by the reduction of total urinary glycosaminoglycan (uGAG) excretion.

Study 201 was initiated in Europe prior to submission of IND (b) (4) or IND 123788. Three patients with MPS VII were enrolled in three different study centers ((b) (6)) for this first-in-human study.

Trial Design

The dose exploration Study 201 was divided into 2 phases where different doses of vestronidase alfa were intravenously infused every other week with a maximum duration of 168 weeks. The study design was based upon previous clinical studies of enzyme replacement therapies (ERTs) in other mucopolysaccharidoses where decline in uGAG levels was noted within four to six weeks after initiation of ERT therapy. The impacts of ERT upon pulmonary

function and/or sustained walk (6MWT) were evaluated within a 12-to 24-week timeframe for these studies. The Applicant chose an 8-week period for analysis of the change in uGAG levels after each dosage during the Forced-dose Titration period of this study. The Applicant considered 36 weeks sufficient to determine the impact of vestronidase alfa on both uGAG excretion and clinical measures of endurance and pulmonary function.

The Applicant planned to enroll up to 5 patients with MPS VII, but ultimately only 3 patients were enrolled due to limited patient availability. At the end of the study, subjects completed up to 132 weeks of treatment, with final study visits at weeks 118, 124, and 132. (**Figure 2)**

Figure 2: Study 201 Schema

	First Phase					Long-term Extension Phase
	Initial Treatment Period (14 weeks[a,b])	Forced-dose Titration Period (24 weeks[b])			Continuation Period (up to 36 weeks[b])	Long-term Extension Period (up to 168 weeks[b])
Week	0 to 12	14 to 20	22 to 28	30 to 36	38 to 72	74 to 240
Dose (mg/kg)[c]	2	1	4	2	2	4

Source: BLA 267047, Study UX003-201 CSR Table 2.1 (page 5 of 197)

[a] The Initial Treatment Period was referred to as a 12-week period in the protocol though exposure to UX003 was 14 weeks; the dosing schedule for this 14-week period was accurately reflected in all versions of the protocol.

[b] Duration of treatment is the number of weeks from the first dose through the last dose + 2 weeks (e.g., Initial Treatment Period dose administration occurs every other week (QOW) at Week 0 through Week 12; therefore, duration of treatment is 14 weeks).

[c] Dosing was IV QOW throughout the study

The initial dosing of 2 mg/kg was chosen based upon the dosing explored in the non-clinical studies and the dosing of previously approved ERTs for other MPS diagnoses (ranging from 0.58 mg/kg to 2 mg/kg administered weekly via IV). During the forced titration period, the percent changes in uGAG excretion (total, DS and CS) were compared after change in vestronidase alfa dosing, during the continuation period and during the long–term extension phase. The dosage that demonstrated the largest change in uGAG excretion from baseline was to be selected for dosing in future vestronidase alfa studies.

Study Endpoints

The Applicant used the term “efficacy endpoints” throughout the clinical study report (CSR) for study 201. The efficacy assessments used in this study were the following:

- Maximum change in baseline of uGAG on 4 mg/kg infusion provided every other week.
- Change in liver and spleen volume
- Cardiopulmonary function as assessed by spirometry (FVC, FEV1, MVV)
- Change from baseline in cardiac size and function (LVMI and ejection fraction)
- Mobility/endurance (6MWT, 3MWT)
- Motor skills (BOT-2)
- Musculoskeletal (change in baseline of growth velocity as measured by height and weight) and shoulder range of motion (flexion and extension)
- Quality of life questionnaire to assess change from baseline in self-care, mobility, and caregiver assistance (MPS HAQ total score).

Medical Officer Comment: At the time of initiation of Study 201, the clinical endpoints chosen were either endpoints used to demonstrate efficacy for approved enzyme replacement therapies (ERTs) for other mucopolysaccharidosis programs (MPS I, MPS II, MPS IVA and MPS VI) or for non-MPS conditions with similar clinical presentations. However, as there were a limited number of subjects and therefore limited natural history data in MPS VII, these clinical endpoints were primarily exploratory in nature.

Statistical Analysis Plan

The initial Statistical Analysis Plan (SAP v1.0) for Study 201 was submitted on October 19, 2015. In this plan, a preliminary analysis was conducted prior to completion of the forced dosage titration period that evaluated uGAG reduction at 4 mg/kg relative to 2 mg/kg. The formal protocol specified analysis at 36 weeks, but this preliminary analysis was conducted earlier, after each subject completed exposure to 4 mg/kg dosing of vestronidase alfa. A revised SAP v1.1 was submitted on August 26, 2016. The Applicant stated that the major change made in SAP v1.1 affected the missing data imputation rules, which were updated to be consistent with rules of other studies in the vestronidase alfa development program. Sample size was based upon the ability to identify patients who met inclusion criteria.

The database was locked on September 9, 2016.

Protocol Amendments

The date of the original protocol was May 2, 2013, and two amendments followed. The two most significant changes noted in Protocol Amendment 1 (November 22, 2013) specified a long-term extension period and clarified that the number of patients enrolled would be three and not five as originally specified. The duration of study 201 increased from 74 weeks until 240 weeks, with clarification that at 74 weeks all subjects would receive dosing at 4 mg/kg QOW.

During the long-term extension, efficacy (serum GAG, 6MWT, 3MSCT, BOT-2, PFTs, anthropometrics, goniometry, Visual Acuity, and PGI-C) would be assessed every 6 months through week 240 and an echocardiogram would be performed annually. A PK assessment would be obtained at week 84 only.

Protocol Amendment 2 (December 1, 2014) contained minor revisions, intended for the purposes of clarification.

Medical Officer Comment: These Amendments were reviewed and are acceptable.

Data Quality and Integrity: Applicant's Assurance

The Applicant provided a statement of assurance regarding the integrity of the data provided in Study 201, in addition to both clinical and laboratory audit certificates.

Medical Officer Comment: This is acceptable.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP) guidelines.

Medical Officer Comment: This is acceptable.

Financial Disclosure

The Applicant submitted financial disclosure information for clinical investigators in accordance with 21 CFR part 54. FDA form 3454 was submitted for all principle investigators and sub-investigators involved in Study 201 and the Applicant certified that none had a financial arrangement with the Applicant whereby the value of compensation could have affected the outcome of the study.

Patient Disposition

The initial protocol for Study 201 stated that up to five patients would be enrolled. Ultimately, three patients in two countries ([(b) (6)]) were enrolled and followed in their home country as well as the UK, the coordinating center for this study. All three patients (A1, A2, and A3) discontinued the study prior to 240 weeks to commence "compassionate use treatment" of vestronidase alfa. The shortest duration was 118 weeks (patient A1) and the longest duration was 132 weeks (patient A2). There were no deaths.

Protocol Violations/Deviations

The Applicant reported a total of 137 protocol deviations in study UX003-CL201, including a total of 5 major protocol deviations, with at least one in each subject (**Table 6**).

Subject A1 was reported with 66 total protocol deviations while subjects [(b) (6)] and A3 were reported with 34 and 37 total protocol deviations, respectively

Table 6: Study UX003-CL201 Summary of Major Protocol Deviations

Subject ID/Site	Category	Visit (week)	Protocol Deviation
A1/[(b) (6)]	Other	54	From Week 54 through Week 66 the site had inadequate or missing documentation of vital signs, concomitant medications, and adverse events.
A1/	Dose Miscalculation	70	Week 62 through Week 70 infusions were prepared according to an earlier (lower) weight of 24.5 kg obtained at Week 44. Infusions should have been prepared according to the subject's weight at Week 60 (27.4 kg). Subject weight on Weeks 62 through 70 was 24.5 kg.
A1/	Procedure Not Done	92	Subject was unable to receive infusions or perform assessments due to unrelated surgical complications. The subject missed 3 consecutive visits (Weeks 88, 90, and 92).
A2/	Dose Miscalculation	124	The Week 124 infusion was prepared according to an earlier (lower) weight of 47.9 kg obtained at Week 96. The infusion should have been prepared according to the subject's weight at Week 120 (49.0 kg).
A3/	Dose Miscalculation	94	Week 82 through Week 94 infusions were prepared according to a greater weight of 78.4 kg obtained at Week 82. Infusions should have been prepared according to the subject's weight at Week 72 (75 kg).

Source: BLA 761041; Adapted from CSR Study UX003-201, Table 9.2.1 (page 72 of 197).

Medical Officer Comment: Given the duration of Study 201, the number of total protocol deviations appears acceptable although patient A1 followed at site [(b) (6)] was noted to have more total and major protocol deviations of greater concern. The report of inadequate or missing documentation of vital signs, concomitant medications and adverse events for 12 weeks is the

most concerning as it may have impacted the report of infusion related hypersensitivity reactions. All three patients were under-dosed (based upon weight) for at least one infusion. Detailed explanations of these protocol deviations were not provided by the Applicant.

Demographic Characteristics

The demographic characteristics for patients enrolled in Study 201 are presented in **Table 7.**

Table 7: Demographic Characteristics in Study 201

Demographic Parameters	A1	A2	A3
Sex	Male	Female	Male
Age (years)	5.5 years	9.4 years	25.1 years
Age at diagnosis	> 1 year	> 1 year	5 years
Race	White	White	Asian
Ethnicity	Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino
Country of Enrollment (Site)	(b) (6)		

Source: BLA 761047; Study UX003-CL201, Section 16.2.4
Patient A1 = FDA Patient # (b) (6)
Patient A2 = FDA Patient #
Patient A3 = FDA Patient #

A summary of demographic characteristics for Study 201 is provided in **Table 8** and the general baseline characteristics for these subjects are provided in **Table 9**.

Table 8: Summary Demographic Characteristics in Study 201

Demographic Parameters	Total n (%)
Gender	
Male	2 (67)
Female	1 (33)
Age	
Mean years (SD)	10 (SD 9.26)
Median (years)	9.4
Min, max (years)	5.5,25.1
Age Group	
< 17 years	2 (67)
≥ 17 - < 65 years	1 (33)
Race	
White	2 (67)
Asian	1 (33)
Ethnicity	
Hispanic or Latino	1 (33)
Not Hispanic or Latino	2 (67)
Region	
Europe	3 (100)

Source: BLA 761047; Study UX003-CL201, Section 16.2.4

Medical Officer Comment: The three patients enrolled were reflective of the spectrum of patients enrolled in pivotal Study 301 (described later in this review) based upon age and gender. As MPS VII pathology can begin in utero with the presentation of non-immune hydrops fetalis (NIHF), it is this reviewer's opinion that the youngest patients may provide the most information on the ability to improve clinically after exposure to vestronidase alfa, particularly those who are critically ill with non-immune hydrops fetalis as 40% of these patients are anticipated to die within the first year of life. However, the applicant did not target the NIHF population in this development program.

Biochemical testing was not sufficiently detailed to determine whether the older patients (9.4 and 25.1 years) had higher residual beta-glucuronidase activity; therefore, it is not possible to assess how age at enrollment may have impacted the interpretation of symptom severity and response to treatment in the patients enrolled in Study 201.

Table 9: Additional Baseline Features of Patients in Study 201

Other Baseline Features	Subject A1	Subject A2	Subject A3
Laboratory Diagnosis			
Enzyme Activity Level	unknown	3.4 mmol/h	unknown
Molecular Analysis	N/A	N/A	N/A
Clinical Features			
Height (cm)	102.5	123.9	157.3
Weight (kg)	20.6	34.6	79.1
History of Hydrops fetalis	Yes	Yes	Unknown
Cognitive Delay	Yes	Yes	Yes
Sleep Apnea	Yes	Unknown	Unknown
Shortness of breath	Yes Mechanically ventilated during protocol due to spinal cord injury related to surgery	Yes	Yes
Hepatosplenomegaly	Yes	Yes	Yes
Scoliosis	Yes	Unknown	Unknown
Joint Contracture	Yes	Yes	Yes
Cardiac Pathology	Unknown	Yes	Unknown
Corneal Clouding	Unknown	Unknown	Yes
Mobility impairment	Impaired during protocol by spinal cord injury related to surgery	Baseline need for assistive devices to walk and difficulty with transfers	Baseline need for assistive devices to walk (wheelchair and cane) Underwent hip surgery during weeks 36 and 84 of study

Source: BLA 7610477; Study UX003-CL201, Section 16.2.4

Medical Officer Comment: The clinical features were provided in a listing based upon date of diagnosis and were not updated during the study. It is possible that subjects A1 and A3 had cardiac pathology which contributed to their shortness of breath, but results of cardiac evaluations were not available.

Treatment Compliance and Concomitant Medications

During Study 201, patient A1 demonstrated worsening mobility related to a spinal cord injury. Both patients A2 and A3 were noted to use assistive devices at baseline with continuation throughout the study. Additionally, patient A3 underwent hip surgery at some point between weeks 36 and 84 of the study.

Patient A1 missed infusions at weeks 88, 90 and 92 due to surgical complications.

Common concomitant medications included analgesics, inhaled steroids, anti-histamine pre-

infusion and cardiac medications during surgical interventions. A summary of these medications is listed in **Table 10**.

Table 10: Concomitant Medication use in Study 201

Concomitant Medications	Subject A1	Subject A2	Subject A3
Analgesics (e.g. Paracetamol/Ibuprofen)	X	X	X
Antibacterial (e.g. Augmentin)	X	X	X
Diuretic (e.g. spironolactone)	X		
Anesthetics (e.g. fentanyl)	X		X
Psycholeptics (Midazolam)	X		
Cardiac Therapy (e.g. dopamine)[a]	X	X[c]	X[e]
Antihistamine	X	X	X
Steroid	X[b]	X[d]	X
Anti-GI reflux/emesis	X		X
Constipation	X		
Beta-adrenergic	X	X	
Muscle relaxant	X		X
Unspecified herbal medicine			X

Source: BLA 7610477; Study UX003-CL201, Section 16.2.4

[a] Dopamine was provided due to cerebral ventricular dilatation (Study UX003-CL201; Listing 16.2.4.8)

[b] Budesonide for pulmonary disease (Study UX003-CL201; Listing 16.2.4.8)

[c] Enalapril for cardiac hypertrophy, Atropine and ephedrine for surgery (Study UX003-CL201; Listing 16.2.4.8)

[d] Onadron drops for ear (Study UX003-CL201; Listing 16.2.4.8)

[e] Ephedrine for surgery (Study UX003-CL201; Listing 16.2.4.8)

Medical Officer Comment: It is not clear if the use of assistive devices in Study 201 changed for patient A3, particularly around the time of the reported hip surgery. However, review of the forms provided by the Applicant noted that the 6MWT was completed at the following time points without assistive devices: screening, 6 weeks, 12 weeks, 22, 30, 36, 84 and 120 weeks. Individual hip surgeries were sequentially completed at weeks 46 and 64. Thus, it is this reviewer's opinion that there was consistency for patient A3 in the 6MWT evaluations for the duration of the study.

Efficacy Results – Primary Endpoint

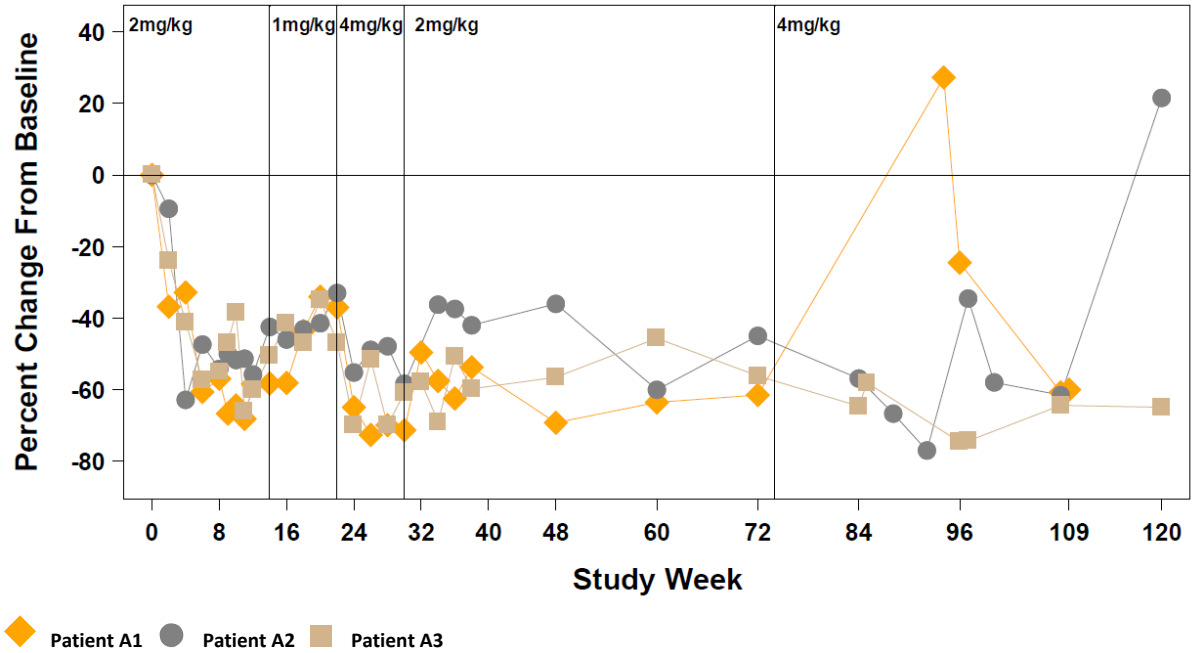
The primary efficacy endpoint of the phase 1/2 Study 201 was the percent reduction of individual uGAG excretion for each dosage of vestronidase alfa. The dosage that demonstrated the largest change in uGAG excretion from baseline was to be selected for dosing in future vestronidase alfa, though only 2 mg/kg and 4 mg/kg dosages were evaluated for sustained periods of 36 weeks or greater. Total urinary GAG excretion was subdivided to evaluate

dermatan sulfate (DS), chondroitin sulfate (CS) and heparan sulfate (HS) and was measured by both liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) and non-reducing end oligosaccharide (NRE) methodology.

The primary method of uGAG analysis was via liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) technology and the percentage reduction compared to baseline was reported for the three major components; dermatan sulfate (DS), chondroitin sulfate (CS) and heparin sulfate (HS). However, as the HS uGAG was within the normal range at baseline for these patients, the Applicant focused upon the changes in DS and CS. Ultimately the percent change in urine DS and urine CS were similar in these patients (**Figure 3** and **Figure 4**) and the Applicant chose to focus on urine DS changes in subsequent studies (Studies 301/202 and Study 203.

In exploratory analyses, all three patients demonstrated rapid reduction in dermatan sulfate (DS) excretion within 4 weeks of initiation of vestronidase alfa infusion at 2 mg/kg. Urinary DS reduction from baseline was evaluated during dosage changes (**Figure 3**) and appeared to be dose-related, with the largest percentage reduction from baseline noted at 4 mg/kg (**Table 11**). In general, the change in urinary DS was also highest for each patient with 4 mg/kg dosing.

Figure 3: Percent Change in Urine Dermatan Sulfate (DS) by Patient in Study 201



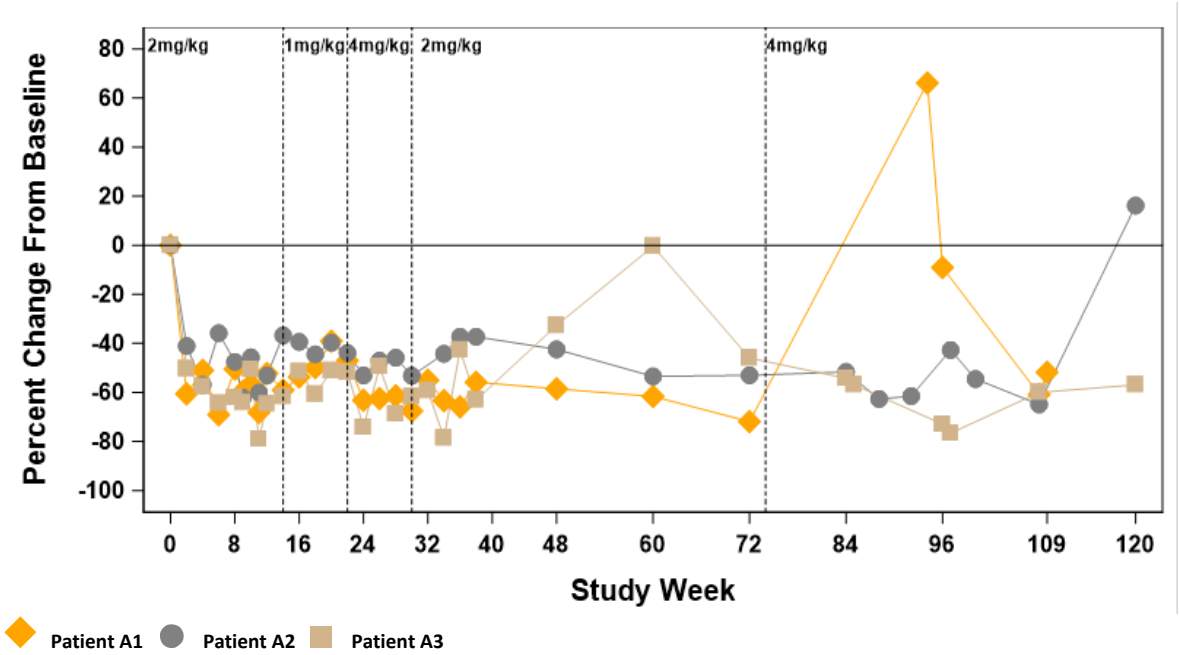
Source: BLA 761047, Protocol UX003-CL201 CSR, Figure 10.1.1.1.

Table 11: Percent change in urine DS by dosage of vestronidase alfa in Study 201

% Change from Baseline	Patient A1	Patient A2	Patient A3
4 mg/kg vestronidase alfa			
Mean (SD)	-50 (32)	-50 (25)	-65 (7)
Median	-63	-57	-65
Min, Max	27, -73	22, -77	-51.6, -75
2 mg/kg vestronidase alfa			
Mean (SD)	-57 (117)	-45 (13)	-52 (11)
Median	-60	-47	-56
Min, Max	-27, -69	-9, -63	-2, -69
1 mg/kg vestronidase alfa			
Mean (SD)	-43 (9)	-41 (5)	-43(5)
Median	-40	-43	-44
Min, Max	-34, -58	-33, -46	-35, -47

Source: BLA 761047, Protocol UX003-CL201 CSR, calculated from listing 16.2.6.1

Figure 4: Percent Change in Urine Chondroitin Sulfate (CS) by Patient in Study 201



Source: BLA 761047, Protocol UX003-CL201 CSR, Figure 10.1.1.3

Medical Officer Comment: All patients missed at least one vestronidase alfa infusion at the 4mg/kg dosing. Patient A1 missed infusions during weeks 88, 90, and 92. Patient A2 missed infusions during weeks 74, 96,118 and 112. Patient A3 missed infusions during weeks 112 and 116. The variability in DS and CS uGAG levels may be reflective of these missed infusions and this may affect the calculated mean and median calculations. Despite these missed infusions, ***Figure 3*** *appears to reflect an improved trend of sustained DS uGAG decrease over at least 109 weeks of exposure to vestronidase alfa at all dose levels, but more so at the 4 mg/kg dosing. This appears to justify dosing at the 4 mg/kg in Study 301.*

Summary conclusion on uGAG reduction: *QOW dosing of vestronidase alfa induced a rapid reduction in substrate as measured by uGAGs that was consistent with the drug's mechanism of action. This reduction was maintained over several weeks, despite missed infusions, and the % decrease in dermatan sulfate uGAGs appeared to be dose-dependent in all three patients.*

Data Quality and Integrity – Reviewers' Assessment

No OSI evaluations were conducted for the sites involved in Study 201. As noted in **Table 6**, one site reported multiple protocol violations involving poor collection of vital signs and improper dosing. Data quality was also impacted by subject inability to understand or comply with testing and testing by multiple assessors (see discussion of efficacy results, below). As this

trial was essentially designed as a dose finding protocol with exploratory endpoints, these deficiencies are acceptable. However, the inability to comply with multiple endpoint analyses due to underlying cognitive disability should have been considered in subsequent study design, and was not. The impact of this will be discussed under Section 6.2 (Study 301).

Efficacy Results – Secondary and other relevant endpoints

Study 201 was a European based trial that began prior to the submission of IND 123788. The chosen clinical endpoints were not discussed with the Agency prior to initiation. The secondary and exploratory endpoints of Study 201 were described in Section 6.1.1.

There was a significant age difference in the three enrolled patients (5.5 -25.1 years), but the two youngest were not able to complete at least three assessments (6MWT, BOT-2, PFT) due to their cognitive impairment as they were either not able to comply with the instructions or they were not able to understand the instructions. These results are shown in **Table 12**.

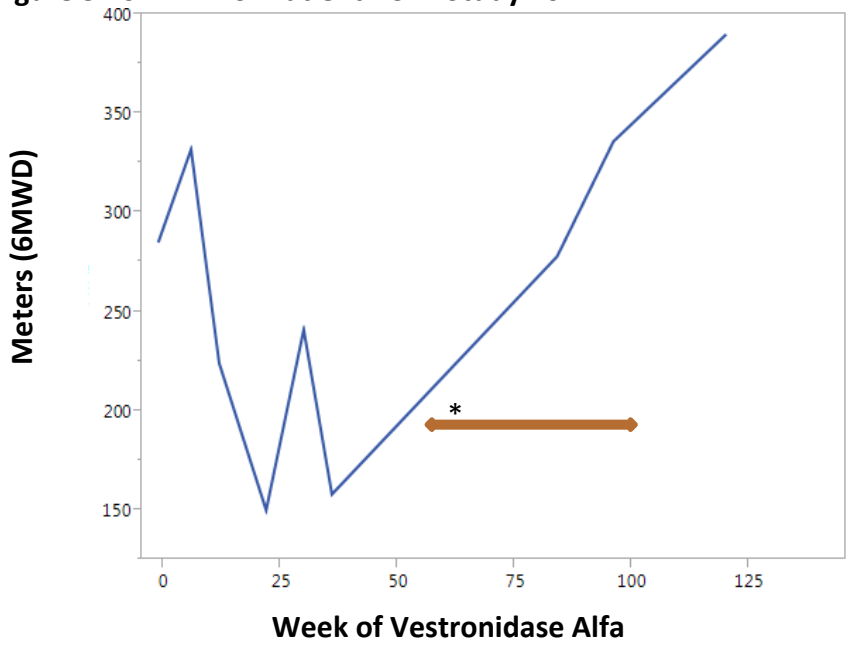
Table 12: Secondary Endpoint Evaluations in Study 201

Other Efficacy results	Patient A1	Patient A2	Patient A3
% Change from baseline (study week evaluated)			
Liver volume* **Liver Volume:** Estimated volume: % body weight baseline/36 weeks	-24.1% 4.4x/2.9x	-53.3% 3.8x/1.4x	Increased 2.0x/2.8x
Spleen volume* **Spleen Volume:** Estimated volume: % body weight baseline/36 weeks	-28.3% 0.5x/0.3x	-46.7% 0.6x0.3x	-13.5% 1.0x/0.8x
FVC	Subject unable to complete testing (Week 84)	Subject unable to complete testing (Week 120)	+21% (Week 120)
6MWT	No meaningful change (Week 72)	No meaningful change. Subject showed varying degrees of cooperation with testing protocol (Week 120)	An improvement of 105 meters at Week 120 compared to baseline (distance walked = 390 m; 49.6% predicted). (Week 120)
Cardiac LVMI (g/m)	-3.7 (Week 36)	+11.1 (Week 84)	-6.7 (Week 84)
Cardiac Ejection fraction	3% (Week 36)	-6% (Week 84)	3% (Week 84)
BOT-2	Subject unable to complete testing (Week 72)	No meaningful change (Week 120)	No meaningful change (Week 120)
Visual acuity	Normal at Baseline Unchanged (Week 36)	Corrective Lenses at baseline Unchanged (Week 120)	Corrective Lenses at baseline Unchanged (Week 120)

Source: BLA 761047, Protocol UX003-CL201 CSR, modified from Table 10.1
*As measured by Ultrasound at study Week 36 compared to baseline, Study UX003-CL201 CSR, Figures 14.2.5.1 and 14.2.5.2

Only one patient A3 could demonstrate what was interpreted as a meaningful change in the 6MWT, with an improvement of 105 meters at 120 weeks compared to baseline. (**Figure 5**)

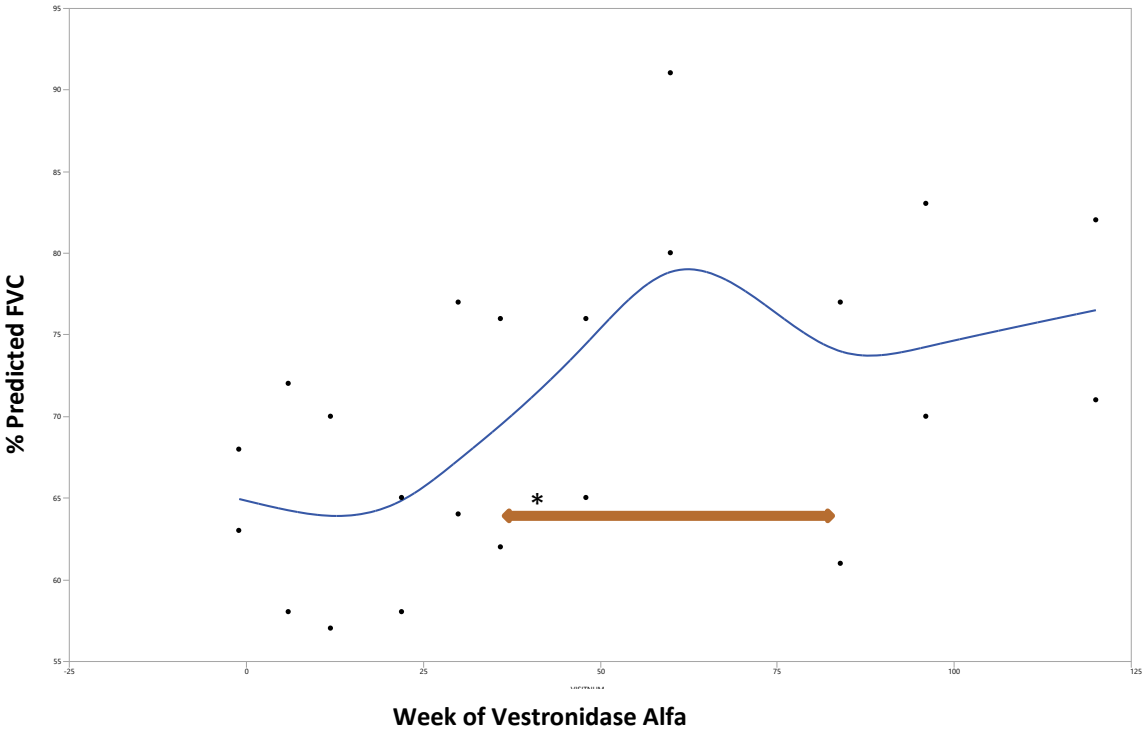
Figure 5: 6MWD for Patient A3 in Study 201



Source: BLA 761047, Study UX003-CL201, Adwalk analysis dataset
* Patient underwent hip surgery at week 46 and week 60. Due to surgery and recovery, assessments were not completed between weeks 36 and 84, as noted by the brown arrow (⟷)

In general, none of the three patients could demonstrate a meaningful change in the BOT-2 testing. Pulmonary function testing (FVC) was only interpretable in the oldest patient (A3) as this patient was the only one able to comply with testing and demonstrated a general trend of improvement with an absolute increase in % predicted FVC of 21% at 120 weeks. (**Figure 6**) This FVC result could be clinically significant for this patient.

Figure 6: % Predicted FVC for Patient A3 in Study 201



Source: BLA 761047; CSR Study UX003-CL201; Pulmonary Function Tests data set xp.xpt
Note: This patient completed two pulmonary function tests (PFTs) at each study visit that was assessed.
* Patient underwent hip surgery at week 46 and week 60. Due to surgery and recovery, assessments were not completed between weeks 36 and 84 as noted by the brown arrow (⟷)

In review of the cardiac evaluations, two patients showed slight improvement in their left ventricular mass index (LVMI) and ejection fraction.

Medical Officer Comment: The Division of Cardiovascular and Renal Products (DCRP) reviewed the original echocardiogram reports for the patients enrolled in Study 301 (Section 6.2) and did not find evidence of clinical benefit with exposure to vestronidase alfa. The cardiac evaluations of patients enrolled in Study 301 were similar to those of two patients enrolled in Study 201 (-3.7% for subject A1 and -6.7% for subject A3) in LVMI and ejection fraction (3%). Therefore, these findings are interpreted as within the normal range of variation and not as supportive evidence for efficacy.

Splenic and hepatic volumes were assessed by ultrasound at baseline, weeks 12 and 36 in Patients A1 and A2, and both patients were noted to have decreased splenic and hepatic volumes at 36 weeks. Patient A3 was assessed by MRI at baseline, weeks 12 and 36. He had a normal hepatic measurement at baseline but noted a slight decrease in splenic enlargement at 36 weeks.

While two of the three patients had impaired visual acuity at baseline, neither demonstrated significant visual improvement as measured by Snellen eye chart, with and without corrected vision, after long term exposure to vestronidase alfa.

Medical Officer Comment: Overall, these efficacy endpoints were not collectively informative because of the variability associated with assessments in only 3 patients of different ages, but were individually informative as these subjects were exposed to vestronidase alfa for almost two years' duration.

Improvement in the 6MWT for one subject (A3) at 120 weeks is clinically meaningful. However, this reviewer also acknowledges that subject A3 underwent hip surgery between weeks 36 and 84 of the trial, so any interpretation of clinical improvement for walking is confounded by a possible contribution of the orthopedic repair. Subject A3 was also assessed for FVC and demonstrated improvement of 21% at 120 weeks. In contrast, the outcome measures were not able to demonstrate consistent or significant improvement for any patient for the motor function (BOT-2) or cardiopulmonary measures (LVMI or ejection fraction). Patients A1 and A2 were not able to demonstrate evaluable improvement in any of these measures.

The only change which was consistently noted in all three patients was a decrease in spleen size; two of these also had hepatomegaly at baseline and had a reduction in liver size. This suggests that vestronidase alfa may be able to modify disease in some MPS VII related visceral pathology, and provides additional evidence of substrate reduction consistent with reduction in urinary GAGs. However, these patients were evaluated by different methodologies (ultrasound and MRI). The specific MRI methodology was not provided for review to compare with the imaging methodologies employed in Study 301 or 203, though all patients were reported to have a consistency in the modality of evaluation during the study.[4]

This reviewer believes that the limitations imposed by MPS VII related cognitive disability impaired the completion of many of these tests, leading to substantial amounts of missing data. As the pivotal study (301) was initiated prior to completion of Study 201, many of these endpoints were proposed and utilized as endpoints in the Applicant's Multi-domain responder index (MDRI) for Study 301.

The cognitive disability noted in the patients enrolled in Study 201 is also representative of patients enrolled in Study 301 (below) and the chosen instruments to assess the trial endpoints may not have been optimal or informative in this disease population for evaluating the efficacy of vestronidase alfa in MPS VII.

[4] BLA 761047 IR response submitted on 26 Sep 2017

6.2. Study 301

6.2.1. Study Design

Overview and Objective

Study 301 is the Applicant's only "phase 3" trial to assess efficacy of 4 mg/kg vestronidase alfa. Eligible subjects diagnosed with MPS VII were aged 5 to 35 years of age. The primary objective of this study was dual, as it planned to address the specific requests for approval of different regulatory agencies (i.e., the US and the EU):

- For US regulatory approval, the primary objective was the determination of efficacy of vestronidase alfa based upon the totality of the clinical data "on a per subject basis."
- In the EU (and rest of the world) the primary objective was the determination of efficacy as evaluated by the percent reduction of the uGAG excretion after 24 weeks of treatment in comparison to pre-treatment baseline.

Secondary objectives were to evaluate:

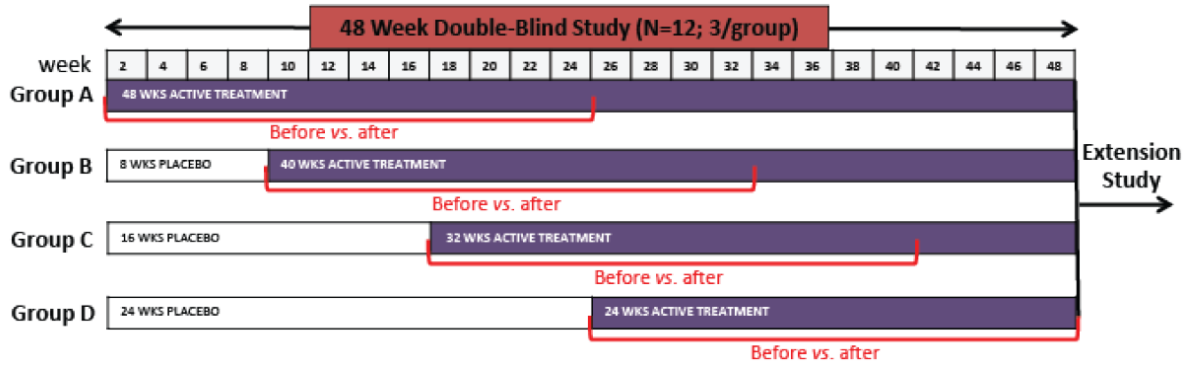
- Safety and tolerability of vestronidase alfa after 48 weeks exposure
- Efficacy as evaluated by a multi-domain clinical responder index after 24 weeks of vestronidase alfa exposure
- Efficacy after 24 weeks of vestronidase alfa exposure as determined by the proportion of subjects who achieved a positive individualized clinical response (ICR) outcome
- Clinical effects of vestronidase alfa after 24 weeks of exposure on pulmonary function, walking distance, shoulder flexion, fine motor function, gross motor function.

Medical Officer Comment: These evaluations were similar to the exploratory objectives evaluated in Study 201, where patients received vestronidase alfa for at least 118 weeks.

Trial Design

Study 301 was a phase 3 multicenter, randomized delayed start, study to assess the efficacy and safety of 4 mg/kg vestronidase alfa in patients diagnosed with MPS VII who were aged 5 to 35 years of age. A total of 12 enrolled subjects were divided into four cohorts based upon placebo exposure of 0, 8, 16 or 24 weeks in duration prior to initiation of vestronidase alfa infusions. (**Figure 7**)

Figure 7: Study UX003-CL301 Schema



Source: BLA 761047, Study UX003-CL301 CSR, Figure 8.1.1

Study Endpoints

As agreed upon with the Agency (see **Section 3.2**), study 301 did not have a pre-specified primary endpoint. Instead, efficacy would be determined based upon the totality of the evidence including the secondary and exploratory outcomes. These exploratory outcomes were evaluated individually and collectively in a multi-domain responder index (MDRI) described in **Table 19**.

Medical Officer Comment: As the use of the "totality of evidence" was agreed as a review principle, this reviewer cannot comment further. However, as the duration of the pivotal phase 3 study is significantly shorter than that of Study 201 (n=3) or the information provided by the expanded access INDs (n=2), these additional resources will aide in the provision of pertinent information for review.

Statistical Analysis Plan

The Applicant submitted a draft version of a statistical analysis plan (SAP) followed by four subsequent versions. The Applicant submitted Statistical Analysis Plans (SAPs) that specified changes directed specifically toward either US or EU regulatory requirements.

Version 1.4 of the SAP (submitted April 19, 2016) was the last version of the SAP for Study 301. This version was identical to Version 1.2 and Version 1.3 for US regulatory purposes, stating that "efficacy will be based on the totality of the clinical data on the per subject basis. No primary endpoint is declared." It established that dermatan sulfate (DS) would be the specific analyte used for the uGAG analysis. Urinary chondroitin sulfate (CS) levels also decreased after exposure to vestronidase alfa in a similar manner in most patients, However, the Applicant decided to define the primary analysis of uGAG DS as the PD biomarker to be analyzed in Study 201 and all subsequent studies.

The database was locked on June 16, 2016.

Medical Officer Comment: The SAP for Study 301 may have more relevance to the EU regulatory requirements as the primary endpoint of the EU study is the percent change in uGAGs from baseline to 24 weeks of exposure to 4mg/kg vestronidase alfa provided QOW. It is the opinion of this medical officer that the review will need to be based upon the evaluation of relevance of the endpoints which demonstrated clinical change from baseline in Study 301 (including open-label extension Study 202), Study 201 and expanded access INDs.

Protocol Amendments

The original protocol for Study 301 was dated March 9, 2014, (b) (4) . A total of 5 protocol amendments followed, the last submitted on April 18, 2016. (b) (4), the protocol was submitted to IND 123788 (**Amendment 1**). Additional protocol amendments occurred after submission of IND 123788 on October 10, 2014, and focus on the evaluations of the current protocol. As IND 123788 was submitted to the Agency on 10 October 2014 only Protocol Amendment 2 and above are summarized below.

Most of the protocol changes were minor. However, in review of these Amendments, these changes were the most notable:

- **Protocol Amendment 5** (18 April 2016)
  - The protocol clarified that complement levels would only be obtained for a reported drug-related infusion associated reaction (IAR) that is potentially a complement mediated (anaphylactoid) hypersensitivity reaction.
- **Protocol Amendment 4** (18 December 2014)
  - A full PK profile (an additional blood sample to be collected 6-8 hours after the end of infusion) was added to weeks 16 and 26, in addition to week 24
  - Testing for anti-drug antibodies directed against rhGUS will be obtained every 4 weeks until week 40, with an additional assessment at week 46
- **Protocol Amendment 3** (7 October 2014)
  - Further clarification stating that for US regulatory purposes, no primary endpoint will be declared for Study 301, as the review of the totality of the clinical data will determine efficacy.
  - The assessment and scoring of clinical problems that were determined to be most impactful to an individual patient's daily living was added to the protocol as an efficacy measure with the use of a Likert scale.
  - A patient/parent/caregiver global impression scale with accompanying patient narratives was added as an additional efficacy measure.

- **Protocol Amendment 2** (18 September 2014)
    - Dose selection was updated to 4 mg/kg QOW rather than 2 mg/kg QOW, based upon data from Study 201 that indicated greater % change in uGAG (DS) excretion at the higher dosage.

Medical Officer Comment: The protocol amendments include changes that are relevant to either EU or US regulatory requirements. As there is no pre-specified primary endpoint in Study 301 for the US review process, most protocol amendments were directed toward the EU regarding changes in technology and analysis of uGAG detection.

Data Quality and Integrity: Applicant's Assurance

The Applicant provided appropriate documentation for the provision of data quality assurance and integrity.

Medical Officer Comment: This is acceptable.

6.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that the studies were conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with good clinical practice (GCP) guidelines.

Medical Officer Comment: This is acceptable.

Financial Disclosure

The Applicant submitted financial disclosure information for clinical investigators in accordance with 21 CFR part 54. FDA form 3454 was submitted for all principle investigators and sub-investigators involved in Study 301 and the Applicant certified that none had a financial arrangement with the Applicant whereby the value of compensation could have affected the outcome of the study.

Patient Disposition

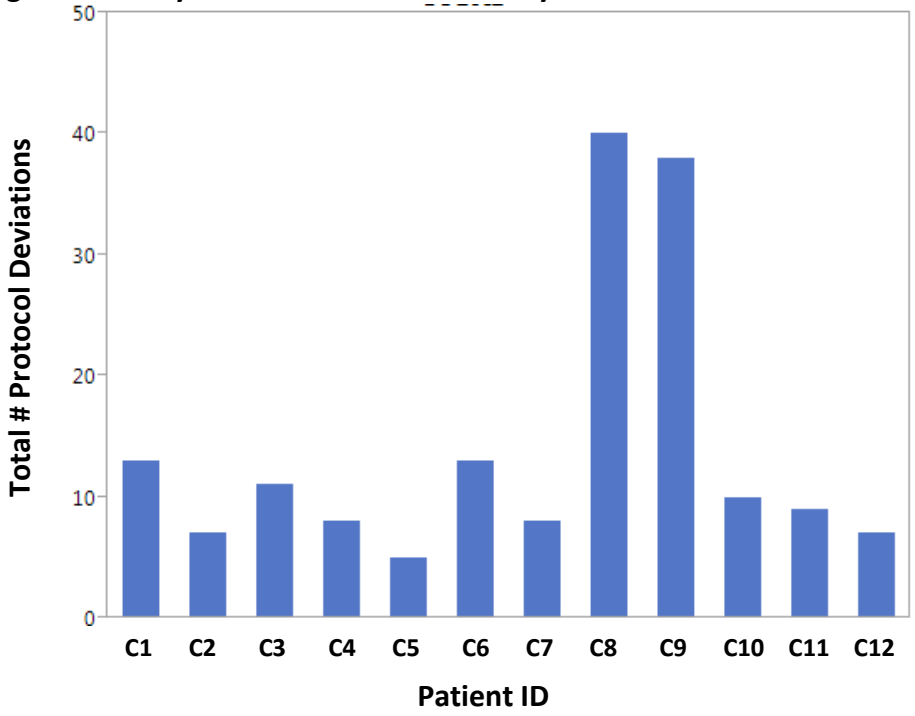
A total of 14 patients were screened and 12 patients were enrolled. The 2 patients who were not enrolled were listed as screening failures and withdrew consent prior to treatment initiation. All 12 patients who were enrolled completed the 48-week study. There were no deaths or adverse events (AEs) leading to study discontinuation. A total of 4 patients relocated to the US from (b) (6) (1), (b) (6) (2) and (b) (6) (1) to participate in the study.

Medical Officer Comment: *This is acceptable***.**

Protocol Violations/Deviations

The Applicant reported a total of 169 protocol violations in Study 301, with at least 5 (range of 5-40) per patient major or minor protocol violations. Two patients (C8 and C9) were reported with a total of 40 and 38 protocol violations, respectively; significantly higher than any other patient. Both patients were treated at the same site (site (b) (6)) and were the only patients enrolled at that study site. In comparison, all but two patients (C3 and C10) were reported to have a single major protocol violation. **(Figure 8**)

Figure 8: Study 301 Protocol Deviations by Patient



Source: BLA 761047 DV.XPT dataset for Study 301

The most common major protocol deviation for Study 301 was the inability to meet an inclusion criterion that stipulated that patients were required to have an elevated uGAG excretion at a minimum of 3-fold over the mean normal for age at the screening evaluation. A total of 5 of the 12 enrolled patients failed to demonstrate> 3-fold elevation of uGAG excretion, and their enrollment was noted as a deviation. (**Table 13**)

One patient received a bolus of vestronidase alfa after the resolution of a mechanical blockage in the IV tubing. Immediately after the bolus infusion this patient (C2) experienced anaphylaxis which resolved after treatment with steroids and epinephrine. Bolus infusion was not specified in the protocol.

Table 13: Major Protocol Deviations for Study 301

Patient Number	Visit	Protocol Deviation
C6, C8 C9, C11, C12	Screening	Patients did not meet inclusion criterion #2, which required elevated uGAG excretion at a minimum of 3-fold over the mean normal for age (at screening) (Section 9.2.1)
C7	Week 18	Pharmacist inadvertently used investigational product (IP) vials that were not dispensed by the study interactive web response system (IWRS), resulting in the patient receiving active IP rather than placebo at Week 18.
C2	Week 22	Initial infusion was stopped due to blood backed up in IV tubing and into filter. Site cleared with saline flush resulting in a bolus of study drug being administered to subject (Section 14.3.3)
C1 C4	Week 46	Urine pregnancy tests were not done at Week 46 for both subjects. Test kits were inadvertently not included with all other lab testing kits for the Week 46 visits for these patients. Subsequent urine pregnancy tests were performed at their respective baseline visit of the extension study (UX003-CL202) 2 weeks later, and both results were negative.
C5	Unscheduled	Site did not report a SAE of "closed head trauma (left side temporal area)" within 24 hours of knowledge of event, per protocol. The initial treatment non-related SAE occurred on 30 Dec 2015 and resolved the next day on 31 Dec 2015. The site became aware of the event on 30 Dec 2015, and reported the event to Ultragenyx Pharmacovigilance on 05 Jan 2016.

Source: Listings 16.2.1.2, 16.2.2, and information outside the clinical database. IP=investigational product; IWRS= Interactive Web Response System; PVG=Pharmacovigilance; SAE=serious adverse event

Medical Officer Comment: Of the 10 reported major deviations from protocol, 5 were due to the inability to meet inclusion criterion #2 (minimal uGAG excretion of 3x the upper limit of normal). As the natural history (and therefore variation in uGAG excretion amongst MPS VII patients) is not well known, this is acceptable as patients were diagnosed either molecularly or enzymatically. Of the other 5 reported major deviations, the most significant was the failure to report an SAE in the appropriate time frame (site (b) (6)), however this occurred only once.

The reported minor deviations were of greater concern, particularly as subjects C8 and C9 demonstrated more total protocol deviations by at least 3x and up to 8x relative to other subjects enrolled in Study 301. Both were the only subjects enrolled at the site (b) (6) in (b) (6). In review of their reported deviations, a significant number involved assessment of vital signs (temperature, heart rate, respirations, blood pressure), clinical evaluations (complete eye exam for acuity or corneal clouding, neurologic exam) or incomplete echocardiograms. These protocol deviations occurred throughout the execution of the trial, from screening through week 48.

Table 14: Minor Protocol Deviations Recorded at Site (b) (6)

Minor Protocol Deviation (incomplete assessments)	*Subject C8*	*Subject C9*
Vital sign assessment	*16/39*	*18/37*
PK draw		
Physical Exam	*9/39*	*6/37*
Echocardiogram	*3/39*	*2/37*
Laboratory Testing (PK, uGAG, etc.)	*8/39*	*7/37*
Other	*3/39*	*6/37*

Source: BLA 761047; Study UX003-CL301, DV.XPT file

Medical Officer Comment: It is unclear if any of the deviations from assessment of full vital signs may have impacted the reporting of transfusion related hypersensitivity reactions.

*By comparison, Study 201 **(Section 6.2**) reported significantly fewer protocol deviations (at most 3 per patient) for a group of patients who received vestronidase alfa at least one year longer in duration. It is not clear if these differences can be explained by the fact that patients enrolled in Study 201 received infusions in two different countries, if the frequency and extent of assessments were higher in the phase 3 study, or if there were other factors not considered.*

Demographic Characteristics

Baseline demographics for all 12 patients enrolled in Study 301 are noted in **Table 15**.

Table 15: Study 301 Baseline Demographics

Demographic Parameters	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Sex (M/F)	F	F	F	F	M	F	M	M	F	F	M	F
Age (years)	14.7	8.5	13.4	12.8	10.1	17.4	10.5	25.3	22.6	22.5	16.5	11.5
Age at diagnosis (years)	5.7	8	5	9	10	< 1	< 1	< 1	16	< 1	16	10
Race	W	Other	W	W	Other	Other	W	W	W	W	W	W
Ethnicity	HL	(b) (6)	NHL	HL		(b) (6)	HL	NHL	NHL	HL	HL	HL
Weeks on placebo	0	8	0	8	24	16	24	24	16	16	8	0

Source: BLA 761047; Study UX003-CL301, DM.XPT and SUPPDM.XPT

(b) (6), HL = Hispanic or Latino, NHL = Not Hispanic or Latino, W = White

C1-through C12 are identifiers of the individual patients in the study.

Patient C1 = FDA Patient # (b) (6)
Patient C2 = FDA Patient #
Patient C3 = FDA Patient #
Patient C4 = FDA Patient #
Patient C5 = FDA Patient #
Patient C6 = FDA Patient #
Patient C7 = FDA Patient #
Patient C8 = FDA Patient #
Patient C9 = FDA Patient #
Patient C10 = FDA Patient
Patient C11 = FDA Patient
Patient C12 = FDA Patient

As there are four study arms in this randomized start protocol, demographics were also assessed by study arm as noted in **Table 16**.

Table 16: Study 301 Demographics by Blinded Start Study Arm

Demographic Parameters	Study 301				Total (N=12) n (%)
	Study Arm A 0 weeks placebo 48 weeks UX003 (N=3)	Study Arm B 8 weeks placebo 40 weeks UX003 (N=3)	Study Arm C 16 weeks placebo 32 weeks UX003 (N=3)	Study Arm D 24 weeks placebo 24 weeks UX003 (N=3)	
Gender					
Male, n (%)	-	1 (33)	-	3 (100)	4 (33)
Female, n (%)	3 (100)	2 (67)	3 (100)	-	8 (67)
Age					
Mean years (SD)	13.2 (1.7)	12.5 (4.0)	20.8 (3.4)	15.2 (8.6)	15.4 (5.5)
Median (years)	13.4	12.8	22.5	10.5	14.1
Min, max (years)	11.5,14.7	8.4,16.4	17.3,22.6	10.1,25.2	8.5, 25.2
Age Group					
< 17 years, n (%)	3 (100)	3 (100)		2 (67)	8 (67)
≥ 17 - < 65 years, n (%)			3 (100)	1 (33)	4 (33)
Race					
White, n (%)	3 (100)	2 (67)	2 (67)	2 (67)	9 (75)
Other, n (%)		1 (33)	1 (33)	1 (33)	3 (25)
Ethnicity					
Hispanic or Latino, n (%)	2 (67)	2 (67)	1 (33)	1 (33)	6 (50)
Not Hispanic or Latino, n (%)	1 (33)	1 (33)	2 (67)	2 (67)	6 (50)

Source: Source: BLA 761047; Study UX003-CL301, CSR Table 9.4.1 DM.XPT and SUPPDM.XPT

Medical Officer Comment: As MPS VII is a rare disease with less than 150 individuals diagnosed world-wide, this reviewer anticipates that there may be uneven distribution of ages in the study arms. Study arm C (16 weeks placebo/32 weeks vestronidase

alfa) is an example of this uneven age distribution. The mean age in this cohort is almost twice the age of the patient cohorts in the three other study arms. Two study arm cohorts (0 weeks placebo and 16 weeks placebo) did not did not contain male patients, however it is not clear if gender impacts disease progression.

Table 17: Additional Baseline Characteristics for Patients Enrolled in Study 301

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Laboratory Diagnosis												
Age at confirmatory testing (years)	5.7	6.1	5.1	9.8	9.9	0.5	0.1	0.3	In utero	11.5	16	11
Enzyme Activity Level	5.0 unk [a]	0.8[b]	6[c]	1.6[d]	1[g]	0.7[e]		1.3[a]	1.2[a]	3[f]		
Molecular Analysis	unknown	UK c.526C<T Not reported[h]		c.526C>T Not reported[h]			Not reported[h]	c.1051C>T c.1289T>C	c.1051C>T C1289T>C		c.1222C>T c.1244C>T	c.1222C>T c.1244C>T
Clinical Features												
Standing Height (cm)	143.9	104	135	146.3	99	128.6	143.5	173.2	160.7	129.9	149.9	143.9
Weight (kg)	55.1	15.1	51.1	24.8	19.7	44.2	41.8	101	75.9	53	74.5	59.8
Hydrops fetalis				X	X							
Cognitive Delay	X	X	X	X	X	X	X	X	X	X	X	X
Sleep Apnea		X	X		X		X					X
Shortness of breath/ Asthma	X			X	X		X				X	
Hepatosplenomegaly			X	X	X	X	X			X		X
Scoliosis/Joint pain/ Spine abnormalities	X	X	X	X	X	X	X	X	X	X	X	X
Joint Contracture	X	X	X	X	X	X	X				X	
Cardiac Pathology	X	X	X	X	X	X	X		X	X	X	X
Corneal Clouding/ Visual Acuity	X	X		X	X		X					X
Mobility impairment		Yes, but did not use assisted devices	Assisted devices for walking Wheelchair bound at baseline	Wheelchair bound			Wheelchair bound			Began using a wheeled walker between study weeks 24 and 32	Cane	
Therapies												
Speech Therapy	X	unk[b]	X	unk[b]	unk[b]		X	X		unk[b]		unk[b]

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Physical Therapy	X						X					

Source: BLA 761047, Study UX003-CL301, MO.XPT dataset; IND 123788 Briefing Package for type B Meeting October 2016; BLA 761047 expanded IR response submitted on June 7, 2017; BLA 761047 IR response submitted June 21, 2017
St = standing, si = sitting, unk = unknown
[a] unknown units
[b] attended special education classes but unknown if received therapies[b] nmol/h/mg (reference lab lower limit of normal 23-151)
[c] nmol/h/mg (reference lab lower limit of normal 156)
[d] pmol/disc (reference lab lower limit of normal 59.3)
[e] nmol/h/ml (reference lab lower limit of normal 23)
[f] nmol/h/ml (reference lab lower limit of normal 21)
[g] nmol/h/mg (reference lab lower limit unknown)
[h] Mutations not reported in dataset

Medical Officer Comment: *Review of the clinical features noted at baseline and at week 48 were not sufficiently descriptive to be informative for this reviewer. For example, all patients had cognitive disability, but the level was not described well enough to understand if this disability was mild, moderate or severe. All patients had reported joint contractures, but not enough to be labeled as "abnormal" on baseline shoulder flexion. It is unclear if this may be related to differences in medical and educational standards of care by country, as four of the enrolled subjects relocated from three different countries to participate in Study 301.*

Three patients used either a walker or were wheelchair bound at baseline (C3, C4 and C7). Patient C11 consistently used a cane at baseline and with 6MWT evaluation. Patient C3 could be evaluated in the 6MWT but did not participate for BOT-2 gross motor testing. Neither patient C4 nor C7 could participate for either 6MWT or BOT-2 gross motor testing. Finally, patient C10 did not use any assistive devices at baseline but initiated the use of a walker between study weeks 24 and 32 (between week 8 and 16 of vestronidase alfa exposure). The initiation of assisted device use was discouraged but not prohibited during Study 301. However, this reviewer believes that initiating the use of an assistive device during the trial is a confounder for mobility testing and may impact interpretability of this patient's results as the patient may have been more rested at the time of the 6MWT and BOT-2 gross motor evaluations.

Because the Applicant had acknowledged during the pre-BLA meeting on October 6, 2016, that thorough developmental histories would be an important context for the interpretability of patients' endpoint assessments, a request for detailed developmental history was made after BLA submission. Review of the Applicant's initial response and the updated response (received on June 8, 2017) was critically helpful as all patients were noted to have moderate to severe cognitive disability as determined by information provided by the caregivers or via evaluations and observations made by the study personnel. Many patients also demonstrated baseline fine motor disabilities.

This reviewer believes that the levels of baseline fine motor and cognitive disability for patients enrolled in 301, as reported by caregivers and study personnel, significantly impacted the evaluation of efficacy in this study as patients were not able to complete or understand how to complete assessments. Regardless, this reviewer finds this spectrum of baseline disability informative and consistent with the current narratives available in the literature for patients with MPS VII (Montano AM, Lock-Hock N et al. 2016). This reviewer believes that the baseline disability of these patients is critical for contextualizing their capacity to complete tasks for Study 301.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All vestronidase alfa doses were administered by study personnel and were not provided directly to patients or their caregivers. Only two doses were missed in individual patients. One patient (0 weeks placebo) missed the vestronidase alfa infusion at Study Week 42 and another patient (16 weeks placebo) missed a placebo infusion at Study Week 6. These patients were at different study sites.

As noted in **Table 17**, patient C10 did not use any assistive devices at baseline but initiated the use of a walker between study weeks 24 and 32 (between week 8 and 16 of vestronidase alfa exposure). The initiation of assisted device use was discouraged but not prohibited during Study 301. However, this reviewer believes this initiation may impact interpretability of this patient's results as the patient may have been more rested at the time of the 6MWT and BOT-2 gross motor evaluations.

Concomitant medications for all 12 patients appeared appropriate for the symptoms associated with MPS VII disease pathology **(Table 18**). All patients received antihistamines prior to infusion. Two patients received oral or IV steroids during Study 301 for the treatment of anaphylaxis and rash, respectively (**Table 12**). This rash was reported during the placebo phase of their protocol treatment.

Table 18: Concomitant Medication Use in Study 301

Concomitant Medications	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Analgesics	X	X	X	X	X	X	X	X	X	X	X	
Antihistamines	X	X	X	X	X	X	X	X	X	X	X	X
Beta adrenergic	X	X										
Muscle relaxant	X		X					X	X			
Psycholeptic			X		X				X			
Anesthetic	X	X	X	X	X	X					X	X
Antibiotic				X	X	X	X	X		X		
Oxygen				X								
Steroid		X							X, X[a]	X[B]		
Birth Control									X			
Anti-viral									X			
Anti-hypertensive								X	X			
Anti-epileptic					X							
Herbal extract	X								X			

Source: BLA 761047; Protocol UX003-CL301, Listing 16.2.4.8
[a] Topical steroid ointment
[B] Nasal spray

Efficacy Results - Primary Endpoint

As agreed upon when IND 123788 was allowed to proceed, there is no pre-specified primary endpoint for Study 301. The assessment of efficacy was to be based upon the totality of the evidence provided by all endpoints. As no statistical analysis plan was agreed upon a priori, differences between the Applicant's approach and the Agency's approach were anticipated for key issues such as handling of missing data, analytic methods and thresholds for clinically meaningful differences. Ultimately, the only endpoint with enough interpretable data to support a statistical analysis was the Six Minute Walk Test (6MWT). The FDA statistical team's review of the 6MWT is described below, followed by the clinical team's description of supportive efficacy findings.

Statistical Review

The statistical team confirmed the Applicant's findings from the Multi-Doman Responder Index (MDRI) described in **Table 19**, but notes that the Applicant's analytic approach is not well-suited to the study design and fails to leverage the placebo period data. The FDA statistical team performed ANCOVA to evaluate the superiority of vestronidase alpha over the placebo period for the Six Minute Walk Test (6MWT).

The ANCOVA analysis was adjusted for treatment group (i.e., time to cross-over), age, and baseline 6MWT value. The analysis includes data from five patients during the placebo period and eight patients during the vestronidase alfa period. The statistical team chose to exclude patients who were wheelchair bound or who used assistive mobility devices. Due to the small size of the study, the ANCOVA results should be interpreted with caution. Please refer to Efficacy results, **Table 20**, for details.

Data Quality and Integrity

The natural history of MPS VII is not well understood and clinical information that might suggest a history for clinical progression in each patient is important for this review, to assess the relevance of changes from baseline on treatment. The development and progression of clinical features are context for MPS VII disease progression for each patient. They are also important for understanding if a patient encountered difficulty in completion of an endpoint evaluation. An information request (IR) was sent on March 29, 2017 to the Applicant requesting more comprehensive developmental histories on each patient in accordance with the Division's request in the pre-BLA meeting on October 5, 2016. The Applicant responded on April 12, 2017 with the available developmental and cognitive history on each enrolled patient. However, details of any motor, cognitive or speech delays as assessed by formal testing were not available for any of the patients. The cognitive history available for review was limited, and was solely based upon the parental or caregiver descriptions offered in the previously

conducted Study UX003-CL002, entitled "A Non-Interventional Study to Collect Information on the Functional Status of Patients Living with MPS VII." In that Study UX003-CL002, a total of 10 of the 12 patients who subsequently enrolled in Study 301 had a family member or care giver complete survey information by telephone about each patient's general MPS VII related medical history. No documentation was requested or required to be submitted in this survey.

Medical Officer Comment: No formal developmental or cognitive evaluation was completed either at initiation or during Study 301 for any enrolled patient. The background information for subjects enrolled in Study UX003-CL002 who were subsequently enrolled in Study UX003-CL301 was only parental or caregiver history, stating whether a patient was believed to have cognitive disability or received services for cognitive, motor or speech disability. This reviewer believes the lack formal cognitive testing in the protocol was a missed opportunity in the vestronidase alfa development program.

The standards for developmental and cognitive evaluation of children are age dependent and often include multi-domain screening instruments that are meant to be completed by professional evaluation. As testing is often used to aide in school placement or initiation of therapy, testing can be specific to evaluate motor skills, language skills, behavior, or may include more than one type of domain. Formalized testing is particularly informative when a child has an underlying diagnosis where the natural history of disease progression is unclear.

This reviewer feels that individual patient developmental or cognitive disability may impact the quality of several assessments. This was already demonstrated in Study 201, where 2 of 3 enrolled patients were unable to comply with testing due to the impact of their cognitive disability on their ability to comprehend the instructions.

In Study 301, the motor assessments included in the MDRI are directly impacted by each patient's cognitive disability. The Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) is designed to assess individuals aged 4-22 years and evaluates normal motor development. Age equivalence was assessed indirectly during the testing and most patients tested with the abilities of a child aged 4-6 years. The Applicant acknowledged that interpretation of this testing was difficult in children whose age equivalence was near the lower end of testing.

The use of a totality of evidence approach was initially considered acceptable as there were few patients available to inform the vestronidase development program. This reviewer believes that when a review is based upon this approach, the data provided by the Applicant should consistently be of high quality and depth for interpretation. It is this reviewer's opinion that the degree of cognitive disability of patients enrolled in Study 301 impacted the quality and consistency of the clinical data collected, as the chosen endpoints were not optimized for this limitation. This reviewer has chosen to evaluate what is interpretable from Study 301, despite the limitations of the Application.

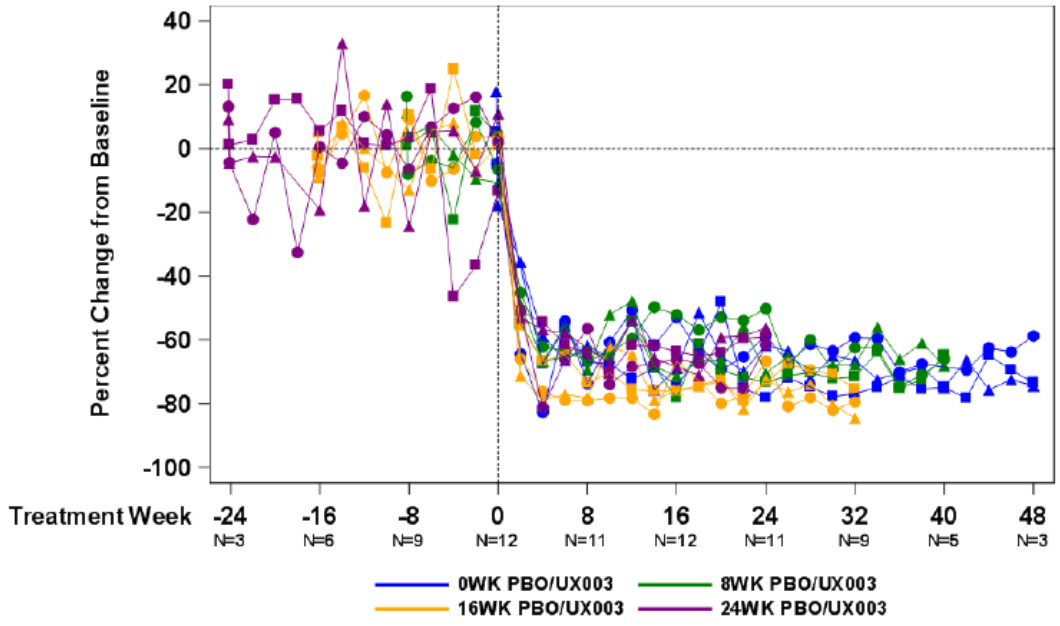
Efficacy Results

Biochemical Endpoint:

Study 301 was designed as a Phase 3 study for approval in both the European Union (EU) and the United States (US). As discussed above, evaluation of the percent change in uGAGs was the primary efficacy endpoint in the EU and a secondary endpoint in the US. Each specific mucopolysaccharidosis is characterized by a pattern(s) of urinary excretion levels for dermatan sulfate (DS), chondroitin sulfate (CS), heparin sulfate (HS) or keratin sulfate (KS). For MPS VII, the levels of CS and KS are generally within normal limits but the levels DS and CS are significantly elevated and appeared to respond similarly to exposure to vestronidase alfa in Study 201. For consistency within the vestronidase alfa development program, the Applicant elected to focus on the uGAG excretion pattern of DS. Similar to Study 201, all patients demonstrated a decrease in dermatan sulfate (DS) uGAG excretion upon exposure to vestronidase alfa infusion. (**Figure 9**)

For this endpoint, a patient was identified as a "responder" if there was ≥50% reduction in uGAG (DS) excretion. All patients in Study 301 were identified as responders for this endpoint.

Figure 9: Percent Change from Baseline uGAG DS Excretion by Visit and Patient in Study 301



Source: BLA 761047, Study UX003-CL301 CSR, Figure 10.1.2 (adapted from Figure 14.2.1.2)
PBO = placebo; UX003 = vestronidase alfa

Clinical Endpoints:

Because of the lack of significant natural history information and the known heterogeneity in the previously surveyed patient populations (Study UX003-0002), Study 301 utilized a Multi-Domain Responder Index (MDRI). The MDRI consisted of 6 domains. The domains and pre-defined responder definitions are noted in **Table 19.**

Table 19: Study 301 MDRI Domain Components and Responder Definitions

Domain	Minimally Important Difference ("Responder Definition")
6-minute walk test (6MWT)	23 meter AND 10% change from baseline
Forced vital capacity (FVC)	5% absolute change or 10% relative change from baseline in FVC% predicted
Shoulder flexion	20-degree change of passive shoulder range of motion
Visual acuity	3-line improvement (corrected, both eyes) using Snellen chart
BOT-2[a] fine motor	Fine Motor Precision: change 0.72 Manual Dexterity: change of 1.47
BOT-2[a] gross motor	Balance: 0.57 Running Speed and agility: 0.59

Source: BLA 761047, Table 8.8.5.3.1.1 CSR for UX003-CL301
[a]BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency

Each domain used a pre-specified "minimally important difference" (MID) to identify responders. A responder for a MDRI domain was given a score of "+1". Worsening via the same pre-specified MID was identified by a score of "-1" and no change in exam was identified via a score of "0". The scores were tabulated into a total MDRI score.

Medical Officer Comment: None of the predefined minimally important differences (MID) provided by the Applicant were well justified, except those for FVC. Additional discussion regarding these concerns is as follows:

- *6MWT: In children, the completion of the 6MWT is impacted by age, but height, weight and motor ability.(Geiger 2007) However, children with skeletal dysplasia demonstrate aberrant linear growth and these published guidelines may not directly apply to MPS. In comparison, the label for elosulfase alfa, an ERT used to treat subjects with MPS IVA, notes that a mean change of 23 m was observed from their placebo controlled trial with subjects aged 5 to 57 years of age. The additional requirement of a 10% increase from baseline is appropriate, particularly to compare patients who could walk > 200 meters at baseline compared to those who could walk >400 meters at baseline. For the MDRI scoring, the Applicant defined worsening in the 6MWT as 23 meters less and 10% shorter than baseline.*

It is this reviewer's opinion that the threshold for worsening on the 6MWT is too high. Review of the literature noted an evaluation of all reported studies of Morquio A (MPS IV A) patients who received enzyme replacement therapy. This paper reported that patients receiving ERT improved by at 2x the distance in the 6MWT compared to the worsening distances reported in a natural history cohort. (Schrover 2017) Because the rate of gross motor decline is not well understood in patients with MPS VII, there is not a good comparator cohort for the 6MWT data collected in Study 301. However, it is this reviewer's opinion that clinically meaningful decline for any of the endpoints assessed in this population may not require as large a threshold.

- *FVC: The responder definition proposed for FVC appears reasonable. The literature for idiopathic pulmonary fibrosis supports a decline in an FVC of ≥ 10% (absolute change) and has also proposed that using a change ≥ 10% relative to baseline can improve sensitivity of identifying a clinically meaningful improvement (Loveman 2015).*

- *Shoulder flexion: This reviewer could not identify set standards for range of motion to interpret the suitability of this endpoint from a regulatory standpoint. The Applicant cites the improvement of shoulder flexion (17.4°± 3.6°) in patients enrolled in a 3 year extension phase after completion of a 26 -week placebo controlled trial of iduronidase in 45 subjects with MPS I ages 6 through 43 years. (Clarke 2009). It is important to note that this change was observed after two years of exposure to iduronidase (not 24 weeks), and only 25 of the originally enrolled patients were evaluated. On a clinical level, most MPS VII patients do not tend to have surgical interventions at the shoulder joint (vertebra and hips are most common), so an improvement or a worsening in mobility at this joint could impact independent activities of daily living (eating, schoolwork, self-care). From a clinical standpoint, the proposed MID for this endpoint appears to be generous given the 24-week duration of the study.*

- *Vision: An improvement in three lines of a Snellen chart with corrected vision is not an acceptable change in clinical trials as the chart does not have an equal number of letters per line or equal spacing between lines. In addition, there are large differences in the reading difficulty of individual letters. On a standardized eye chart, in contrast, a three-line change is considered to be a minimally significant change. Please refer to the DTOP consult from Dr. Wiley Chambers for additional discussion.*

- *BOT-2: The Applicant cites Wuang et al (2009) for the rationale of their proposed MID. This review calculated the minimal detectable change (MDC) and minimal important difference (MID) in a population of 100 children with intellectual disability aged 4-12 who were evaluated on three separate occasions. In this study, the MID was defined as the difference in mean change of BOT-2 scores for children classified as "improved and the mean change score for children classified as "no change" for each subtest. It is also*

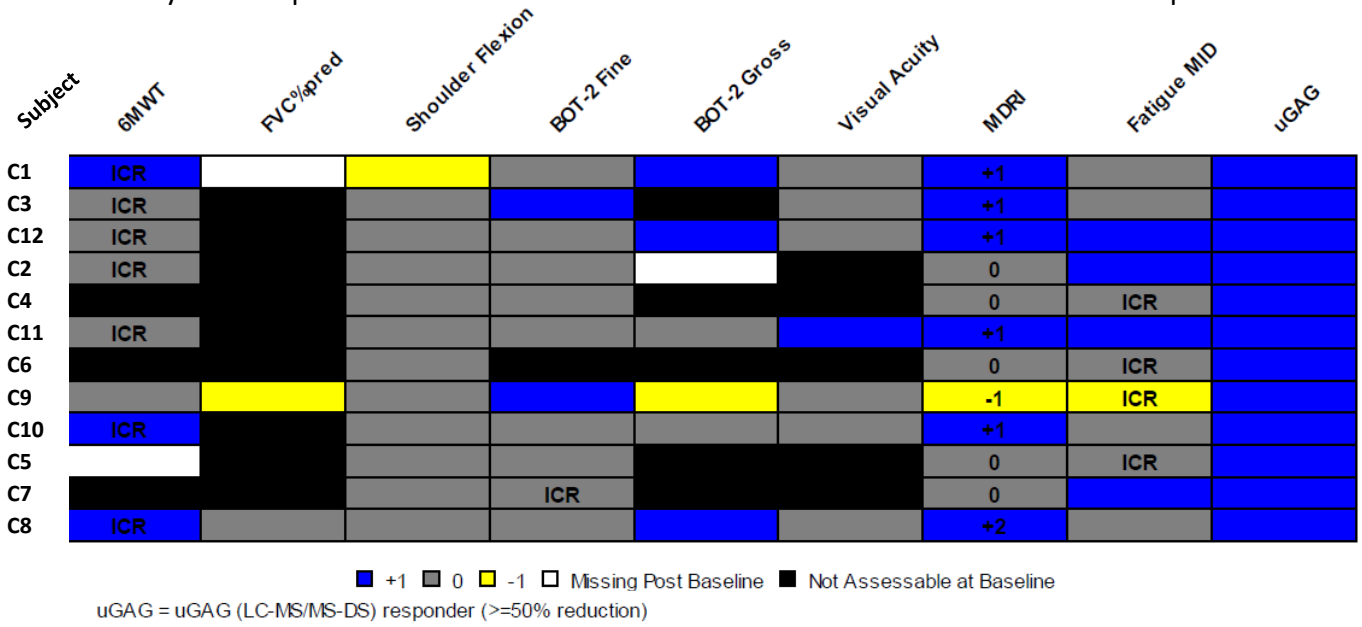
not clear that the subjects with worsening scores should have the same MID from this report.

- *Overall Approach: Ultimately, the assessment of efficacy was based upon a small cohort of patients exposed to vestronidase alfa who were often not able to complete assessments that were interpretable. The interpretation of efficacy will need to consider data that are missing after screening and baseline evaluations. This data may not be missing at random, due to patient level compliance. The review will need to take consideration of this missing data into account of the totality of the evidence provided.*

Dr. Donohue (CDTL) Comment:
I concur with the limitations of the MDRI noted by Dr. Zand above. In addition, the handling of missing data in the MDRI is problematic. The Applicant assumes that data are missing at random, when that is not the case. In fact, most patients attended study visits faithfully, but their cognitive impairment was such that ability to complete functional testing varied. Properly accounting for missing data would largely eliminate the positive results observed in the Applicant's analysis of the MDRI.

The initial protocol also pre-specified an individualized clinical response (ICR) for each enrolled patient. The ICR was developed from Study UX003-CL002, a non-interventional study based upon data obtained from a phone survey with each parent/caregiver to identify what might be a clinically meaningful response for each patient. (**Figure 10**)

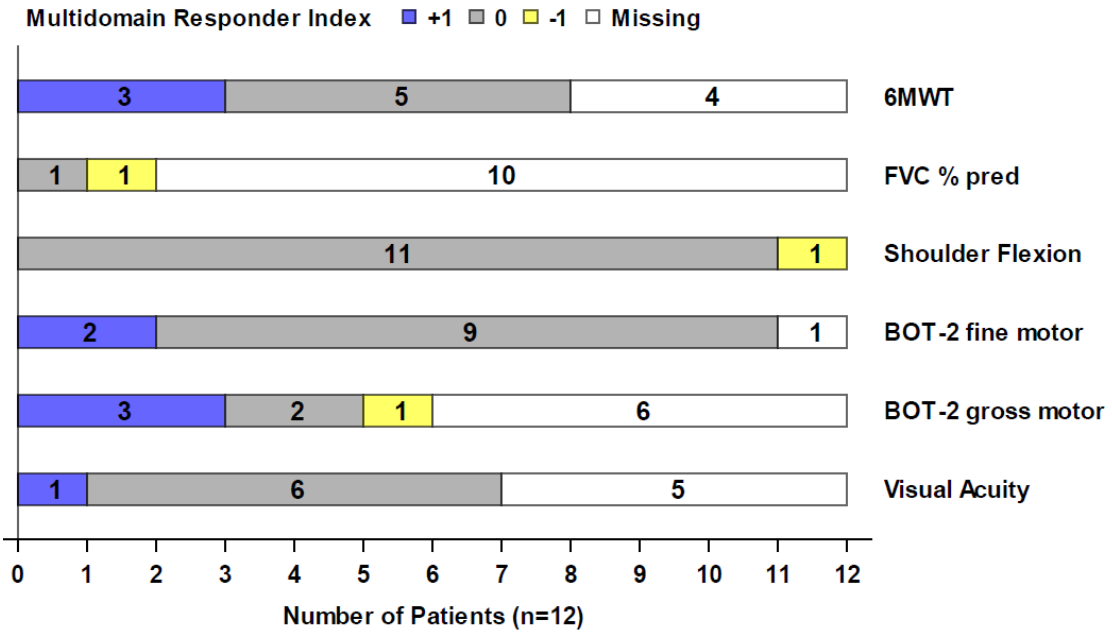
Figure 10: Study 301 Endpoints Defined with MID and Tabulated in the MDRI at 24 Weeks Exposure to Vestronidase Alfa



ICR: Individualized Clinical Response for each subject
When any domains are missing for MDRI at UX003 Treatment Week 24, the MDRI domain at UX003 Treatment Week 32, if exists, is used for imputation. If the MDRI domain at UX003 Treatment Week 32 is missing, then the MDRI domain at UX003 Treatment Week 16, if available, is used.
The missing MID values are counted as 0 to calculate MDRI total score
uGAG responders are subjects ever reached >= 50% reduction from baseline in uGAG excretion during the first 24 weeks of UX003 treatment.
Not assessable at Baseline: defined as when the subjects could not perform the test at Baseline (prior to UX003 treatment) due to the disease and/or age/cognition.
Missing (post baseline): When a subject had baseline evaluation but the MID score at treatment week 24 was missing and could not be imputed
\\dc1\Project Workspace\UX003\Clinical\Clinical Operations\UX003-CL301\11.0 Biostatistics\Week48\Programs\f-admdri-all2.sas
Source: BLA 761047, Study UX003-CL301 CSR, Figure 14.2.2.2.1; Adapted by D. Zand

Based upon the Applicant's summary of results, many assessments were unable to be completed by patients, and therefore could not be included in the total MDRI score. For example, only two patients could be evaluated for FVC % predicted and 5 patients were not able to be evaluated for visual acuity at baseline. (**Figure 11**) The limitations of endpoint completion (due to either difficulties with patient comprehension or effort) added to the difficulty of interpretation of endpoints for this study.

Figure 11: Graphical Summary of MDRI Responder Analysis in Study 301



Source: BLA 761047, Study UX003-CL301 CSR, Figure 14.2.2.1.

Medical Officer Comment: This reviewer acknowledges the difficulty in identification of optimal endpoints for patients with MPS VII. Endpoint selection was also complicated by the fact that no clinical examinations were completed during the non-interventional Studies UX003-CL001 and UX003-CL002 that could inform endpoint selection, only secondary reports of evaluations and parent/caregiver descriptions.

While MPS VII may resemble other mucopolysaccharidoses (MPS I and MPS II), the Applicant acknowledged that the degree of joint immobility due to contractures was considerably less as most patients had normal flexion. In addition, the degree of cognitive disability appeared to be underestimated by the survey history obtained in study UX003-CL002, directly impacting endpoint completion and interpretation.

This reviewer suspects that the interpretability of Study 301 was impacted by the Applicant's choice to use clinical endpoints used by other MPS indications (MPS I and MPS II) in addition to the limitations presented by the use of caregiver surveys to identify clinical concerns associated

with MPS VII patients. The decision to use endpoints derived solely from these considerations, and a trial design that was 24 weeks in duration, may have impeded a clear understanding of how vestronidase alfa may affect disease progression. It is the opinion of this reviewer that the dissimilarities in clinical presentation and rate of disease progression of the different MPS diagnoses are significant. It also appears that not all endpoints from MPS related diagnoses can be evaluable in all MPS diagnoses.

MPS VII disease progression may not occur at the same rate as improvement on treatment. In addition, small changes from baseline in disease progression may be clinically meaningful for patients. However, the pre-specified responder definitions for the endpoints that comprise the MDRI do not account for how a lack of improvement or symptom worsening may be suggestive of continued disease progression. Conversely, these definitions also do not account for how disease stabilization, without significant improvement or reversal, may be clinically important to this patient population.

MDRI Responses

The Applicant concluded that six of twelve patients were responders based upon a positive MDRI score at 24 weeks of vestronidase alfa exposure: patients C1, C3, C8, C10, C11, and C12 (**Figure 10**). Review of individual domain results noted the following:

6-minute walk test (6MWT): This endpoint was used previously to demonstrate efficacy and support the approval of enzyme replacement therapies used to treat MPS I (laronidase), MPS II (idursulfase) and MPS IVA (elosulfase alfa); galsulfase used to treat MPS VI was approved based upon a similar endpoint, the 12MWT.

In Study 301, six patients could be evaluated at baseline and at 24 weeks exposure to vestronidase alfa. Additional information including evaluations during the open-label extension Study 202 was provided in the 120-day update that allowed for an evaluation of 10 subjects.

Based solely upon results from Study 301, the Applicant interpreted three patients (C1, C8, and C10) as responders. For these patients, the mean improvement in 6MWT as evaluated by a % change from baseline was 41 m (standard deviation of ± 29 m).

However, in review by the Division, patient C10 was noted to have initiated the use of an assistive device between Week 8 and 16 of vestronidase alfa exposure. The introduction of the device confounds interpretation of the results and was imputed to "0" in the ANCOVA analysis (shown in Section XX) of both Study 301 and the open label extension Study 202

Medical Officer Comment: The progression of neuromuscular disease in other mucopolysaccharidoses was reviewed in the available natural history studies for patients with

MPS II and MPS IIIA. In these disorders, the rapidity of clinical decline of neuromuscular function appeared to correlate with the severity of cognitive disability and was accompanied by a subsequent plateau.

Holt et al. described the clinical progression of 50 patients with MPS II. Their report describes two trajectories; faster decline for patients with neural parenchymal disease compared to patients with a milder cognitive phenotype. For those subjects with neural parenchymal disease, fine motor skills were most rapidly impaired and a developmental plateau was reached by 48 months of age for gross motor skills with rapid decline thereafter. The authors stated that assessments were standardized to cognitive abilities so that motor assessments were not underestimated.

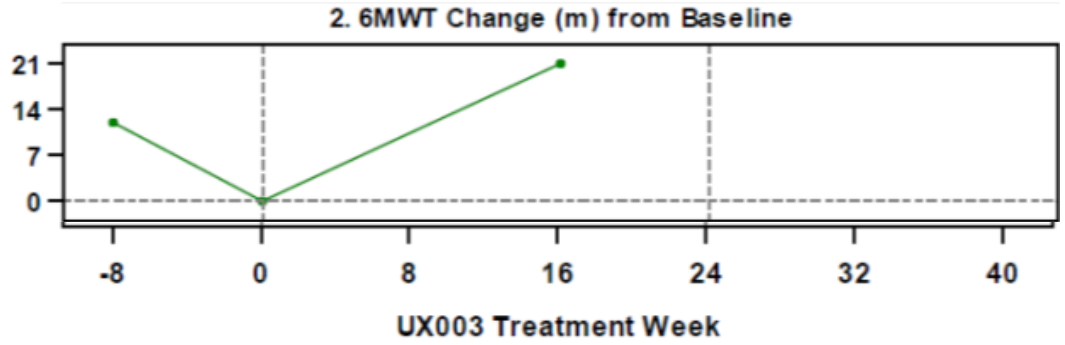
Similarly, 25 patients with MPS IIIA were followed for at least 12 months and assessed and ultimately classified into categories of either "slow progression" vs. "rapid progression". (Shapiro EG 2016)

It is this reviewer's opinion that the degree of cognitive disability in patients enrolled in Study 301 is similar to the severe MPS II and MPS IIIA patients described in the literature, however not enough is known about the disease progression to limit expectations to a single trajectory. The design of Study 301 did not make attempts to correlate motor abilities to cognitive level, lending concern that the decline in 6MWT during the placebo period could be artefactual or related to testing compliance from intellectual disability.

This reviewer believes that when assessed correctly, the 6MWT can be a global test of ambulatory gross motor function. Disease progression is better understood when patients can follow instructions well enough to complete testing at baseline. When subjects are unable to complete testing at follow up, it may reflect progression of the neurocognitive component of MPS disease or other components (e.g., cardiopulmonary function), not necessarily progression of motor skills. However, if the inability to complete follow-up testing is related to noncompliance, the challenge of how to account for missing data points becomes critical to interpretation of efficacy for these endpoints.

For example, patient C2 was randomized to receive 8 weeks placebo and 40 weeks vestronidase alfa and did not demonstrate improvement after 16 weeks exposure. This patient could complete the 6MWT at screening, baseline and after 16 weeks exposure to vestronidase alfa. However, they were not able to complete an evaluation at weeks 8, 24 and all subsequent follow-up evaluations as noted in ***Figure 12.***

Figure 12: Line Graph of 6MWT Assessments for Subject C2



Source: BLA 761047 (refer to Appendix A)

Review of the individual case report forms (CRF) documented the following reasons for lack of completion of the 6MWT in this subject:

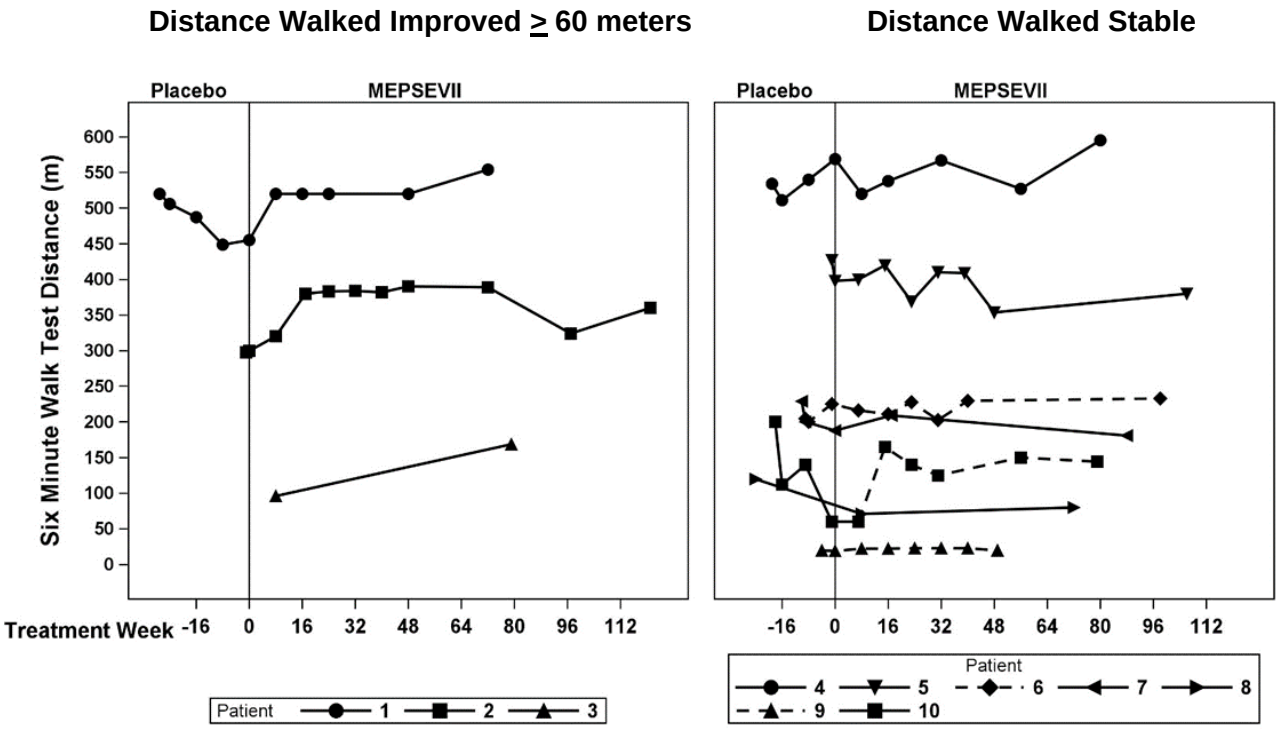
- *"Subject continues to do her own "way" stops and starts and never completes full laps. She does not cognitively understand testing ". The individual scoring the test did not consider the test valid.*
- *"Testing did not meet standard of acceptability and is not valid."*
- *"Not able to comprehend and follow test instructions."*
- *"Subject never completed one lap, and chose not to go on, we stopped the test."*

*It is this reviewer's opinion that the missing data in this patient's 6MWT assessments may be more reflective of cognitive impairment than of deterioration in her gross motor deficit. The overall interpretation of this concern will be discussed in the Integrated Summary of Effectiveness (**Section 7**)*

Durability of 6MWT Response and Correlation with Other Endpoints

At the time of the BLA 761047 data cut-off date, patients enrolled in the open label extension Study 202, were still enrolled and continued to receive vestronidase alfa. To assess the durability of response, the Agency requested additional data for review. The updated follow-up information received on July 28, 2017 and September 22, 2017 was mostly interpretable for the 6MWT distances shown in **Figure 13**

Figure 13: 6MWT Distance for MPS VII Patients in Studies 301 and 202



Patient 10 did not use an assistive device at baseline but started using an assistive device post-baseline from Treatment Week 8. Patients 6 and 9 consistently used assistive device at all visits. A solid line indicates the unassisted assessments and a dotted line indicates the assisted assessments.

Patients enrolled in Study 301 were identified differently during this BLA review compared to the label for vestronidase alfa. Patient identifications correlate as noted:

Figure 13 (Label): Patient 1 = C8 (Study 301)
Patient 2 = C1
Patient 3 = C6
Patient 4 = C9
Patient 5 = C12
Patient 6 = C11
Patient 7 = C2
Patient 8 = C5
Patient 9 = C3
Patient 10 = C10

Patient C1 improved in the 6MWT to a peak of 90 meters at week 16 of vestronidase alfa treatment and maintained this level through week 48. BOT-2 gross motor performance improved at week 16 through 48. The fatigue score improved at week 32 through 48.

Patient C8 demonstrated decline from screening until baseline, with subsequent improvement from baseline on vestronidase alfa to a peak of 66 meters from 8 to 24 weeks. There was no

change in BOT-2 gross motor performance and the fatigue score worsened during this 24-week period. The reason for decline in fatigue score is unclear.

In comparison, patient C10 initially improved in the 6MWT with a peak of 105 meters at week 16 that declined to 70 meters at week 32. The BOT-2 gross motor test improved at weeks 8 and 16, then declined at week 24. However, this patient initiated use of a wheeled walker between weeks 8 and 16 of exposure to vestronidase alfa as reported in **Table 17.** It was noted that the patient did not use the walker during the 6MWT. While this improvement would be considered clinically significant, it is unclear to this reviewer if the use of an assisted device also contributed to the improved mobility via improved reserve or ability to rest core musculature, and these distances were imputed to zero in the ANCOVA analysis performed by the statistical team.

Statistical Review

The statistical team confirms the Applicant's findings from the Multi-Doman Responder Index (MDRI), but notes that the Applicant's analytic approach is not well-suited to the study design and fails to leverage the placebo period data. The team then performed ANCOVA to evaluate the superiority of vestronidase alpha over the placebo period for the Six Minute Walk Test (6MWT).

The ANCOVA analysis was adjusted for treatment group (i.e., time to cross-over), age, and baseline 6MWT value. **Table 20** summarizes the least squares mean difference between the vestronidase alpha period and placebo period in 6MWT at different treatment durations. After 24 weeks of treatment, the least squares mean difference in 6MWT between vestronidase alpha and placebo periods is approximately 18 meters with a relatively large standard error of 33. Due to the randomized start design, there was no placebo period for the three patients who received 48 weeks vestronidase alfa. Therefore, more data were available for analysis during the treatment period (n=8) than during the placebo period (n=5). In addition, because of the small size of the study, standard errors are large.

Table 20: Mean Difference in 6MWT Distance (meters) Between MEPSEVII and Placebo Treatment (Study 301) in Patients with MPS VII

Duration of MEPSEVII Treatment	LS mean 6MWT (meters) (± Standard Error)*	Number and Treatment Assignment of Patients Included in Analysis**
8 weeks	-11 (± 24)	5 placebo period; 8 MEPSEVII period
16 weeks	13 (± 32)	5 placebo period; 8 MEPSEVII period
24 weeks	18 (± 33)	5 placebo period; 8 MEPSEVII period

*ANCOVA analysis of change from baseline in least squares (LS) mean between placebo and MEPSEVII for different periods, after adjusting for study cohort, age, and baseline 6MWT distance. Patients who used assistive devices were imputed as zeros in the analysis.

**Number and treatment assignment of patients included in the analysis was based upon a randomized start trial design and patient ability to complete testing. Due to no placebo period for the three patients who received 48 weeks of MEPSEVII in the

first cohort of the randomized start design, more data were available for analyses during the treatment period (n=8) than during the placebo period (n=5). While data from 8 participants were available at each time point, due to missing observations, the 8 participants were not the same across all timepoints.

The statistical review team concluded that no substantial evidence of efficacy is demonstrated in these data for 24 weeks of vestronidase alpha treatment in patients with MPS VII. The statistical team acknowledges the challenges faced when evaluating patients with rare, clinically heterogeneous disease, including that there may be too few patients who share similar characteristics to perform the study design chosen by the Applicant.

Dr. Donohue CDTL Comment: The point estimate of an 18-meter increase in mean 6MWT distance after 24 weeks of treatment may reflect a trend toward clinically meaningful improvement. The clinical team notes that the rarity and heterogeneity of the disease are reflected in the large standard errors reported in the ANCOVA analysis. Furthermore, the results cannot exclude a range of potential point estimates for the 6MWT that we would find clinically meaningful. In fact, careful review of individual patient narratives identified 3 patients with 65 to 105-meter improvement in 6 MWT with longer durations of treatment. A fourth patient may have also achieved a similar degree of improvement. It is our conclusion that it may not be feasible in this exceedingly rare and heterogeneous disease to generate statistically significant evidence of efficacy for a drug with a modest, but clinically meaningful, effect size. We also acknowledge that the lower bound of the standard error includes the possibility for harm, that treatment with vestronidase alpha may reduce walking distance. Though we cannot exclude this possibility, we believe it is unlikely, and can be monitored in planned post-marketing safety studies. Thus, the clinical team is willing to accept this degree of uncertainty at the week 24 time point and recommend approval based upon the 18-meter increase in the 6MWT along with the observation of much larger improvements with longer treatment durations, reduced urinary GAGs, and pulmonary improvement in expanded access patients.

Forced vital capacity (FVC): This endpoint was utilized to support approval of laronidase/Aldurazyme for use in patients with MPS I. It was also evaluated as an endpoint in the idursulfase (Elaprase) development program in patients with MPS II, but there was no treatment-related improvement observed in MPS II. Due to the underlying cognitive disability in the MPS VII patients that resulted in an inability to comprehend instructions, only two patients could attempt pulmonary function testing. In general, this was not an interpretable endpoint for patients with MPS VII during the time frame of Study 301.

Shoulder flexion: Most patients in Study 301 demonstrated normal shoulder flexion at baseline. Therefore, in general, this was not a sensitive endpoint for patients with MPS VII during the time frame of Study 301.

Bruininks-Oseretsky Test of Motor Proficiency (BOT-2): This test is a standardized, norm referenced evaluation usually given by physical or occupational therapists to assess motor development in subjects aged 4 years through 21 years and 11 months. The initial testing (BOTMP) was updated as a second edition (BOT-2) in 2005 and is composed of 8 subtests grouped into four broad categories of motor functioning based upon the specific muscle groups and limbs involved in the movements assessed. In healthy children, the test has demonstrated an ability to detect changes in performance over time (Stratford 1996). This test has also been interpreted to be reliable in subjects with cognitive disability (Wuang 2008). However, it is important to note that in this study, the 100 children enrolled were evaluated by a single rater with over 13 years' experience in administration of the BOT-2.

In review of the Clinical Evaluator User Manual for Investigators, the Applicant has selected four of the eight subtests included in the complete BOT-2 assessment: fine motor precision, manual dexterity, balance and running speed, and agility. These were the same subtests utilized in the BOT-2 for Study 201. The four subtests not evaluated in study subjects were the following: fine motor integration, bilateral coordination, upper-limb coordination and strength.

Multiple evaluators administered the BOT-2 to 9 of the 12 patients enrolled in Study 301 (**Table 21**).

Table 21: Number of BOT-2 Evaluators per Subject in Study 301

Subject	Number of Physical Therapist(s) Involved in Assessing BOT-2
C1	2
C2	3
C3	2
C4	2
C5	2
C6	2
C7	1
C8	2
C9	1
C10	1
C11	3
C12	2

Source: BLA 761047 IR Response 15 May 2017

The Applicant acknowledged that the use of multiple evaluators could introduce variability in the collection of study data. In response to a request to assess inter-rater reliability, the Applicant stated that there was no opportunity to perform a post-hoc assessment of inter-rater reliability and as the BOT-2 evaluation was developed for the assessment and diagnosis of fine

and gross motor function in a clinical setting, the training received by the evaluators would most likely be consistent enough to mitigate the risk of variability of assessments.

Scoring instructions were provided by the BOT-2 manual and involved a raw test score that was subsequently converted to a total point score. An improvement by at least one "minimally important difference" (MID) for any test score was noted by a +1 to the MDRI domain. Conversely, a decrease by at least one MID for any subset test was noted by a -1 to the MDRI domain. The minimal important difference (MID) for each subtest was the MID calculated in a publication used to demonstrate validity of the entire BOT-2 instrument in children with cognitive disability (Wuang 2008).

In consultation, the Clinical Outcomes Assessment (COA) review commented that the BOT-2 testing (both fine motor and gross motor assessments) is generally not fit for purpose in patients with MPS VII due to the cognitive limitations of this patient population. Please refer to Michelle Campbell's review for additional detail.

Medical Officer Comment: *This reviewer concurs with the COA review. In addition, this reviewer noted that the MID used for each subtest was the group level MID (i.e., the difference of the average BOT-2 change scores between the "improved" and "no-change" groups from the Wuang et al. article) and not subject level MID for the BOT-2 analyses. Therefore, the subject level minimally important differences (MID) for the BOT-2 subtests used in Study 301 were not known.*

- **BOT-2 fine motor evaluation:** This evaluation was comprised of both the BOT-2 fine motor precision and manual dexterity subtests.

    - **Fine Motor Precision:** This subtest consists of 7 items (filling in the shape of a circle, filling in the shape of a star, drawing lines through a crooked path and drawing lines through a curved path, connecting dots, folding paper and cutting out a circle) for a total point score of 41. The Applicant pre-defined "minimal important difference" (MID) in this score was a change of 0.72.

    - **Manual Dexterity**: This subtest consists of 5 items (making dots in circles, transferring pennies, placing pegs into a pegboard, sorting cards, stringing blocks) with a maximum score of 45. The Applicant pre-defined MID for this score was a change of 1.47.

    Two of twelve patients (C3 and C9) were reported to improve on the BOT-2 fine motor evaluation. However, all patients tested at age equivalence to < 4 to 10 years, with the lower level of interpretation for this testing reported at 4 years. One of the two patients tested at an age equivalence of 4-6 years. Mild improvements were noted for manual

dexterity in the specific items of sorting cards and making dots in circles. The fine motor precision items assessing the patient's ability to connecting dots also improved. However, each subtest also contained items that also were noted to worsen. The second patient was at the age limit for normal testing but her age equivalence was assessed at about 8 years of age.

Comparison of the percent change from baseline for both subtests did not demonstrate significant improvement over placebo or over time.

Medical Officer Comment: This reviewer believes that the BOT-2 fine motor evaluations may not be sufficiently consistent to support efficacy. While the BOT-2 has been reported to be validated in children who have cognitive disability (Wuang 2008), this validation was provided by a single evaluator with greater than 13 years of experience in test administration and the severity of cognitive disability of these patients was not described. Therefore, a direct comparison to the patients with moderate to severe cognitive disability enrolled in Study 301 may not be appropriate. In addition, the Applicant's use of the MID identified in this publication was not appropriate as these MIDs were based upon group level analyses. The MIDs do not reflect subject level data and therefore cannot be used to analyze individual patients.

*Nine of 12 patients were administered the BOT-2 subtests by at least 2 evaluators in Study 301. **(Table 21**) The Agency's Office of Scientific Investigation's audits noted that all discrepancies in the BOT-2 fine motor assessments occurred in the transfer of the raw data to the point score. It was their interpretation that the complexity of the evaluation in the hands of inexperienced administrators may have led to unreliable point scores. It is this reviewer's opinion that reliability of the BOT-2 fine motor scoring was impacted by the lack of consistency of the evaluations.*

The BOT-2 fine motor assessment did not demonstrate improvement over placebo, or over time. In addition, the introduction of multiple assessors may have introduced variability into these evaluations. These conclusions suggest to this reviewer that the BOT-2 fine motor endpoint cannot, on its own, be used to demonstrate efficacy.

- **BOT-2 gross motor evaluation**: This evaluation was comprised of both the BOT-2 Balance and Running speed and Agility subtests:
    - **Balance:** This subtest consisted of 9 items (standing with feet apart on a line with open eyes, walking forward on a line, standing on one leg on a line eyes open, standing with feet apart on a line eyes closed, walking forward heel to toe on a line, standing on one leg on a line eyes closed, standing on one leg on a balance beam eyes open, standing heel to toe on a balance beam, standing on

one leg on a balance beam eyes closed), with a maximum point score of 37. The Applicant pre-defined MID for this score was a change of 0.57.

- **Running speed and agility:** This subtest consisted of 5 items (shuttle run, stepping sideways over a balance beam, one legged stationary hop, one legged side hop, two-legged side hop) with a maximum point score of 52. The Applicant pre-defined MID for this score was a change of 0.59.

A total of 6 of 12 patients were unable to complete testing for this endpoint, and 4 of those were also unable to complete testing for the 6MWT. Six patients could complete baseline and 24 week assessments and 3 patients (C1, C8 and C12) were reported as responders for BOT-2 gross motor skills. Of those, two (C1 and C8) also demonstrated improvement in the 6MWT, while patient C12 had improvement in their fatigue score. The initiation of an assistive device by Week 16 of treatment confounds interpretation of the 6MWT results at this time point and thereafter.

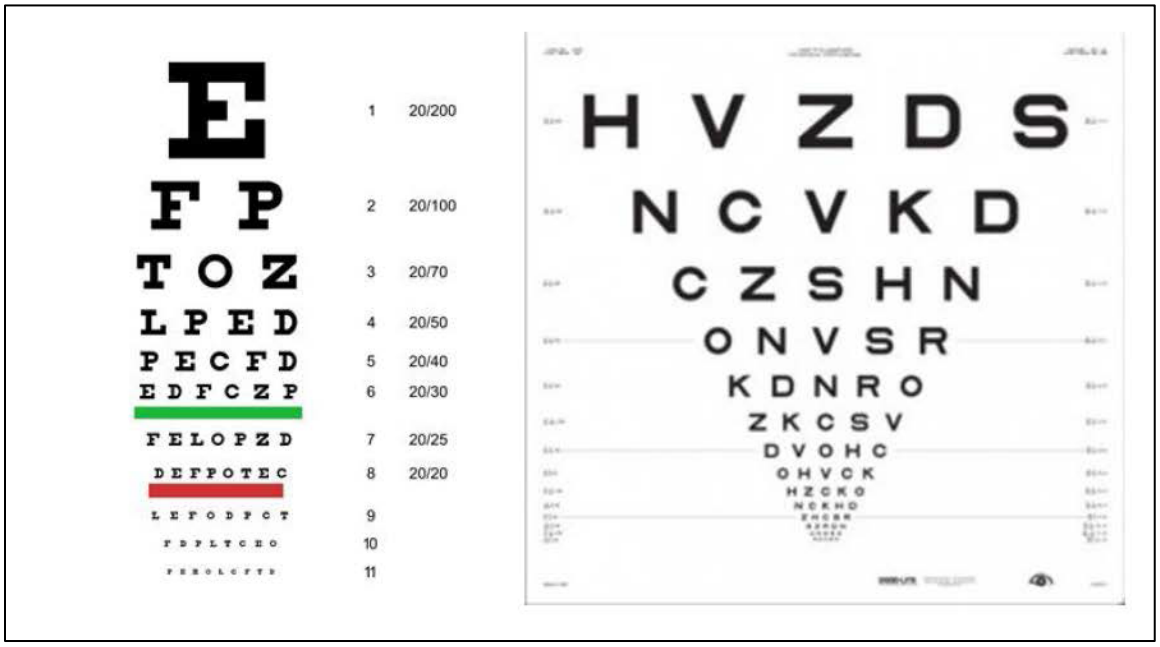
Medical Officer Comment: As the BOT-2 Balance assessment suggested improvement in 2 patients who also improved in the 6MWT, additional sensitivity analyses were completed to assess statistical correlation or trend toward correlation between the BOT-2 balance assessments and the 6MWT. These sensitivity analyses did not demonstrate a strong statistical correlation, however given that improvement on balance may improve walking ability, these results can be considered supportive evidence for Patients C1 and C8 for their improvement in 6MWT.

Visual acuity: A responder was pre-specified as a patient whose corrected vision improved by at least 3 Snellen lines for both eyes. Five of 12 patients were not able to be evaluated for this endpoint due to their inability to comprehend instructions while 7 patients could complete the uncorrected visual acuity assessment. Although the protocol specified that vision would be assessed both uncorrected and corrected, no patient was evaluated using corrective lenses. One patient, C11 was considered a responder by the Applicant.

The reader is referred to the consultation of Dr. Wiley Chambers of the Division of Transplant and Ophthalmology Products (DTOP) for detailed concerns regarding the visual acuity assessment used in Study 301. These concerns impact the interpretability of this evaluation, as summarized below:

- The charts used to measure visual acuity in the trial were not adequate for evaluating changes in visual acuity. As described in the protocol's reference articles, the Snellen visual acuity chart lacks having an equal number of letters per line, equal spacing between lines and an equal reading difficulty of letters. (**Figure 14**).

Figure 14: Comparison of Snellen Eye Chart (Left) vs/ the ETDRS chart (Right)



Source: Dr. Wiley Chambers, FDA/DTOP

- The clinical trial failed to use a methodology to measure visual acuity that would accurately assess the visual acuity potential of subjects in the clinical trial. The protocol and case report forms indicated that corrected visual acuity would be evaluated. However, none of the subjects had a refraction performed. None of the subjects had their visual acuity measured with correction. In the absence of a corrective lens, subjects may "squint" to varying degrees, altering their ability to recognize letters.

- Clinically significant improvement in visual acuity has not been demonstrated in any of the patients treated with vestronidase alpha. The variation observed from visit to visit is commonly seen when visual acuity measurements are repeated on different days.

Medical Officer Comment: The methodology used to evaluate visual acuity was vulnerable to false positive findings, thus visual acuity should not be factored into the totality of evidence in the consideration of efficacy for vestronidase alfa. Additionally, Dr. Chambers, the consultant from DTOP, recalculated the LogMAR visual acuities due to concern that they were incorrectly calculated by the Applicant. Based upon these recalculations, this consultant's interpretation was that the visual acuity of the patients enrolled in Study 301 was variable on and off vestronidase alfa exposure and consistent with the expected test, re-test variability noted for

this evaluation. It is the opinion of this reviewer that based upon the consultation provided by DTOP, that visual acuity cannot be considered as an efficacy endpoint in Study 301 and subject C11 cannot be considered a responder for the MDRI.

Fatigue: While fatigue was not formally part of the MDRI scoring, it was considered a "secondary" endpoint and was evaluated using the Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL-Multidimensional Fatigue Scale).

The PedsQL Multi-Dimensional Fatigue Scale contains three domains: general fatigue, sleep/rest fatigue and cognitive fatigue with each domain containing six questions. The response options are a 5-point Likert scale (0= Never to 4=Almost Always) for the Child Report (age 8-12) and the Teen and Adolescent Report (age 13-18). For the PedsQL Multi-Dimensional Fatigue Scale for the Child Report for Young Children (age 5-7), the response options are a 3-point Likert Scale (0=Not at All, 2=Sometimes, 4=A lot). The instructions allow for face cartoons to be used for children age 5-7 who do not understand the question to assist in responding to the question. The parent version of the PedsQL response options are on the 5-point Likert scale.

No information was provided regarding the content validity of the PedsQL Fatigue Scale in patients with MPS VII. Additionally, supportive information on the measurement properties of the PedsQL Fatigue Scale was not provided. There is a marked difference in the recall period between the child and teen reports versus the young children's report. The child and teen report has a one month recall period while the young children report refers to a recall period of the last few weeks. In general, the use of different recall periods introduces concern for the comparability of the data. Lastly, the fact that there are duplicate items between the three fatigue domains also introduces concern for redundancy.

The parent version of the PedsQL Fatigue Scale was used as an observer-reported outcome measure. However, some of the items cannot be adequately assessed by observers (e.g., parents). Items such as "feeling too tired to spend time with his/her friends", "resting a lot", "trouble remember what he/she was just thinking" can only be assessed directly by the patients. Due to the degree of cognitive impairment in the MPS VII subjects it was unclear if patients could reliably self-report.

Medical Officer Comment: This reviewer concurs with the Clinical Outcomes Assessment Staff review that the results of the PedsQL Fatigue Scale alone were not interpretable by themselves as supportive evidence of efficacy.

Additional "Tertiary" Efficacy Endpoints

Cardiac Assessments: Echocardiograms were performed on all 12 patients at baseline and at week 48. Screening medical history noted 9 of 12 patients with pre-existing cardiac disease. The spectrum of baseline evaluations included mitral valve incompetence, stenosis and sclerosis. Aortic valve incompetence and sclerosis in addition to tricuspid valve incompetence were also noted. Cardiomegaly, ventricular dilatation and right atrial dilatation were reported in one patient, each at baseline.

The reported baseline findings are common in other MPS diagnoses, but are more prevalent in those MPS syndromes in which dermatan sulfate catabolism is predominantly altered.[5]

Following treatment with vestronidase alfa for 24-48 weeks, an increase in left ventricular diastolic volume was identified, but was interpreted by the Applicant to be of unclear significance. The Division of Cardiovascular and Renal Products (DCRP) reviewed the clinical narratives and echocardiogram reports for the 12 patients enrolled in Study 301. In their evaluation, cardiac ejection fractions were normal at baseline and at the end of week 24. The echocardiographic data from all 12 patients suggested normal cardiac function and did not indicate a clinically meaningful change of cardiac status following ERT for 24, 32, 40 or 48 weeks' duration. In addition, the echocardiographic valvular image findings were reviewed and showed valvular GAG deposition, consistent with what is known about the cardiac pathophysiology of MPS VII. Please refer to DCRP consult for additional details.

Medical Officer Comment: The Applicant, this reviewer and DCRP concur that the cardiac evaluations of patients in Study 301 did not suggest improvement of cardiac status during the time period assessed. *The updated cardiac information submitted in the 120-day safety update did not change this reviewer's analysis of the DCRP consult. These 120-day echocardiograms continued to demonstrate worsening valvular deposition as might be anticipated for other MPS diagnoses (Gniadek TJ, Singer N et al. 2015).*

Hepatosplenomegaly: Liver and spleen volume were to be evaluated by MRI at Week 0 and Week 48. If an MRI could not be performed, liver and spleen size were to be assessed qualitatively by physical exam. Four patients were evaluated by clinical exam at baseline, but 3 of these 4 subjects did not have evaluations after 48 weeks. One patient was reported to have decreased liver and spleen on palpation from baseline at 48 weeks as evaluated on clinical exam. One patient was evaluated by clinical exam only at 48 weeks and not at baseline. In

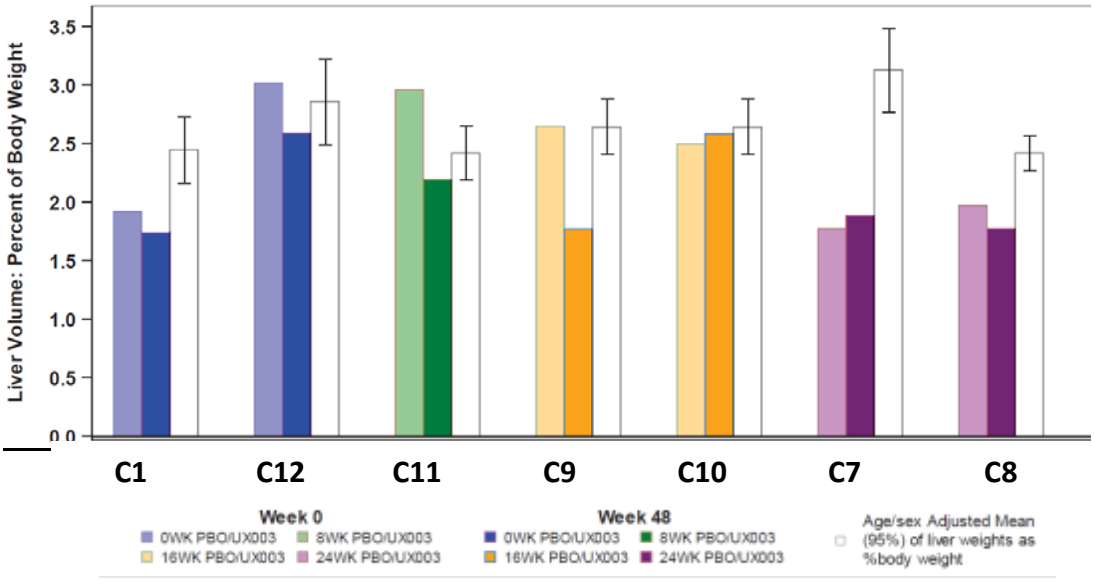
[5] Braunlin E, et al Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. JIMD 2011: 34; 1183-1197.

general, the Applicant stated that the incidence of liver or spleen enlargement at baseline was less than anticipated compared to other MPS disorders.

Of the 7 patients evaluated by MRI or ultrasound, 5 were noted to have normal sized or slightly smaller sized livers compared to normal at study initiation. (**Figure 15**) Of these patients, there was relatively no change after 24 to 48 weeks of exposure to vestronidase alfa. Two patients were noted to have a slightly increased liver size at baseline (C11 and C12) and slight reductions in liver size at 32- and 48-weeks, exposure to vestronidase alfa, respectively. Most liver volumes were normal or below normal size at baseline (mean 1,591 ml, range 742 to 2,207 ml), and on average were unchanged after treatment (mean 1,459 ml, range 876 ml to 1,851 ml).

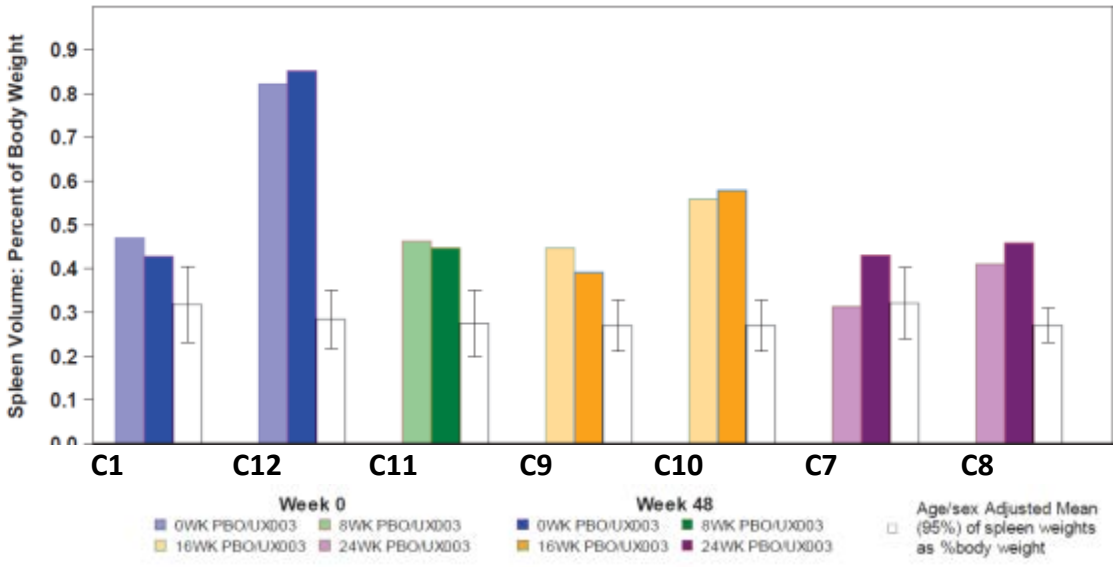
Spleen volumes generally were normal or below normal size at baseline (mean 339 ml, range 131 to 491 ml) and on average were unchanged after treatment with MEPSEVII (post-treatment mean 336 ml, range 200 to 582 ml). (**Figure 16**)

Figure 15: Liver Volume Relative to Body Weight (%) by Study Week and Subject



Source: BLA 761047, CSR Study UX003-CL301 Figure 14.2.19.1 (page 628 of 970)
Patients were evaluated at baseline and at 48 weeks of enrollment. Patients were also stratified by weeks of exposure to placebo (noted in figure legend)

Figure 16: Spleen Volume Relative to Body Weight (%) by Study Week and Subject



Source: BLA 761047, CSR Study UX003-CL301 Figure 14.2.19.2 (page 629 of 970)
Patients were evaluated at baseline and at 48 weeks of enrollment. Patients were also stratified by weeks of exposure to placebo (noted in figure legend)

Medical Officer Comment: It is this reviewer's opinion that the degree of hepatosplenomegaly that was observed in patients with MPS VII is less severe than for other MPS diagnoses, making assessment of a treatment effect difficult.

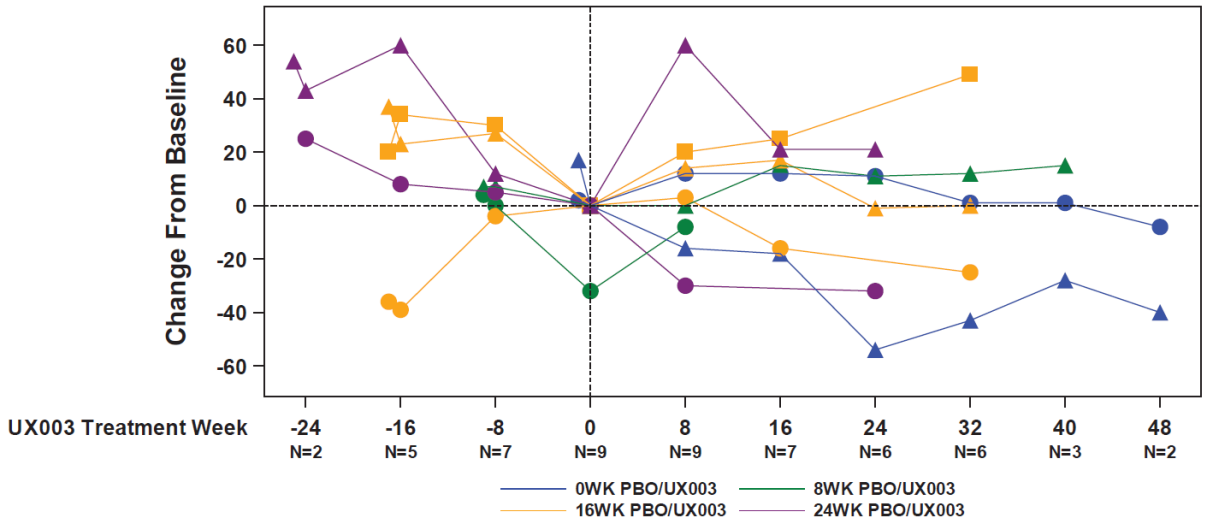
The protocol stipulated either MRI or clinical palpation to determine organ size. Seven of the 12 patients enrolled in Study 301 had imaging to determine liver and spleen size. And while the exact methodology used for MRI (T1/T2 weighted images; ISITE Enterprise software; 3T) or ultrasound evaluation were different, there was consistency in the method used sequentially on each patient.

One patient was evaluated by ultrasound (US). Of the 6 patients evaluated by MRI, two were noted to have slightly increased hepatomegaly at baseline and both demonstrated a slight reduction of liver volume after 32 and 48 weeks of vestronidase alfa exposure, respectively (C11 and C12). In comparison, other subjects (C10 and C7) were noted to have a slight increase in hepatic size after 48 weeks. This reviewer is not confident that these findings are significant or directly interpretable as supportive evidence, particularly as these MPS VII patients did not demonstrate significant organomegaly at baseline.

Dr. Donohue (CDTL) Comment:
I suspect that the changes observed in spleen and liver size may reflect reversion to the mean rather than true substrate reduction. There were several limitations in study conduct with respect to abdominal imaging, and most patients had normal or below normal organ size at study start. As a percentage of body weight, three patients had a < 1% reduction in spleen volume and four had a < 1% increase. Similarly, five patients had a < 1% reduction in liver volume and two had a < 1% increase.

3-Minute Stair Climb Test (3MSCT): A 3MSCT was completed at the screening visit. Patients who were reliably and safely able to complete the test would be evaluated at Week 8, 16, 24, 32, and 48 weeks. (**Figure 17**) Review of patients who could complete this assessment were notable for worsening for all patients who were interpreted as improved in the 6MWT (patients C1, C8 and C10 noted below as blue triangles, red circles, etc.).

Figure 17: Change from Baseline in Three Minute Stair Climb (Steps) by Treatment Week and Patient



BLA 761047 Study UX003-CL301, Figure 14.2.15.2, CSR page 621 of 970

Medical Officer Comment: In general, patients appeared to demonstrate variable results on this evaluation, regardless of duration of exposure to vestronidase alfa. The lack of correlation of improvement with those patients who demonstrated improvement in the 6MWT is concerning, but may be reflective of the need of increased strength, level of coordination and cardiopulmonary reserve required for completion of the task.

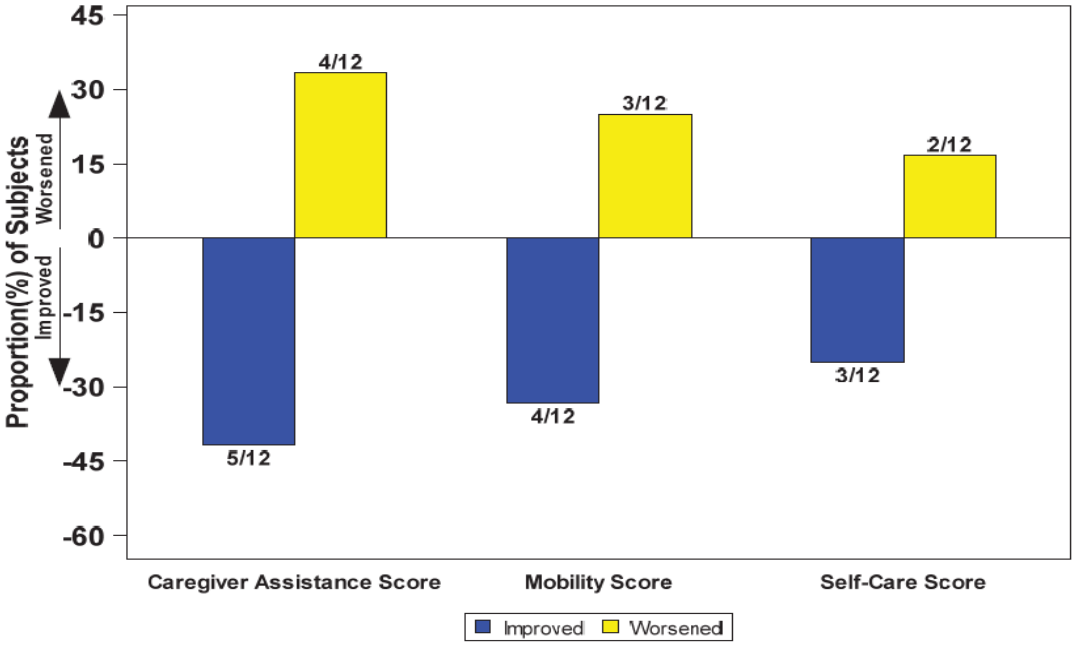
Growth: Standing height (or sitting height) and weight were assessed at baseline and at Week 48. Growth velocity was assessed on height only. Anthropometric measurements and weight were only assessed on 8 of the 12 enrolled patients (males ≤18 years of age and females ≤15 years of age), and did not demonstrate a significant change over the time period of the study.

Medical Officer Comment: There were no clinical or laboratory assessments to evaluate pubertal age that could be identified during the review. As this is an ultra-rare disease with skeletal involvement, pubertal growth changes may not be easy to identify by age only. In addition, this reviewer is unclear of the etiology of the comparison of growth used as the "historical increase". Overall, the duration of the study may not be sufficient to demonstrate significant changes in either growth velocity or the underlying skeletal dysplasia. The presence of the skeletal dysplasia is expected to interfere with a predictable growth pattern.

Subject-Reported Disability and Pain: the MPS Health Assessment Questionnaire (HAQ), initially developed to assess the self-care and mobility skills of patients with MPS 1 (Hurler disease) was used for evaluation. In addition, either the Childhood Health Assessment Questionnaire (CHAQ) or Health Assessment Questionnaire (HAQ) was used as appropriate for age. Patients, parents or caregivers were to complete this evaluation on a consistent basis throughout the study. The proportion of patients who were reported to have improved or worsened are noted by both composite and domain scores. (**Figure 18** and **Figure 19**)

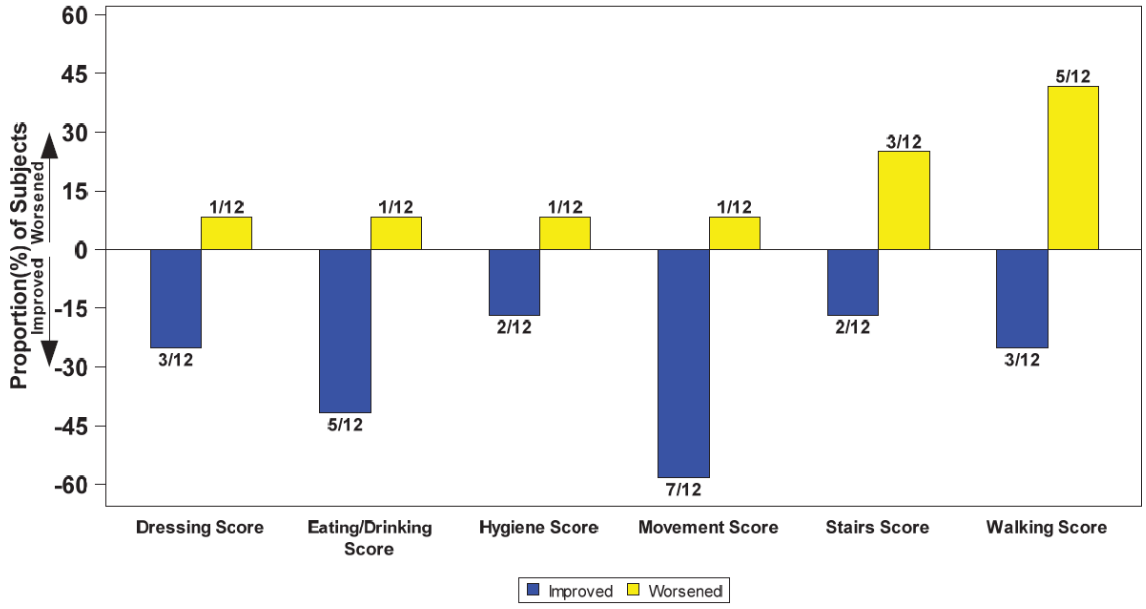
The caregivers of 10 patients and the 2 adult patients completed the MPS HAQ. Lower scores were interpreted as improved outcome and higher scores were interpreted as worsened outcomes. The eating /drinking and movement domains were reported to show the largest changes from baseline (**Figure 19**), but the overall changes in composite scores (positive vs. negative) were similar (**Figure 18**).

Figure 18: Proportion of Patients Who Improved or Worsened at Vestronidase Alfa Treatment Week 24 in MPS HAQ Composite Scores



Source: BLA 761047, Study 301 CSR; Figure 10.3.6.1 (page 132 of 970)

Figure 19: Proportion of Patients Who Improved or Worsened at Vestronidase Alfa Treatment Week 24 in MPS HAQ Domains Scores



Source: BLA 761047, Study 301 CSR; Figure 10.3.6.2 (page 132 of 970) and ADHAQ Analysis dataset.

Decreased scoring in this evaluation represents a reported improvement. The individual MPS HAQ Walking domain scores were notable for a general report of worsening in patients. Review of the MPS HAQ Walking score for Patient C8, who had improved on the 6MWT had a patient reported score of "3" at baseline and to" 2" after 24 weeks exposure to vestronidase alfa. The parental reported score for Patient C1 went from "2" at baseline to "1" after 24 weeks exposure of vestronidase alfa.

Medical Officer Comment: This reviewer interprets the composite results as equivocal and difficult to interpret in the context of this clinical development program. It is hopeful that the two patients who improved on the 6MWT also reported (via caregiver or self) improvement in the MPS HAQ walking score at 24 weeks, though the durability of this report is not known.

Dose/Dose Response

A single dose of 4 mg/kg was chosen based upon the percent change in uGAG (DS) excretion noted in Study 201. The Applicant compared 1 mg/kg, 2 mg/kg and 4 mg/kg dosing by evaluation of the percent change in baseline uGAG excretion and determined that 4 mg/kg demonstrated the highest overall change in uGAG excretion in all three patients evaluated, and this dose was evaluated in Study 301. In Study 301, all patients demonstrated a decrease in uGAGs after exposure to vestronidase alfa (**Figure 7**)**.**

Durability of Response

As Study 301 was only 48 weeks in duration and the efficacy endpoints were assessed only after 24 weeks of exposure to vestronidase alfa, this reviewer feels that the durability of response was assessed with information provided by the open-label extension Study 202 (**Figure 13**).

Review of study 201 also demonstrated improvement in the 6MWT for one subject after 120 weeks of infusion. While supportive of the findings in Study 301, the data are still limited. Ultimately, understanding the natural disease progression for MPS VII assessed in this clinical development program is somewhat limited by the degree of cognitive disability present in most subjects. Younger subjects demonstrated greater difficulty in evaluations. However, as this is a slowly progressive disorder, this reviewer does not believe that short term changes are necessarily representative of long term exposure of vestronidase alfa in MPS VII. The durability of response to vestronidase alfa for the 6MWT will require study of longer duration post-approval.

6.3. Expanded Access Case Narratives

Information from two individual expanded access (EA) program INDs for patients in the US was submitted by the Applicant to support their claim of efficacy for vestronidase alfa. Both INDs were submitted by the patients' physicians prior to the submission of the commercial IND by the Applicant (IND 123788) and both patients have received vestronidase alfa at 4 mg/kg for a longer duration than any patient enrolled in Study 301.

6.3.1 IND 119935

Treatment with vestronidase alfa was initiated under an emergency IND (eIND) on (b) (6) in a 12-year-old Asian male with MPS VII and worsening pulmonary status with chronic CO_2 retention.

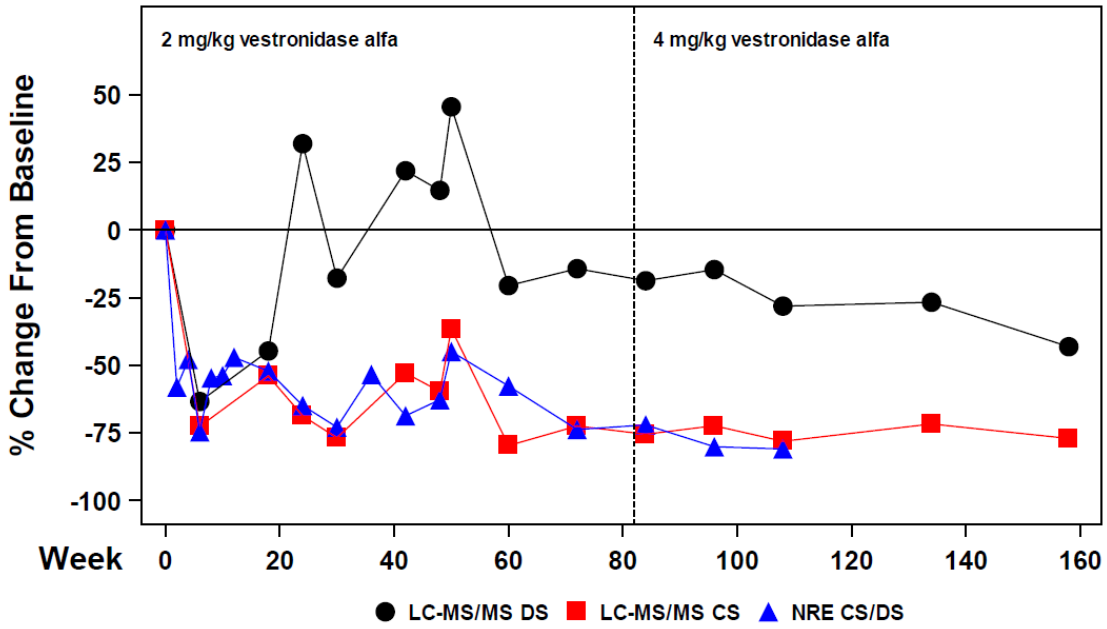
This child was originally diagnosed biochemically (fibroblast and blood analysis) and molecularly (c.863G>T and c.1454C>T) at 17 months of age after presentation with the following clinical findings consistent with MPS VII:

- History of non-immune hydrops fetalis (NIHF) in an infant born at 35 weeks' gestation with hepatosplenomegaly
- Severe scoliosis
- Cardiac abnormalities (mitral valve prolapse, mitral valve regurgitation, dysplastic aortic valve and dilated aortic root)
- Pulmonary insufficiency requiring tracheostomy placement at 3 years
- Recurrent aspiration requiring g-tube placement and feeding

Due to progressive worsening of pulmonary function with chronic CO_2 retention, increased ventilation/perfusion (V/Q) mismatch, and new onset ventilator dependence, treatment with vestronidase alfa was requested. Infusions were initiated on (b) (6), at 2 mg/kg QOW and continued for 20 months, then increased to 4 mg/kg QOW on (b) (6).

Initial infusions were notably accompanied by a "mild hive like rash" that resolved after provision of prophylactic antihistamine. Symptomatic fluid overload post infusion was mitigated with provision of a diuretic.

Figure 20: Percentage Change in uGAG from Baseline by Exposure Time (IND 119935)



Baseline is the average of all assessments prior to or on the date of first dose of vestronidase alfa.

Source: BLA 761047 IR response; 3 May 2017 (page 7 of 10)

Urinary GAG (uGAG) concentration was analyzed at baseline and compared throughout vestronidase alfa administration using the same methodology used for Studies 201 and 301. This patient missed two infusions (Week 16 and Week 48) due to illness and by clinician report, four infusions 2mg/kg infusions were delayed by up to one week due to recovery during these illnesses. There appeared to be an initial drop in uGAG excretion upon initiation of vestronidase alfa infusions, however there was discordance between dermatan sulfate (DS) and chondroitin sulfate (CS) patterns of excretion, particularly between Weeks 16 and 48. After Week 60, CS and DS excretion plateaued, with greater CS excretion in this subject.

<u>Medical Officer Comment:</u> As mentioned in Studies 201 and 301, throughout the clinical development program, the Applicant has chosen to focus on DS as the primary uGAG analyte. The reasons for the observed discordance in DS and CS levels are unclear, and it appears that there may have been a rebound of urine DS after doses were missed. Similar variability was seen in Study 201 and to a lesser extent in Study 301. It is possible that the missed dosing at weeks 16 and 48 contributed to increased variability in DS levels compared to CS in most subjects with MPS VII, however missed dosing in other patients has not resulted in a similar "rebound" effect. In view of the % change in uGAG over time, it appears that the trend is toward persistent decline over the duration of infusion, particularly at 4 mg/kg dosing.

Clinically, the most notable changes after 164 weeks of vestronidase alfa infusions are the following:

- Pulmonary: Prior to initiation of vestronidase alfa infusion, this patient was noted to have extremely elevated end tidal CO_2 consistent with impending respiratory failure (IMV RR 18, TV200, PS 10, PEEP6 FIO_2 40% continuously). After 164 weeks of vestronidase alfa infusion, this patient required ventilator support for a total of 15 hours per day. By clinician report, about 60 weeks after initiation of vestronidase infusions the patient tolerated off-ventilator challenges for 1 hour, and 20 weeks after the vestronidase alfa dosage increase to 4 mg/kg this patient tolerated two, two hour off-ventilator challenges per day, without increases in end tidal CO_2.

- Cardiac: Prior to initiation of vestronidase alfa infusion he was diagnosed with mild aortic regurgitation and reported borderline normal function. This has remained unchanged.

- Cognitive: This patient could speak single words in early childhood, but became non-verbal by the time of infusion initiation. At the time of BLA submission, he was reported to show improved ability to provide gestural prompts and use of his upper extremities with the ability to communicate via use of a computer tablet or talk tech.

Medical Officer Comment: The Applicant offers that this patient's clinical course worsened due to MPS VII related pulmonary findings with chronic CO_2 retention and impending respiratory failure, prior to vestronidase initiation.

It is this reviewer's opinion that long term vestronidase alfa infusions have altered this clinical course such that this patient currently only requires ventilatory support 15 hours per day. In addition, his cardiac exam has remained stable and he has enough strength to demonstrate communicative skill via the use of assisted technology. Based upon the information provided, this reviewer concurs that a spontaneous improvement in symptoms was not anticipated. There did not appear to be an underlying infection and this patient had already undergone tracheostomy, which would have stented their airway prior to the progression toward respiratory failure. The stenting would have provided mechanical support to tracheal dysplasia of MPS VII.

These findings provide clinical and biochemical evidence of efficacy for vestronidase alfa when administered long-term. This reviewer does note the initial 80 weeks of infusion were at 2 mg/kg dosing and during this period initial ventilatory changes were made. It is not clear if the continued pulmonary improvement that was observed is related to dosing (2 mg/kg vs. 4 mg/kg) or to length of exposure to vestronidase alfa.

6.3.2. IND 123764

Vestronidase alfa treatment was initiated under an emergency IND (eIND) on (b) (6) in a 5-month-old infant boy who was born prematurely at 30 weeks after a prenatal diagnosis of non-immune hydrops fetalis (NIHF). Diagnosis was confirmed at the age of 4 months by biochemical and molecular testing (c.1A>G; c.1524G>A).

The infant presented with anasarca, ascites, respiratory insufficiency and required continuous non-invasive ventilation. Clinically, this child deteriorated quickly as noted by multiple episodes of desaturation with or without bradycardia, and bronchoscopy noted severe pharyngeal collapse with critical tracheal stenosis, moderate tracheomalacia, severe bronchomalacia and skeletal deformities consistent with GAG deposition. One week prior to initiation of vestronidase alfa infusions, the patient underwent surgical placement of a tracheostomy tube but still experienced frequent episodes of hypoxia and bradycardia.

Baseline abdominal ultrasound revealed ascites, hepatomegaly (8.3 cm) and spleen length of 5.5 cm. Baseline neurologic exam at 5 months was consistent with developmental delay and showed poor visual tracking, non-purposeful movements, truncal hypotonia and brisk reflexes.

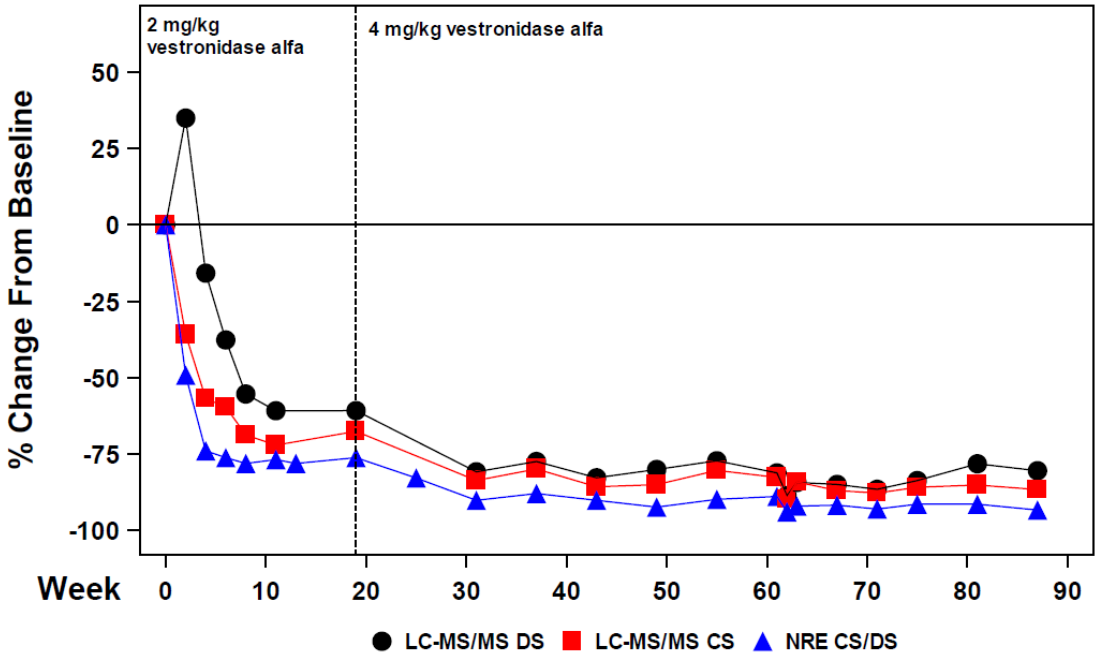
While the uGAG profile (**Figure 21**) improved by 10 weeks of treatment, the patient suffered a tension pneumothorax during infusion at Week 12, which was felt to be related to his severe pulmonary disease and high ventilatory settings. Vestronidase alfa infusions were initiated at 2mg/kg and the dose was increased to 4mg/kg at Week 18. At Week 26, abdominal ultrasound and therapeutic paracentesis confirmed worsening ascites which was attributed to his underlying diagnosis of MPS VII. Desaturations were noted less frequently from weeks 35 through 39, but hydrocephalus and anterior subluxation of C1 and C2 were noted on cranial and C-Spine MRI, respectively. The patient was diagnosed with cervical spinal cord compression and underwent a suboccipital craniectomy and C1 laminectomy at Week 41. This child was diagnosed with critical tracheal stenosis related to subglottic stenosis and non-destructing tracheal granuloma at Week 58.

Evaluations at infusion week 60 (about week 48 of 4 mg/kg vestronidase alfa) noted an 81% reduction of DS compared to baseline levels; echocardiogram noted mild mitral valve prolapse and insufficiency, mild dilatation of the aortic sinuses of Valsalva and otherwise normal exam. Liver and spleen size were reported as reduced (7.2 cm and 4.6 cm) from Week 48 (7.6 cm and 5.0 cm respectively). Intermittent oxygen desaturations continued.

After week 60, this subject transitioned to another protocol (Study 203; Patient (b) (6)) to continue infusions at 4 mg/kg. He was stable enough to be transferred to a long-term care facility from the ICU for continued care.

Daily valium was required by week 48 of care and desaturations were reported weekly or less frequently. At Week 108 of infusion, this patient was transferred to another long-term care facility where his ventilatory settings were reported to be stable. He was ultimately diagnosed with MPS VII related tracheal and bronchus dysplasia that requires long term airway stenting. At the time, this information was presented for review, this child had received infusions for a total of 142 weeks or 2 years and 9 months' duration.

Figure 21: Percentage Change in uGAG from Baseline by Exposure Time (IND 123764)



Baseline is the average of all assessments prior to or on the date of first dose of vestronidase alfa.

Source: BLA 761047 IR response; 3 May 2017 (page 10 of 10)

Urinary GAG (uGAG) excretion was analyzed at baseline and compared throughout vestronidase alfa administration using the same methodology used for Studies 201 and 301. Upon initiation of vestronidase alfa infusions, there was an initial drop followed by a sustained reduction in uGAG excretion with similarity between dermatan sulfate (DS) and chondroitin sulfate (CS) patterns of excretion, with a slightly higher percentage of change from baseline after increasing dosage from 2 mg/kg to 4 mg/kg.

Medical Officer Comment: *The limited information of the natural history of MPS VII described by the Montano et al. survey (Section 2.1) suggests that, of those patients diagnosed with MPS VII who presented with a known history of non-immune hydrops fetalis (NIHF), 40% die within*

the first year of life. Clinically, when a surviving patient presented with NIHF, symptoms were reported to have resolved by 4 months. However, this patient's clinical course worsened due to the MPS VII-related findings of spinal cord compression and critical tracheal stenosis. Additionally, though uGAGs decreased upon initiation of vestronidase alfa infusions, hepatic ascites progressed through week 26 of infusions; however, at weeks 48 and 60 liver and spleen sizes were decreased from baseline.

This reviewer believes that this patient's available clinical history is informative for both the clinical course of MPS VII and the durability of response.

- *The NIHF was the presenting symptom for this child but, by clinical report, most symptoms of anasarca had improved by 4 months of age.*
- *Pulmonary pathology related to MPS VII was the most critical pathology for predicting disease course for this child.*
- *A treatment-induced possible respiratory improvement is difficult to discern from the medical interventions completed. Release of spinal cord compression may have improved a central component to respiratory drive. In addition, the frequent tracheostomy changes may have improved airway stenting, given the tracheal dysplasia. While vestronidase alfa infusions may have improved ventilatory status, a clear time course for improvement is not apparent from the information provided.*

While a direct comparison with other MPS VII patients is not available, it might be reasonable to believe that the pulmonary status of this child may not have been sufficient for survival past 12 months of life, given the clinical presentation. This patient's surgical interventions may have contributed greatly to his clinical improvement. The level of clinical details submitted by the Applicant in response to an IR was significantly informative. While it is still difficult to assess the full contribution of vestronidase alfa to this patient's complex clinical course, the available data do provide evidence of substrate reduction in terms of uGAG excretion and liver/spleen sizes with long term administration.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

A total of 17 patients with MPS VII have been treated with vestronidase alfa for a period of about 24 weeks to 164 weeks at the time of receipt of the 120-day update. There were 9 females and 8 males, with an age range of 5 months to 25 years. Patients have a range of

ethnicities. At least 4 of the 17 patients were reported to have a history of non-immune hydrops fetalis. The reader is referred to Section 1.3 for a summary of the biochemical and clinical effects of treatment. The strengths and limitations of these observations are discussed in Section 1.2.

The available data suggested that up to 5 out of 17 patients enrolled in the vestronidase alfa development program demonstrated clinical findings that this reviewer interprets as suggestive of clinical efficacy. The 5 patients with the most persuasive improvements are listed below:

1. **IND 119935 (Expanded Access IND; 164 weeks exposure):** This 12-year-old male demonstrated a reduced need for mechanical ventilation after 164 weeks exposure to vestronidase alfa.
2. **Patient A3 (Study 201; 120 weeks exposure):** This 25-year-old male demonstrated improvement in 6MWT (105 meters from baseline to week 120; 285 *meters to 390 meters*) and demonstrated 21 % improvement in predicted FVC. Of note, the patient underwent interim bilateral hip replacement and was not assessed between weeks 36 and 84 of the trial.

   Dr. Donohue (CDTL Comment):
   This patient's improvement in 6MWT likely was due to a combination of treatment effect from vestronidase alfa and bilateral hip replacement. However, the 21% improvement in percent predicted FVC is of sufficient magnitude that it is difficult to explain apart from drug effect, even after accounting for a potential exercise effect from increased mobility.

3. **Patient C1 (Studies 301/202; 120 weeks exposure):** This 15-year-old female demonstrated improvement in the 6MWT of 83 meters at week 24 (*300 meters to 383 meters*) and demonstrated sustained improvement in 6MWT distances during the open label extension. She also improved in the BOT-2 gross motor performance during Study 301, which was felt to be qualitatively supportive.
4. **Patient C8 (Studies 301/202; 80 weeks exposure):** This 25-year-old male demonstrated improvement in 6MWT of 65 meters at week 24 (*455 meters to 520 meters*) and improvements in the BOT-2 gross motor performance that were interpreted as qualitatively supportive. He also demonstrated sustained improvement in 6MWT distances during the open label extension.
5. **Patient C6 (Study 301; 80 weeks exposure):** This 17-year-old female may have demonstrated a treatment effect. She was unable to complete baseline 6MWT but could complete testing after 8 weeks and 80 weeks exposure to vestronidase alfa and demonstrated an improvement of about 73 meters (*96 meters to 169 meters)* between these two time points. A longer duration of exposure may be needed to determine if this effect is sustained.

The small number of subjects able to enroll in the vestronidase alfa development program imposed limitations on trial design, and precluded selection of an independent control group. As such, the efficacy findings observed in this clinical program are not as robust as usually seen for drugs intended for common diseases which can be studied in large controlled trials that undergo formal statistical analyses. Given these constraints, this reviewer believes there is sufficient information across the vestronidase program to suggest that vestronidase alfa can improve clinical symptoms (mobility and pulmonary) in some patients with MPS VII.

Additional evaluations post-approval are recommended so the Applicant can better define the subset of MPS VII patients who demonstrate the highest probability for clinical improvement with vestronidase alfa infusions.

7.1.1. Other endpoints

Urinary Glycosaminoglycans (uGAGs) Excretion

Urinary glycosaminoglycans (GAGs) were measured by two methods: liquid chromatography–tandem mass spectrometry (LC-MS/MS) and Non-Reducing Ends (NRE). Neither method was fully validated. Thus, the extent of uGAG reductions from baseline could not be ascertained quantitatively (b) (4); instead the % uGAG reductions are to be considered qualitative or semi-quantitative measurements only. Nonetheless, all subjects displayed consistent reductions from baseline in the excretion of total uGAG and the individual components, including urinary chondroitin sulfate and dermatan sulfate. uGAG species demonstrated consistent exposure-response relationships as well. Taken together, the pharmacodynamic data demonstrate pharmacological activity and provide supportive evidence for the effectiveness of vestronidase alfa.

7.1.2. Subpopulations

As MPS VII is an extremely rare disease, the number of patients who could be enrolled in a trial was too small to analyze and comment upon efficacy in different subpopulations. Vestronidase alfa pharmacodynamic responses did not appear to be different between males and females or among subjects in different age groups.

7.1.3. Dose and Dose-Response

Dose response was assessed in Study 201 which demonstrates that the percent change in uGAG

excretion changes with dose concentration. A dose of 4mg/kg given every other week (QOW) demonstrated the highest change in uGAGs compared to 1 mg/kg or 2 mg/kg given at the same time interval.

The observed pharmacodynamic responses were dose-dependent over the range of doses tested (1 mg/kg to 4 mg/kg). The excretion of urinary chondroitin sulfate, dermatan sulfate, and total uGAG declined with increasing dose of vestronidase alfa. The % uGAG reduction from baseline increased with vestronidase alfa exposure until uGAG response plateaued at a Cmax of 15 ng/mL and an AUC0-t of 40 ng*h/mL. No such dose-response or exposure response was observed for heparan sulfate.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The effect on uGAG excretion, which occurred in all 17 patients, was relatively rapid, approximately 4 weeks into treatment. The onset of clinical effects appeared later. A total of 4 patients in studies 201 and 301 demonstrated improvement in the 6MWT. Subject A3 (Study 201) demonstrated improvement from baseline at 120 weeks. Onset of response is difficult to assess since the patient underwent hip surgery between weeks 36 and 84 of the trial. Study 301 patients C1, C8 and C6 appeared to improve after 8 weeks of exposure to vestronidase alfa. Patients continued to experience their on-treatment improvements during the open-label extension.

Medical Officer Comment: It is this reviewer's opinion that patients with a longer duration of exposure to vestronidase alfa were the most likely to demonstrate benefit.

From a pharmacodynamic perspective, excretions of urinary chondroitin sulfate, dermatan sulfate, and total uGAG declined to nadirs at around four weeks following the administration of vestronidase alfa at 4 mg/kg QOW, and then plateaued. Subsequently, reductions in these urinary GAGs were maintained at approximately 60% to 80% from baseline. Serum concentration of combined chondroitin and dermatan sulfates decreased slowly to approximately 23% from baseline over a longer duration. However, the temporal profile of heparan sulfate did not show the same consistency of pharmacodynamic response to vestronidase alfa treatment.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarketing Setting

The natural history of MPS VII is poorly understood. A post marketing registry of MPS VII patients who are or are not receiving vestronidase alfa would be informative to clarify our

understanding of the natural history of disease in both populations. Clinical experience to date includes 23 patients exposed for at least 164 weeks exposure to vestronidase alfa. Therefore, the post marketing registry should be of sufficient duration to be informative.

Evaluation of older patients may be difficult due to the persistent uGAG accumulation in storage tissues. Patients surviving non-immune hydrops fetalis (NIHF) may be the most informative group to include in the registry. Based on the natural history survey by Montano et al., 40% of patients diagnosed with NIHF due to MPS VII will not survive through infancy. Early initiation of ERT in surviving patients could provide the most significant information on the impact of vestronidase alfa on morbidity and mortality.

7.3. Integrated Assessment of Effectiveness

All subjects enrolled in Study 201, Study 301 and the US based expanded access INDs had sufficient duration of exposure to vestronidase alfa infusions to evaluate efficacy. All patients demonstrated decreased uGAG excretion upon exposure to enzyme replacement therapy. However, this reviewer believes that the decrease in uGAG excretion is necessary but not sufficient to demonstrate clinical efficacy for vestronidase alfa in patients with MPS VII.

Substantial evidence of effectiveness has been demonstrated based on the following clinical and biochemical considerations: 1) the current understanding of the pathophysiology of MPS VII, 2) the mechanism of action of the drug, 3) the finding of durable clinical responses (ranging from 78 to 164 weeks) in 5 of 17 patients exposed, 4) evidence of substrate reduction as measured by reduction in urinary GAGs consistent with the known mechanism of action of vestronidase alfa, and 5) the known efficacy of other ERTs in patients with related MPS disorders.

Expanded Access

Both expanded access narratives described children who presented initially with non-immune hydrops fetalis (NIHF). One child subsequently developed chronic CO_2 retention and increased ventilatory settings at the age of 12 years and was described as having impending respiratory failure. After 164 weeks of exposure to vestronidase alfa at both 2 mg/kg (82 weeks) and 4 mg/kg, the ventilator settings were significantly decreased from the initial baseline and the child sufficiently improved such that they did not require ventilatory support for about 9 hours per day.

The other child was an infant whose non-immune hydrops fetalis (NIHF) had reportedly resolved by 5 months of age, though the child still required high ventilatory support and was noted to have a significant V/Q mismatch and developed ascites after 26 weeks vestronidase alfa infusions. The initiation of vestronidase alfa infusions coincided with surgical laminectomy

for an anterior cervical spine subluxation and tracheal stenting due to MPS related tracheal dysplasia. After these interventions and the initiation of ERT infusions the episodes of hypoxia and bradycardia were reported as infrequent. It is difficult to comment upon how much vestronidase alfa infusions added to the respiratory stabilization of this child as the surgical interventions may have contributed significant airway stabilization and improvement in central respiratory drive.

It is important to note that neither expanded access patient required a specific baseline of cognitive understanding or effort to complete a pre-specified efficacy measure. The pulmonary disease in these two patients was of such severity that an assessment of reversibility might be evaluated solely upon detailed clinical information. However, a similar determination in MPS VII patients who have mild or moderate pulmonary disease may not be possible unless a patient independent means of evaluation is considered, such as plethysmography.

The known history of MPS VII suggests that 40% of infants with NIHF related to MPS VII die within their first year of life (**Figure 1**). Therefore, an estimated 60% of subjects will survive and improve on their own, without an ERT related intervention. Both US based expanded access patients were diagnosed with NIHF. The older patient appeared to improve but clinically progressed toward end stage respiratory disease at the age of 12 years. The younger patient appeared to have stabilized somewhat, however their spinal cord compression and severe tracheal dysplasia required major surgical intervention that may have improved survival without vestronidase alfa infusion.

Subjects Enrolled in Vestronidase Alfa Studies
Throughout the drug development program of vestronidase alfa, the Applicant has suggested that MPS VII may be clinically similar to other mucopolysaccharidoses (MPS I and MPS II) based upon the literature and limited survey information (UX003-CL001 and UX003-CL002). The reader is referred to Section 2 for additional details.

As noted in **Table 2**, efficacy of the approved enzyme replacement therapies for MPS I, MPS II and MPS IVA was assessed in parallel, placebo-controlled studies evaluating the 6MWT (or the 12 MWT for MPS VI).

Study 301 was smaller and did not have a concurrent placebo control arm. Using an ANCOVA approach, the least squares mean difference between the vestronidase alfa and placebo treatment periods in the 6MWT at 24 weeks was 18 meters (with a standard error of 33m). (Refer to Statistical Review by F. Jiao and M. Min for additional detail).

While the study designs were necessarily different, the improvements in 6MWT seen in the MPS VII patients treated with vestronidase alfa were generally similar to those seen after treatment with other ERTs for the different MPS diagnoses.

While the natural history of disease for MPS VII is not fully understood, the available reports in the literature suggest that the pathology of MPS VII is slowly progressive and initiates with uGAG deposition *in utero*. The emergent clinical events these patients experience are primarily related to bone deposition (spinal stenosis) and pulmonary deposition (upper airway, lower airway and restrictive lung disease). (Muhlebach MS, Wooten W et al. 2011) Therefore, the exposure durations of Study 201 and 301 (24 to120 weeks) may not have been sufficient to demonstrate clinically meaningful and measurable outcomes for all subjects with MPS VII

Medical Officer Comment: In general, this reviewer speculates that while many of the somatic and neurologic symptoms of MPS VII are similar to other MPS diagnoses, the neurocognitive and neuromuscular manifestations are not identical to that of the others MPS conditions. As such, most clinical endpoints used for other MPS drug development programs may not have been ideal for patients with MPS VII.

8 Review of Safety

8.1. Safety Review Approach

The safety review focuses on the data collected on a total of 20 patients enrolled in studies 201, 203 and 301 and in US based emergency INDs (**Table 5**). One of the subjects enrolled in a US based emergency IND was subsequently enrolled in study 203. The 120-day safety update was reviewed and included subjects enrolled in study 202, an ongoing open-label extension study for patients enrolled in Study 201, 203 or 301. In review of this safety update, no new safety signals were identified and the benefit:risk assessment for the use of vestronidase alfa in subjects with MPS VII did not change.

There were three additional subjects enrolled in non-US based INDs. No adverse events were reported in the physician summaries and, therefore, these patients will not be included in adverse event review. These patients did contribute immunogenicity information and are included in Section 8.4.10. Due to incomplete outcome narratives, they were also not included in the efficacy review.

The Applicant stated in their Integrated Summary of Safety (Section 5.3.5.3) that as the size of the studies involved in the vestronidase alfa development program were small, of different study designs and doses administered, they did not consider a formal integration of safety data across studies to be useful. The Applicant chose to collect AE data for pediatric and adult subjects with MPS VII and present side-by-side comparisons across studies.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In total, 23 pediatric and adult patients diagnosed with MPS VII have been exposed to vestronidase alfa via intravenous (IV) infusion. Of these, 20 are evaluable for safety (**Table 22**). Patients enrolled in Study 201 received vestronidase alfa at 1mg/kg, 2 mg/kg and 4 mg/kg dosing. Patients enrolled in Studies 301 and 203 received 4 mg/kg dosing and patients enrolled in US based expanded access programs received 2 mg/kg and 4 mg/kg dosing. Only the Phase 3 Study 301, which used a randomized start protocol, had placebo data for comparison. All other studies and INDs were open label. The mean treatment duration for patients enrolled in Study 301 was 36 weeks compared to 15.8 weeks on placebo.

No healthy volunteers were exposed to vestronidase alfa.

Table 22: Safety Population

Trial Identity	Trial Design	No. of Patients	Regimen/ schedule/ route	Weeks at Dosage for all subjects
UX003-CL201	Phase 1/2 Study: Open-label, uncontrolled study to evaluate safety, efficacy and dose exploration	3	UX003 QOW by IV at the following doses: 2 mg/kg: 14 wks (Wk. 0-12) 1 mg/kg: 8 wks (Wk. 14-20); 4 mg/kg: 8 wks (Wk. 22-28); 2 mg/kg: 44 wks (Wk. 30-72); 4 mg/kg: up to 168 wks (Wk. 74-240)	1 mg/kg: 24 2 mg/kg: 174 4 mg/kg: 182
UX003-CL301	Phase 3 Study: A multicenter, randomized, placebo-controlled, blind-start, single- crossover design	12	UX003 QOW 4 mg/kg by IV	4 mg/kg: 432
UX003-CL203[a, b]	Phase 2 Study: Open label, uncontrolled study to evaluate safety and efficacy	4	UX003 QOW 4 mg/kg by IV	4 mg/kg: 120
IND 119935	Expanded Access	1	Initiated at 2 mg/kg QOW then increased to 4 mg/kg/QOW	2 mg/kg: 68[a] 4 mg/kg: 83
IND 123764	Expanded Access (patient also enrolled into Study 203)	1	Initiated at 2 mg/kg QOW then increased to 4 mg/kg/QOW	2 mg/kg: 17 4 mg/kg: 86

Source: BLA 761047 Summary of Clinical Safety, Table 2.7.4.4.2.1

[a] Two doses were missed (Week 16 and Week 48; refer to **Figure 20**

[b] Patient IND (b) (4) was rolled into Study UX003-CL203 after 103 weeks of exposure to vestronidase alfa and is one of the four patients reviewed

All 20 patients have been exposed to at least 24 weeks of every other week 4 mg/kg dosing. Cumulatively, enrolled patients have been exposed to vestronidase alfa at the following doses and durations noted in **Table 23** and **Table 24.**

Table 23: Total Exposure to Vestronidase Alfa

#Total Subjects	Dosage (QOW)	Total Weeks	Patient Years
3	1 mg/kg	24 weeks	0.15 years
5	2 mg/kg	269 weeks	1.03 years
20	4 mg/kg	1047 weeks	0.84 years

Source: BLA 761047, Calculated from data in Table 21.

Table 24: Duration of Exposure to 4 mg/kg Vestronidase Alfa

Number of Patients Exposed to vestronidase alfa at 4 mg/kg			
>=6 months	>=12 months	>=18 months	>=24 months
N = 4	N = 16	N = 4	N = 4

Source: BLA 761047 Summary of Clinical Safety, Table 2.7.4.4.2.1 and Table 21

8.2.2. Relevant characteristics of the safety population:

The safety population evaluated in this BLA focuses on all patients exposed to at least one dose of vestronidase alfa. This includes studies 201, 203, 301 and available information on patients enrolled in expanded access INDs. Demographic and baseline disease characteristics are summarized in **Table 25**.

Table 25: Demographics of the Safety Population in the Vestronidase Alfa Development Program

	Study 201 (N=3)	Study 203 (N=4)[a]	Study 301 (N=12)	Expanded Access (US patients)[a] (N=2)	Total Safety Population N=20)
Gender					
Male, n (%)	2 (67)	4 (100)	4 (33)	2 (100)	11[b] (55)
Female, n (%)	1 (33.3)		8 (67)	-	9 (45)
Age at enrollment					
Mean years (SD)	13.3 (10)	2.8 (1)	15.4 (6)	6.6 (6)	6.35
Median (years)	9.4	3	14	12.5	4.7
Min, max (years)	5.5, 25.1	1.7,3.4	8.4,25.2	0.6,12.5	0.6,25.2
< 17 years, n (%)	2 (67)	4 (100)	8 (67)	2 (100)	15[b] (75)
≥ 17 - < 65 years, n (%)	1 (33)	--	4 (33)	0.6, 12.5	5 (25)
Race/Ethnicity					
White, n (%)	2 (67)	1 (25)	8 (67)	--	11 (55)
Other, n (%)	1 (33)	3 (75)	4 (33)	2 (100)	9[b] (45)
Hispanic or Latino, n (%)	1 (33)	2 (50)	6 (50)	1 (50)	9[b] (45)
Not Hispanic or Latino, n (%)	2 (67)	2 (50)	6 (50)	1 (50)	11 (55)
History of Hydrops Fetalis, n (%)	2 (67.7)	2 (50)	2 (167)	2(100)[a]	7[b] (35)

[a] One US expanded access IND patient was included the demographic set for study 203
[b] to not duplicate expanded access IND patient subsequently enrolled in Study 203
Source: BLA 761047 Summary of Clinical Safety, Table 2.7.4.4.3.1

In general, the demographics of the safety population represented equal proportions of gender, race and ethnicity. Three quarters of patients were enrolled at less than 17 years of age. In addition, 35% of patients had a known history of non-immune hydrops fetalis (NIHF), similar to the estimated 40% of patients derived from the clinician survey of patients with MPS VII by Montano et al.

8.2.3. Adequacy of the safety database:

As MPS VII is a rare disease, the size of the safety database is small and only 4 patients have received vestronidase alfa at the Applicant's suggested dosing (4 mg/kg QOW) for more than 24 months. Within the constraints of these limitations, the safety database appears adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant submitted clinical safety assessments for each trial or individual patient IND. The datasets contained 121 AEs for Study 301, 103 AEs for Study 201 and 102 AEs for Study 203, for a total of 326 AEs combined from all three studies.

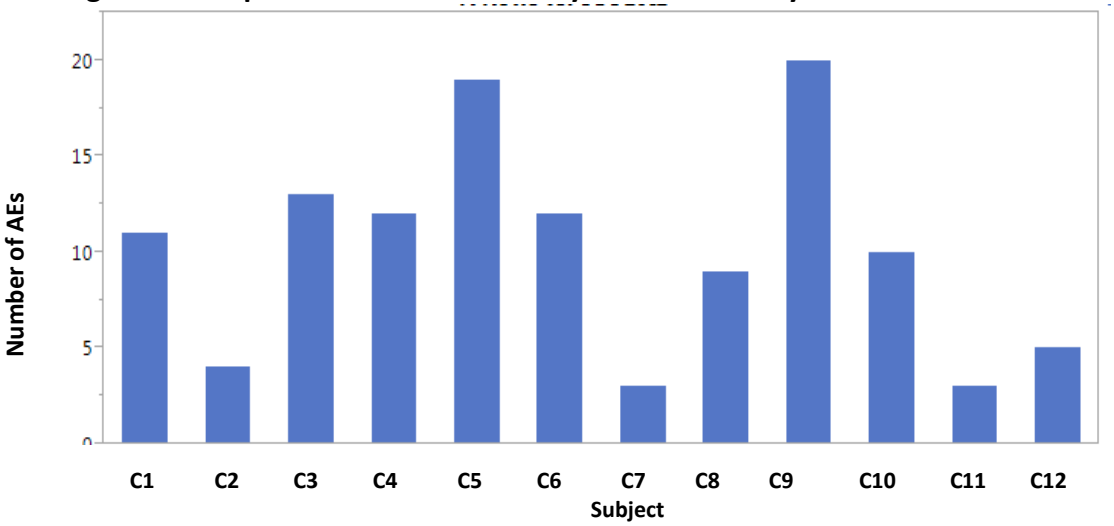
Table 26: Total Number of Adverse Events Reported in Studies 201, 203, 301

Study or IND (N = patients enrolled)	Number of Study Sites	Duration of Study (months)	Mean AE ± SD Per patient	Median (lowest, highest)
Study 201 (N = 3)	3 (1 Central; 2 home based)	27 (1 subject) 30 (2 subjects)	34.3 ± 9.9	39.0 (23,41)
Study 203 (N = 4)	4	3 (1 subject) 7 (2 subjects) 11 (1 subject	25.5 ± 23.0	20.5 (4,57)
Study 301 (N= 12)	4	6 (12 subjects)	10.1 ± 5.7	10.5 (3,20)

Source: BLA 761047 AE datasets from Studies 201, 203, and 301

Medical Officer Comment: The number of AEs reported in Study 301 appears smaller when compared to those reported for Studies 201 and 203. This reviewer notes that Studies 201 and 203 were longer (at least twice to three times the duration of Study 301), such that the difference in study duration may be a factor into this difference. Baseline patient disease status may be an additional factor in this discrepancy. This reviewer noted that evaluation of individual data sets did not appear to demonstrate differences in reporting based upon study sites, as exemplified in **Table 26***.*

Figure 22: Reported Adverse Events by Patient in Study 301



Source: BLA 761047, Study UX003-CL301 ae.xml dataset

8.3.2. Categorization of Adverse Events

The analysis of safety included all patients for whom the Applicant provided accurate definitions of adverse events and serious adverse events in all three protocols.[6] All AEs were coded by System Organ Class (SOC) preferred terms using MedDRA Version 17.1.

An AE was considered treatment emergent (TEAE) if it occurred on or after the first dose of study drug, was not present prior to the first dose, or was present at the first dose but increased in severity during the study. TEAEs from all studies were provided by System Organ Class and Preferred term. Treatment severity was based upon based on NCI Common Terminology Criteria for Adverse Events (CTCAE) grading criteria [Version 4.03].

All patients enrolled in studies 201, 203, and 301 were reported to have AEs, and at least 1 subject enrolled in each study was also reported to have Grade 3 or 4 SAEs by the Applicant (**Table 27**).

[6] 21 CFR 312.32(a) and 314.80

Table 27: Summary Safety overview for Subjects treated with Vestronidase Alfa Enrolled in Studies 201, 203, and 301

System Organ Class Preferred Term	Study 301		Study 201	Study 203
	Placebo (N=9) n (%)	vestronidase alfa (N=12) n (%)	vestronidase alfa (N=3) n (%)	vestronidase alfa (N=4) n (%)
Number of subjects with TEAEs	9 (100)	12 (100)	3 (100)	4 (100)
Number of subjects with treatment- related TEAEs	3 (33.3)	8 (66.7)	2 (66.7)	4 (100)
Number of subjects with SAEs	0 (0)	2 (16.7)	2 (66.7)	1 (25)
Number of subjects with treatment- related SAEs	0 (0)	1 (8.3) [a]	0 (0)	0 (0)
Number of subjects with a Grade 3 or 4 TEAE [b]	0 (0)	1 (8.3)	2 (66.7)	1 (25)
Number of subjects with TEAEs leading to treatment discontinuation	0 (0)	0 (0)	1 (33.3)	0 (0)
Number of subjects with TEAEs leading to study discontinuation	0 (0)	0 (0)	0 (0)	0 (0)
Number of subjects with fatal TEAEs	0 (0)	0 (0)	0 (0)	0 (0)

Sources: UX003-CL301 CSR Table 12.2.1; UX003-CL201 CSR Table 12.2.1; and UX003-CL203 CSR Table 12.2.1
[a] Subject C2 experienced a Grade 3 treatment-related anaphylactoid reaction secondary to an accidental high (bolus) infusion rate occurring during the first hour of UX003 administration. The event resolved and the subject completed the study with no further recurrence of anaphylactoid reaction.
[b] UX003-CL301: anaphylactoid reaction was the only Grade 3 TEAE; UX003-CL201: A total of three Grade 3 TEAEs and one Grade 4 TEAE were reported by 2 subjects; UX003-CL203: Grade 3 TEAEs were reported for one subject and included spinal instability, oxygen saturation decreased, and spinal column stenosis.
[c] Subject A1 was administered an incomplete dose at Week 86 (2.5% completion) and missed doses from Weeks 88 to 92 due to AE (Table 2.7.4.4.2.2.1), and resumed treatment at Week 94. The treatment interruption was incorrectly recorded as treatment discontinuation in the case report form. No subjects had TEAEs leading to treatment discontinuation.

8.3.3. Routine Clinical Tests

Routine safety testing completed during trials 201, 203, and 301 varied by protocol. In Study 301, these assessments included the following analyses:

- Urine pregnancy testing
- Antibodies to rhGUS
- Complement, C3, C4, and CH50 for subjects with infusion associated reactions (IARs)
- Clinical laboratory testing to include hematology, chemistry and urine analysis

Medical Officer Comment: In general, laboratory analyses were appropriately collected.

Per protocol, complement levels were to be obtained after possible infusion associated reactions. Review of the all safety datasets noted that they were obtained in two patients enrolled in Study 301:

- Subject C2: After anaphylaxis caused by accidental administration of vestronidase alfa via bolus (Narrative in Section 8.4.2)
- Subject C3: Before and after vestronidase infusions during an unscheduled clinic visit. (Narrative was not provided).

Evaluation of routine chemistry and hematologic testing from all three studies did not identify any laboratory safety signals or significant abnormalities.

Medical Officer Comment: *The laboratory manual was changed during Study 301. The initial manual was dated November 3, 2014 and was updated on March 31, 2015. As patients needed to consent to the increased testing burden of the updated manual, there was delay for initiation of the increased frequency for ADA and NAb testing for some subjects.*

8.4. Safety Results

8.4.1. Deaths

No deaths were reported during the clinical development program of vestronidase alfa which included those patients enrolled in 201, 203, 301 and expanded access INDs in the US and world-wide (N=23).

8.4.2. Serious Adverse Events

Two subjects in Study 301 had a Serious Adverse Event (SAE) of anaphylaxis, see Section 8.5.1.

A third SAE was reported via MedWatch on February 1, 2017 for a patient in Study 202, the long-term extension study. Patient C9 had headache with elevated intracranial pressure that responded to acetazolamide and topiramate. This patient's medical history was complicated by a previous neck injury and the use of multiple medications.

Medical Officer Comment: *It is unknown if patients with MPS VII are at risk for increased intracranial pressure apart from cervical stenosis.*

120 –Day Safety Report:
Review of the 120-Day Safety Report revealed no new or unanticipated safety signals. The previously discussed benefit:risk ratio remains unchanged.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Two patients were enrolled but electively chose to forego randomization in Study 301. No subjects permanently discontinued after randomization into studies 201, 203, 301 or expanded access INDs in the US. One patient withdrew from an expanded access program in the EU due to hematopoietic stem cell transplantation at 18 months of age.

8.4.4. Significant Adverse Events

Hypersensitivity reactions were the most significant observed adverse events in the vestronidase alfa development program. As vestronidase alfa is an ERT, these adverse events were anticipated. The events were clinically identified via presentation of anaphylaxis, rash, pruritus, edema and bronchospasm. In addition, infusion associated decreases in systolic blood pressure (≥ 30 mmHg) were not identified by the Applicant, but were apparent in review. Refer to Section 8.5.1 for further discussion.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In Study 301, a total of 121 adverse events (AE) were reported (**Table 28**). Of these, 1 occurred during randomization, 41 occurred during infusion of placebo and 79 occurred during infusion of vestronidase alfa. Infusion site extravasation, extremity pain and abdominal pain/diarrhea were the most frequent treatment emergent adverse events (TEAE) in the patients receiving vestronidase alfa compared to placebo (**Table 28**). Anaphylaxis was only reported in patients receiving vestronidase alfa. Additionally, ataxia, headache, diarrhea, hypertension and exertional dyspnea were also only reported while patients were receiving vestronidase alfa.

Table 28: Treatment Emergent Adverse Events Reported in Study 301

	Placebo N=41 episodes	Vestronidase Alfa N=79 episodes
General Disorders and Administration Site Conditions		
Infusion site extravasation	1	5[a]
Catheter site bruise/discomfort	1	3
Edema/peripheral swelling	1	2
Pyrexia or chills	1	2
Skin and Subcutaneous Tissue Disorders		
Rash (macular/popular)	4	3
Urticaria	2	1
Pruritus	0	1
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	3	5
Musculoskeletal stiffness	0	2
Gastrointestinal Disorders		
Abdominal Pain	1	3
Diarrhea	0	3
Vomiting	3	3
Cough	2	3
Immune System Disorders		
Anaphylactoid reaction	0	2
Nervous System Disorders		
Ataxia	0	1
Headache	0	1
Respiratory, Thoracic and Mediastinal Disorders		
Hypertension	0	1
Exertional dyspnea	0	1

Source: BLA 761047 Study UX003-CL301 Analysis Dataset for Adverse Event (ADAE)
[a] Subject was initially listed as infusion site swelling but changed to infusion site extravasation

Review of treatment emergent adverse events across Studies 201, 203 and 301 was notable for infusion site extravasation, diarrhea, vomiting, rash, pain in extremity, arthralgia, and pyrexia as the most commonly reported treatment emergent adverse events (**Table 29).**

Table 29: Treatment Emergent Adverse Events for Patients Treated with Vestronidase Alfa in Studies 201, 203 and 301

SOC Preferred term	Study 201 N=3 n (%)	Study 203 N=4 n (%)	Study 301 N=12 n (%)	Total N=19 n (%)
Infusion Site Extravasation	1 (33%)	1 (25%)	4 (33%)	6 (32%)
Diarrhea	2 (67%)	1 (25%)	3 (25%)	6 (32%)
Vomiting	2 (67%)	1 (25%)	3 (25%)	6 (32%)
Rash	1 (33%)	1 (25%)	3 (25%)	5 (25%)
Pain in Extremity	0	1 (25%)	4 (33%)	5 (26%)
Arthralgia	3 (100%)	1 (25%)	1 (8.3%)	5 (26%)
Pyrexia or Body Temperature Increased	2 (67%)	2(50%)	1 (8.3%)	5 (26%)
Rhinorrhea	1 (33%)	1 (25%)	1 (8%)	3 (16%)
Rhinitis Allergic	1 (33%)	1 (25%)	0	3 (16%)
Edema (Generalized or Peripheral)	0	0	2 (17%)	2 (11%)
Anaphylaxis	0	0	2 (17%)	2 (11%)
Musculoskeletal Stiffness	1 (33%)	0	1 (8%)	2 (11%)
Pruritus	1 (33%)	0	1 (8%)	2 (11%)
Anemia	1 (33%)	1 (25%)	0	2 (11%)
Headache	0	1 (25%)	1 (8%)	2 (11%)
Body Temperature Increased	1 (33%)	1 (25%)	0	2 (11%)
Abdominal Pain	0	1 (25%)	1 (8%)	2 (11%)
Abdominal Pain Upper	0	1 (25%)	1 (8%)	2 (11%)
Abdominal Pain Lower	0	1 (25%)	1 (8%)	2 (11%)
Urticaria	0	0	1 (8%)	1 (5%)

Source: BLA 761047 Summary of Clinical Safety, Table 2.7.4.5.1.1.1

Reviewer Comment: In comparing with of the labels of other ERTs (for MPS I, MPS II, MPS IVA and MPS VI), there are no new safety signals and the rates of the TEAEs appear similar to those reported in the labels. The t the 2 patients with anaphylactoid reactions in Table 28 are the same ones as having anaphylaxis in Table 29.

8.4.6. Laboratory Findings

Refer to Section 8.3.3 for further details

8.4.7. Vital Signs

In general, there were no significant changes in temperature, heart rate or respiratory rate during infusions. However, changes of reduced diastolic blood pressure were noted in five patients with episodes of diastolic blood pressure at 45 mmHg or below. There were also changes in systolic blood pressure. Five patients enrolled in Studies 201 and 301 had decreases

in systolic blood pressure during infusions that were consistent with that component of Sampson's Criteria for anaphylaxis. (Sampson HA 2006) **(Table 30**) All but one of these episodes was associated with changes in ≥10 mmHg decreases in diastolic blood at the same time or within an hour of the drop of systolic blood pressure.

Table 30: Episodes of Change in Systolic Blood Pressure of ≥30 mmHg During Vestronidase Alfa Infusion

Subject	Episodes of decrease ≥ 30% in Systolic BP during infusion	Blood Pressure mmHg	Changed Blood pressure mmHg	Time After Start of Infusion
Study 201				
A1	Week 54	130/82	83/39	1 hour
A2	Week 98	108/61	71/58	1 hour
A3	Week 44	136/80	86/55	2 hours
A3	Week 58	139/79	97/52	2 hours
A3	Week 76	121/68	82/51	2 hours
A3	Week 78	115/66	68/55	4 hours
A3	Week 84	129/79	78/55	4 hours
Study 301				
C1	Week 40	128/59	84/69	30 min
C9	Week 24	145/70	97/58	2 hours

Source: BLA 761047, Study UX003-CL201 dataset vs.xmt; Study UX003-CL203 dataset vs.xmt; Study UX003-CL301 dataset advs.xmt

Medical Officer Comment: In Study 201, there was one reported episode of dizziness around week 56, but it did not appear to be associated with low blood pressure.

8.4.8. Electrocardiograms (ECGs)

Cardiac ECGs and echocardiograms were completed per protocol in Studies 201, 203 and 301. Study 301 contained the most complete cardiac evaluations of the vestronidase alfa development program. Review of these evaluations by DCRP did not suggest either improvement or deterioration of cardiac status during the period assessed. Refer to Section 6.2.2 for further detail.

8.4.9. QT

No subjects were identified with prolonged QT interval during routine evaluations.

8.4.10. Immunogenicity

A total of 23 patients were evaluable for immunogenicity in the vestronidase alfa clinical

development program. This includes the 20 patients evaluable for safety and three additional EA patients treated outside the US.

The Applicant defined that a patient was ADA+ only if they demonstrated a fourfold increase from baseline in ADA titer values, as proposed previously in the literature. (Shankar 2014) Immunogenicity data were available from 23 patients. Eighteen out of 23 patients (78%) developed anti-vestronidase alfa-vjbk antibodies (ADA). Ten of the 18 (56.5%) ADA-positive patients developed neutralizing antibodies (NAb) on at least one occasion. There is no correlation between ADA titer and NAb development.

Refer to the Clinical Pharmacology review by Dr. Christine Hon for additional details.

Medical Officer Comment: Patients enrolled in Study 301 (C6, C7, C9, C10 and C12) were noted to have ADA antibodies at baseline. One patient enrolled in Study 203 also was noted to have ADA antibodies, but he was initially enrolled and received vestronidase alfa in expanded access IND 123764.

As a new ERT, data on immunogenicity can be critical, particularly for long term efficacy. While studies 203 and 301 are shorter in duration to study 201, the development of ADA antibodies and NAb antibodies and their impact on both safety and efficacy will need to be assessed over longer periods of time. This is particularly important given the limited ability to correlate the formation of ADA or NAb antibodies with either genotype or residual enzyme activity in affected patients. Please refer to post marketing requirements and commitments

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Anaphylaxis

Anaphylaxis was observed in 2 of 20 evaluable patients treated with vestronidase alpha. The Applicant was asked to perform a broad standard Medical Dictionary for Regulatory Activities (MedDRA) query for anaphylactic reaction within 24 hours of infusion. The clinical database search included adverse events from initiation of the first vestronidase alpha treatment in humans, October 9, 2013 (for eIND 119935) to August 11, 2016, which is consistent with the information in the original BLA. The search produced a total of 13 adverse events. Narrative summaries were prepared by the Applicant and reviewed by the Agency.

The resulting cases were adjudicated according to standard criteria from the National Institute

of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network (NIAID/FAAN, Sampson et al. 2006). It is the Agency's usual practice to include all cases identified as anaphylaxis by the investigator at the bedside, as well as all cases adjudicated as anaphylaxis by NIAID/FAAN criteria.

Two cases of anaphylaxis were identified, and both were recognized as such by investigators at the bedside. A third case narrowly missed meeting NIAID/FAAN criteria, and was adjudicated both by the Applicant and the Agency as a potential anaphylaxis case.

- Anaphylaxis case No. 1 (Patient C2, Study 301) – The patient was premedicated with 10 mg of loratadine PO. On Treatment Week 22, approximately 16 weeks after beginning therapy with vestronidase alpha (4mg/kg IV QOW), the IV tubing malfunctioned and the patient received a bolus of study drug instead of the 1.5ml/hr infusion rate specified in the protocol. Within minutes, the patient developed respiratory distress. Oxygen saturation decreased to 82%. The patient was agitated, diaphoretic and cyanotic. The infusion was stopped and the patient was treated with epinephrine (0.15 mg IM), supplemental oxygen via face mask, diphenhydramine (15mg IV), and hydrocortisone (30mg IV). The patient's vital signs stabilized and symptoms resolved promptly. The case was recognized as anaphylaxis by the investigator at the bedside. Infusion was resumed, and the subject tolerated subsequent infusions of vestronidase alpha without further episodes of anaphylaxis.

- Anaphylaxis case No. 2 (Patient C5, Study 301) – The patient was premedicated with 10 mg of loratadine PO. During infusion of the first dose of vestronidase alpha, the patient developed diaphoresis and blood pressure dropped to 82/49 mmHg. The infusion was stopped, no other treatment was given, and the patient stabilized. The case was recognized as anaphylaxis by the investigator at the bedside. The infusion was resumed later that day without complications, and the patient tolerated subsequent infusions of vestronidase alpha without further episodes of anaphylaxis.

- Potential anaphylaxis case No. 3 (Patient A3, Study 201) -- The patient was premedicated with paracetamol (300 mg), cetirizine (5 mg), dexchlorpheniramine maleate (5 mg) and dimenhydrinate (12.5 mg). During Treatment Week 104, the patient experienced an 80% increase in heart rate, from 93 to 167 beats per minute thirty minutes into the infusion. Blood pressure remained normal to elevated, from 102/66 prior to infusion to 142/78 at thirty minutes into the infusion, reference range 90-115/50-77. In the 24 hours after infusion the patient developed "bronchospasm and respiratory failure requiring treatment with budesonide (400 ug, BID) and salbutamol (2 puffs, BID)." The infusion was not stopped, and the patient tolerated subsequent infusions of vestronidase alpha without further episodes of anaphylaxis.

Dr. Donohue (CDTL Comment):
Case No. 3 was adjudicated both by the Applicant and the Agency as a potential anaphylaxis case. The NIAID/FAAN criteria for anaphylaxis include reduced blood pressure after exposure to an allergen (for adults: systolic blood pressure of <90 mmHg or >30 % decrease from that individual's baseline). By that standard, case No. 3 does not meet criteria. However, it is not uncommon for clinicians to observe tachycardia and hypertension early in the course of anaphylaxis. In one study, up to 13% of patients with anaphylaxis initially presented with elevated blood pressure (Solmazgul E 2016), thought due to compensatory vasopressor responses.

It is unusual that anaphylaxis was observed to the first dose of vestronidase alpha in one patient, particularly as all three patients with anaphylaxis/potential anaphylaxis to vestronidase alpha tolerated subsequent infusions. These observations suggest that some anaphylaxis to vestronidase alpha may be due to non-IgE mediated mechanisms, similar to what has been observed with Xolair (omalizumab label). Importantly, Xolair has been associated with unusual cases of delayed anaphylaxis, occurring many hours after completion of injection. All cases of anaphylaxis to vestronidase alpha observed during the clinical program have occurred during infusion. Unlike Xolair, no cases of delayed anaphylaxis occurring hours after infusion have yet been observed in the clinical program for vestronidase alpha.

The NIAID/FAAN criteria rely in part on self-reported symptoms such as pruritus. The criteria may lack sensitivity in this program for two reasons. First, many patients had significant neurocognitive limitations that may have impeded self-reporting of symptoms. Second, patients were premedicated with antihistamines, which can mask the early signs and symptoms of anaphylaxis. Given these limitations, it is possible that the rate of anaphylaxis observed with vestronidase alpha in the clinical trial setting is an underestimate. A higher rate of anaphylaxis may be observed in the post-market setting.

Two of 20 patients had anaphylaxis to vestronidase alpha, for an anaphylaxis rate of 10%. Three of the other four enzyme replacement therapies for other mucopolysaccharidoses carry Boxed Warnings for anaphylaxis. The label for elosulfase alpha carries a Boxed Warning for an anaphylaxis rate of 8%. Guidance for Industry[7] states that a Boxed Warning (§201.57(c)(1) is ordinarily used when there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug. All approved enzyme replacement therapies (ERTs) for mucopolysaccharidoses appear to demonstrate anaphylaxis as an expected adverse event.

Medical Officer Comment: It will be important to monitor for anaphylaxis in the post-market setting for vestronidase alpha, and especially for any cases of delayed anaphylaxis. This reviewer recommends a Boxed Warning for anaphylaxis in the label for vestronidase alpha. For

[7] Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format.

patient safety, the drug should be administered by medical personnel equipped to manage anaphylaxis. The benefit:risk ratio should be individually considered for each patient since there are no alternative therapies available for MPS VII.

Post-approval, the Applicant will be required to evaluate the effect of genotype/phenotype on the risk for anaphylaxis in these patients. Mutations shown to correlate with null residual enzyme activity may impact the risk for immunogenicity to enzyme replacement therapy.

8.5.2 Infusion Associated Reactions

Rash/Pruritus: Patient C12 developed rash during infusion (Week 16); patient C11developed pruritus during Week 38. Study 201, Patient A3 experienced palmar pruritus during week 22. Review of the clinical history of the patient treated under expanded access IND 119935 also noted the development of a rash during the initial two infusions of 2 mg/kg vestronidase alfa.

Edema: Patient C10 developed edema but there was insufficient history as to when the edema resolved. Patient A3 (Study 201) during week 10 was reported to have erythema and peripheral edema.

Hypotension: Review of the vital signs data sets noted 11 episodes of decrease in systolic blood pressure (by 30 mmHg or more) during infusion. At least 8 of these episodes were accompanied by a correlative decrease in diastolic blood pressure.

Comparison with other ERTs to treat different mucopolysaccharidoses, infusion associated reactions with vestronidase alfa appeared to be as prevalent but slightly more severe than previously approved ERTs for mucopolysaccharidoses. **(Table 31**)

Table 31: Comparison of Approved MPS ERT Labeling for IAR with Vestronidase Alfa

Disease/Drug	Dosage	Infusion Associated Reactions (IAR)	Significant IAR
MPS VII Vestronidase alfa (Mepsevii)	4 mg/kg QOW	9/20 Subjects (45%) Anaphylaxis, rash, urticaria, pruritus pyrexia, angioedema, bronchospasm, hypotension	10%
MPS I Laronidase (Aldurazyme)	0.58 mg/kg QW	7/22 subjects (32%) Rash, flushing, fever, headache, rash, cough, bronchospasm, dyspnea, urticaria, angioedema, pruritus, tremor	1%
MPS II Idursulfase (Elaprase)	0.5 mg/kg QW	16/108 subjects (15%) Headache, fever, cutaneous reactions (rash, pruritus, erythema, urticaria) hypertension	0.2%
MPS IVA Elosulfase alfa (Vimizim)	2mg/kg QW	44/235 subjects (18.7%) Anaphylactic reactions, urticaria, peripheral edema, cough, dyspnea, and flushing.	7.7
MPS VI Galsulfase (Naglazyme)	1mg/kg QW	33/59 subjects (56%) pyrexia, chills, rash, urticaria, dyspnea, nausea, vomiting, pruritus, erythema, abdominal pain, hypertension, and headache	NA

Source: BLA 761047; Aldurazyme label; Elaprase label; Naglazyme label; Vimizim label

Medical Officer Comment: Based upon the rate of infusion associated reaction noted within the vestronidase alpha development program, it is this reviewer's opinion that the label should contain a Boxed Warning to reflect a risk for anaphylaxis and note the anticipated risks for hypersensitivity reactions associated with infusions.

8.6. Safety Analyses by Demographic Subgroups

There were no apparent differences in safety risk based upon age, gender or ethnicity. Due to the very small clinical trial population, subpopulation analyses were not performed based upon demographics.

8.7. Specific Safety Studies/Clinical Trials

In the vestronidase alfa development program, all studies were used to determine efficacy and safety. No specific studies were done to assess safety based upon drug-drug interactions or drug-disease interactions.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No studies have evaluated the effects of vestronidase alfa on tumor development or carcinogenicity in humans.

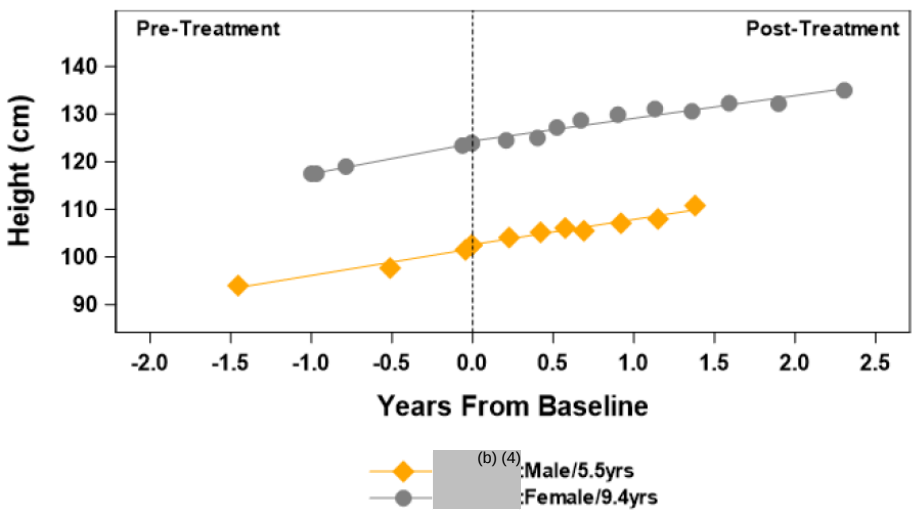
8.8.2. Human Reproduction and Pregnancy

No pregnancies have been reported in the vestronidase alfa development program. There are no clinical data on vestronidase alfa and lactation. All enrolled patients of child bearing age were to use two forms of highly effective forms of birth control. In preclinical studies, adverse genotoxic or reproductive effects were not observed.

8.8.3. Pediatrics and Assessment of Effects on Growth

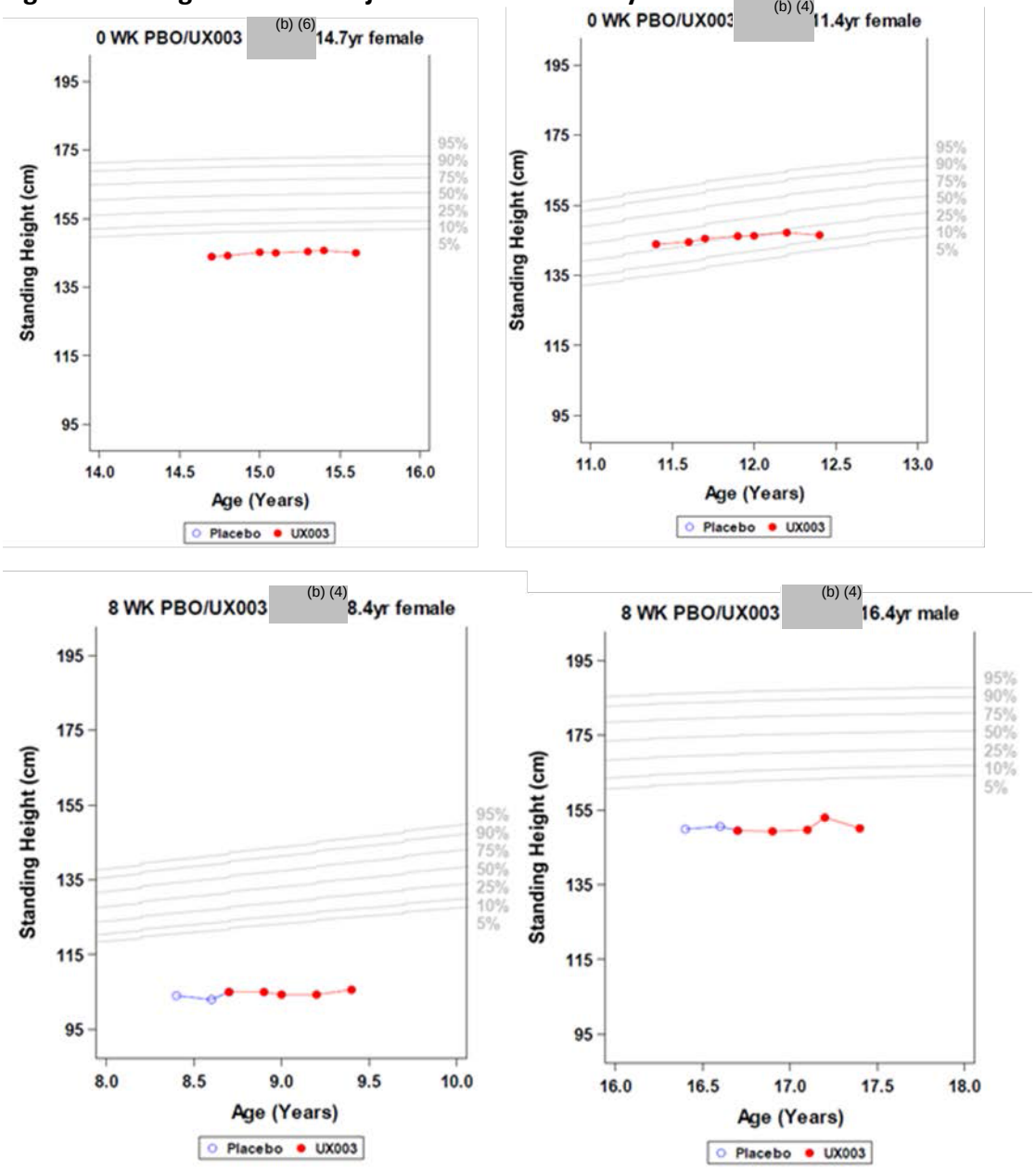
The Applicant assessed skeletal growth by measuring standing height and sitting height in patients enrolled in Study 201 and Study 301 in males aged ≤ 18 years and females aged ≤ 15 years who could comply with measurements through the duration of the study. Linear growth was plotted as change in height over time in 2 of 3 patients in Study 201 (**Figure 23**) and 4 of 12 patients enrolled in Study 301 (**Figure 24**).

Figure 23: Height of Two Patients Enrolled in Study 201 over time



Source: BLA 761047 CSR UX003-CL201; Figure 10.2.5.1

Figure 24: Height of Four Subjects Enrolled in Study 301 Over Time



Source: BLA 761047 CSR UX003-CL301 Figure 14.99.2.20.3

No clinically significant changes of improvement or worsening in height were identified in patients from either study.

Medical Officer Comment: In general, there was no apparent improvement with height over time in pre-pubertal patients enrolled in Study 201 or Study 301. Due to disease heterogeneity

that includes the primary effects of uGAG deposition (skeletal dysplasia) in addition to secondary effects of uGAG deposition (scoliosis and decreased strength from either musculoskeletal or central neurologic), linear growth is difficult to assess in this population. Only 4 of 12 patients could consistently comply with growth assessments and attempts at anthropometric measurements completed in 8 patients from Study 301 did not demonstrate significant changes either. As MPS VII pathology appears to be slowly progressive, the time frame of either of these studies may not be of sufficient duration, or vestronidase alfa may not easily enter into bone tissue (Tomatsu S 2013) to benefit growth.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no known or anticipated potential for overdose or abuse potential. No studies were conducted to investigate the effect of withdrawal or rebound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no post-marketing experience with vestronidase alfa.

8.9.2. Expectations on Safety in the Postmarket Setting

No potentially important differences are anticipated in how the drug was administered and used in the clinical trial versus its expected use in the postmarketing setting that could lead to increased risk. Prescribers of vestronidase alfa will likely be practitioners with expertise or experience in the management of patients with lysosomal storage diseases such as MPS VII receiving ERTs. Off-label use is not anticipated.

The safety database is small and it is likely to allow detection only of the most common adverse events. We anticipate that rarer adverse events will emerge with continued exposure in the post-market setting.

8.10. Additional Safety Issues From Other Disciplines

There were no additional safety issues identified from other disciplines.

8.11. Integrated Assessment of Safety

The safety database included 20 patients treated with vestronidase alfa at the to-be-marketed dose of 4 mg/kg enrolled in open-label or placebo controlled studies. The safety population was comprised of patients enrolled in Study 201 (3 patients), 203 (4 patients) and 301 (12 patients) with two expanded access patients for a total of 20 patients (one EA patient also enrolled in Study 203). Twelve patients were enrolled in the phase 3 Study 301 and 9 of these patients received placebo infusions as part of the randomized start protocol. There were no deaths reported in the development program. There were four serious adverse events, two cases of anaphylaxis and one potential case of anaphylaxis during infusion, and a single instance of head trauma that was not infusion related.

Adverse events that were more common during vestronidase treatment than during placebo included infusion site swelling and extravasation, diarrhea, rash and pruritus.

Medical Officer Comment: A total of 326 adverse events were reported from Studies 201, 203 and 301 and the expanded access patients. All patients enrolled in the vestronidase alfa development program experienced at least one adverse event, though the average number of events per patient experienced in Study 301 was at least 2- to 3- fold less than in Studies 201 or 203, possibly due to the shorter duration of evaluation (6 months vs. ≥18 months).

This reviewer contends that the safety database is currently adequate relative to the global MPS VII patient population. However, due to the limitations imposed by the rarity of subjects with MPS VII, there remains residual uncertainty about the safety profile of vestronidase alfa. This reviewer cannot rule out the emergence of additional safety signals in the post-market period.

Review of the expanded access IND patient narratives and vital sign datasets identified adverse events in addition to those events the Applicant reported. Although this reviewer found expected safety signals at a slightly higher rate than reported by the Applicant, no new or unanticipated safety signals were identified. In general, the safety profile of vestronidase alfa is consistent with the safety profiles of other, previously approved ERT to treat mucopolysaccharidoses. Three of these ERTs have Boxed Warnings on their label for anaphylaxis. As the rate of anaphylaxis is 10%, vestronidase alfa should also have a Boxed Warning for anaphylaxis.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not convened during the review of BLA 761047.

10 Labeling Recommendations

10.1. Prescribing Information

The labeling will be in PLR format. Content and formatting were reviewed to meet the latest best-practices. The final labeling contains all of the labeling revisions negotiated with the applicant.

Medical Officer Comment: As noted in **Section 7.3**, I recommend that vestronidase alfa is indicated for adult and pediatric patients diagnosed with MPS VII. Add the limitation of use here.

In addition, I recommend the following edits to the Applicant's proposed labeling for vestronidase alfa:

- **Boxed Warning**

Recommendation:
A Box Warning for risk of anaphylaxis should be placed on the label.

- **Section 5 (Warnings and Precautions**)

Recommendation:
This section should reflect that severe reactions (primarily anaphylaxis) have occurred when vestronidase alfa was infused according to labeled directions and that currently there is insufficient information to predict which patients are at risk for hypersensitivity reactions or anaphylaxis.

- **Section 6 (Adverse Reactions)**

Recommendation:
This section should state that both anaphylaxis and hypersensitivity reactions have been observed with vestronidase alfa infusion. Due to this risk, infusions should only be administered in a setting where appropriate medical support is readily available.

As currently written, the number of patients reported who developed rhGUS ADA and NAb antibodies is misleading, as not all subjects were actually tested for the development of antibodies. The percentage should be removed and clarification should be provided that testing was not obtained in several patients.

- **Section 8 (Use in Specific Populations)**

Recommendation:

The statement should be revised to reflect that it is not known whether vestronidase alfa can cause fetal harm when administered during a pregnancy, and that administration during a pregnancy should occur only if needed. Additionally, if infusions occur during pregnancy, the pregnancy should be considered high risk and patients should be followed by the Disease Monitoring Program (DMP).

- **Section 14 (Clinical Studies)**

Recommendation:
This section should describe results for the BOT-2 gross motor scoring within the multi-domain responder index (MDRI) as this was the only measure that the review team considered interpretable during clinical review (refer to Section 6.2.2).

- **Section 17 (Patient Counseling Information)**

Recommendation:
This section should clearly communicate the risk for anaphylaxis in addition to hypersensitivity reactions.

10.2. Patient Labeling

Neither a Medication Guide nor patient package insert (PPI) were proposed by the Applicant. The risk of allergic reactions should be communicated via a PI with a Boxed Warning.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

A REMs is not recommended for vestronidase alfa.

12 Postmarketing Requirements and Commitments

Because vestronidase alfa for this indication has an orphan drug designation, the applicant is exempt from pediatric study requirements under the Pediatric Research Equity Act (PREA).

We have determined that an analysis of spontaneous postmarketing adverse events will not be sufficient to assess the known risk of serious hypersensitivity reactions, including anaphylaxis, with use of Mepsevii (vestronidase alfa-vjbk), and to identify an unexpected long-term risk of immunogenicity, and a serious risk of pre- and post-natal developmental adverse effects.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

In accordance with section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, the Applicant is required to:

1. Conduct a prospective, longitudinal study (Study UX003-CL401) to assess the long-term risk of immunogenicity and the risk of serious hypersensitivity reactions (including anaphylaxis) in patients with mucopolysaccharidosis type VII (MPS VII) followed for three years on vestronidase alfa. The following information will be collected and analyzed: (1) incidence rates for serious hypersensitivity reactions, (2) incidence rates for the appearance of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) against vestronidase alfa, (3) temporal associations between ADA or Nab formation and serious hypersensitivity reactions, (4) associations between beta-glucuronidase (GUSB) genotype and serious hypersensitivity reaction risk, (5) association between intrinsic GUSB enzymatic activity and serious hypersensitivity reaction risk, and (6) assessments of the risk of immunogenicity on clinical safety outcomes. To complete these analyses, protocol UX003-CL401 will require collection of molecular genotype and intrinsic GUSB enzymatic activity (apart from any concurrent enzyme replacement). Submit annual study reports that contain results from analyses of interim data. The final study report will be based on a study population that contains at least 12 new patients (including at least six patients less than one year old) treated with vestronidase alfa and enrolled in Study UX003-CL401.

2. Perform a pre- and post-natal developmental study in rats to assess the effects of Mepsevii (vestronidase alfa-vjbk) on pre- and post-natal development. The study should be designed to detect adverse effects on the pregnant/lactating female rat and on the development of conceptus and offspring from implantation through weaning. The dose levels used in the pre- and post-natal developmental study should provide adequate margins of exposure for the clinical dose.

In addition, the Applicant has agreed to conduct the following postmarketing commitments:

3. In MPS VII patients enrolled in the prospective, longitudinal Study UX003-CL401 (PMR-

1), collect and analyze: (1) beta-glucuronidase (GUSB) genotype, (2) in patients without history of vestronidase alfa treatment, baseline intrinsic GUSB enzymatic activity apart from any concurrent enzyme replacement treatment, (3) a complete record of treatments with vestronidase alfa pre- and post-UX003-CL401 enrollment, and (4) results from baseline and periodic tests for MPS VII clinical outcomes to include liver and spleen size measurement, pulmonary function, motor function, and neurocognitive function.

4. Conduct studies to address the bioanalytical method validation of the assay used to measure the pharmacodynamic marker glycosaminoglycans, the Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) method (b) (4). Specifically, perform incurred sample reanalysis (ISR) for samples from Study UX003-CL301, and ongoing studies UX003-CL203 and Study UX003-CL202. Complete the ongoing assessment of long-term sample storage stability and conduct a 2nd long-term sample storage stability assessment to cover the storage duration of all study samples from clinical trials. Use freshly prepared calibrator standards in conducting the ISR for samples from UX003-CL203 and UX003-CL202 and the 2nd long-term sample storage stability analysis.

5. To conduct the bioburden and endotoxin method qualification to include a total of three lots (b) (4).

6. To conduct a repeat rabbit pyrogen test with three Mepsevii (vestronidase alfa-vjbk) drug product lots at the maximum human equivalent dose of 4 mg/kg.

7. To re-evaluate all Mepsevii (vestronidase alfa-vjbk) drug substance and drug product release and stability acceptance criteria when a statistically significant number of lots (25) of drug substance have been manufactured using the commercial manufacturing process and tested using commercial specifications. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

8. To perform a leachable study to evaluate leachables in the Mepsevii (vestronidase alfa-vjbk) drug product container closure system. The analysis will be performed using one drug product lot that has passed the end of shelf-life under the long term (5 ± 3 °C) and accelerated (25 °C/60% RH) storage conditions. Appropriate methods to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

13 Appendices

13.1. Financial Disclosure

The applicant adequately disclosed financial arrangements with the clinical investigators. These arrangements do not raise concern over the integrity of the data

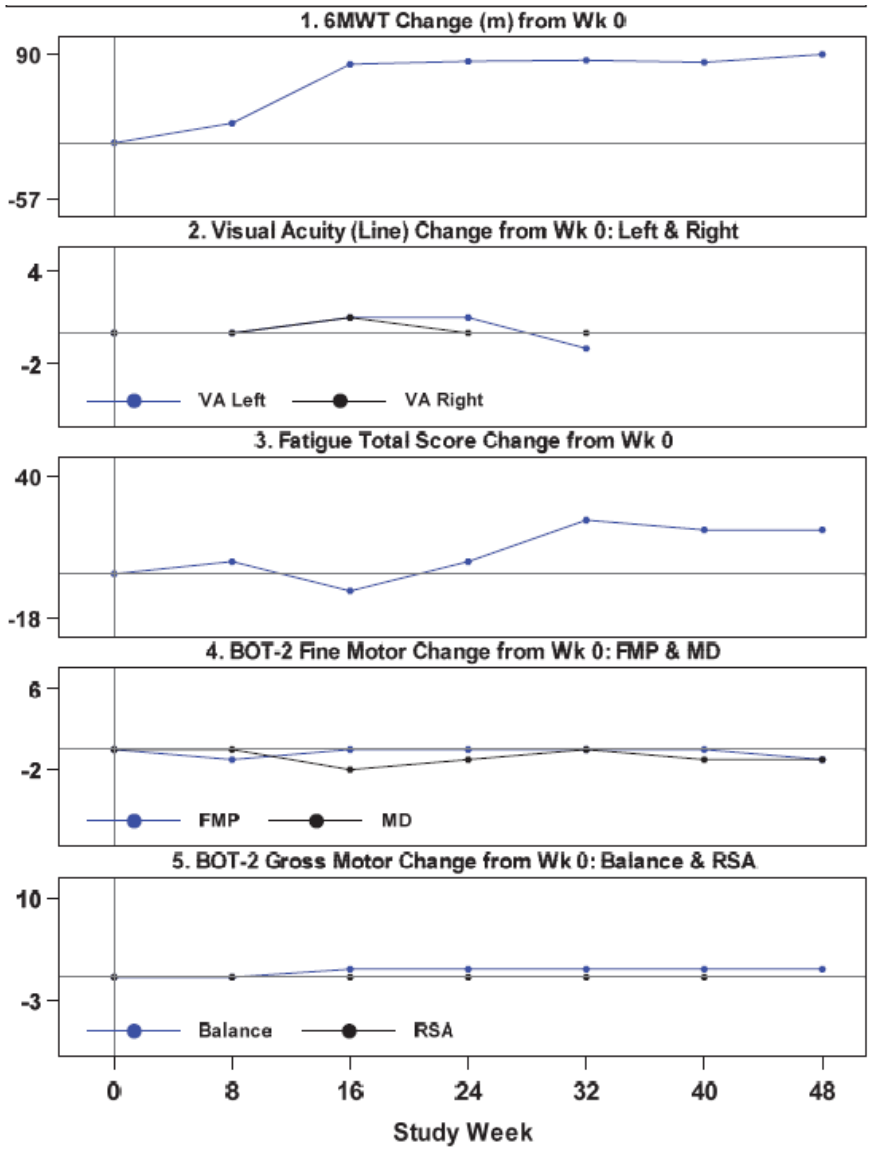
Covered Clinical Study (Name and/or Number): Study UX003-CL201, Study UX003-CL203 and Study UX003-CL301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11 principal investigators, 39 sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.2. Appendix A

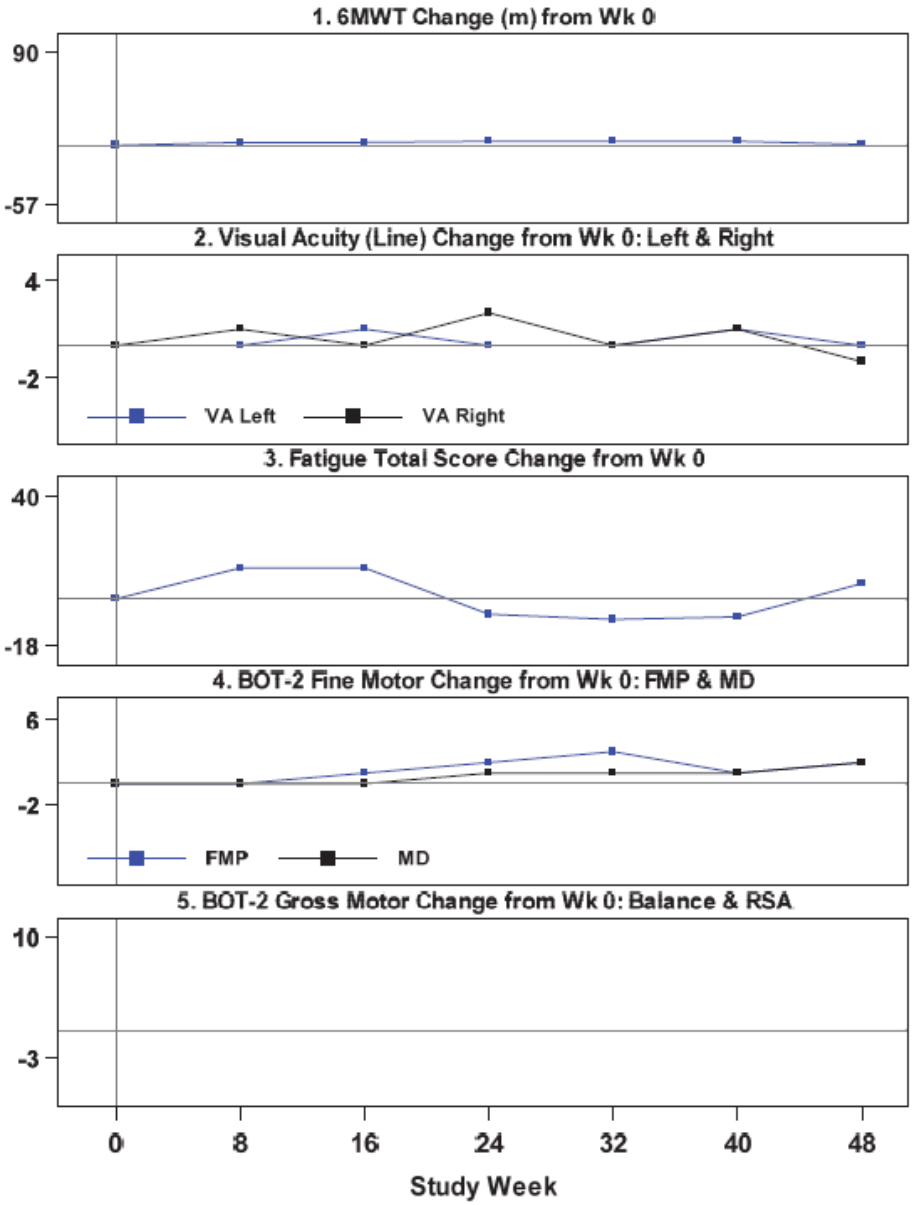
Subject Profiles by Study Week for Study UX003-CL301

Subject C1 (0 weeks placebo/48 weeks vestronidase alfa)



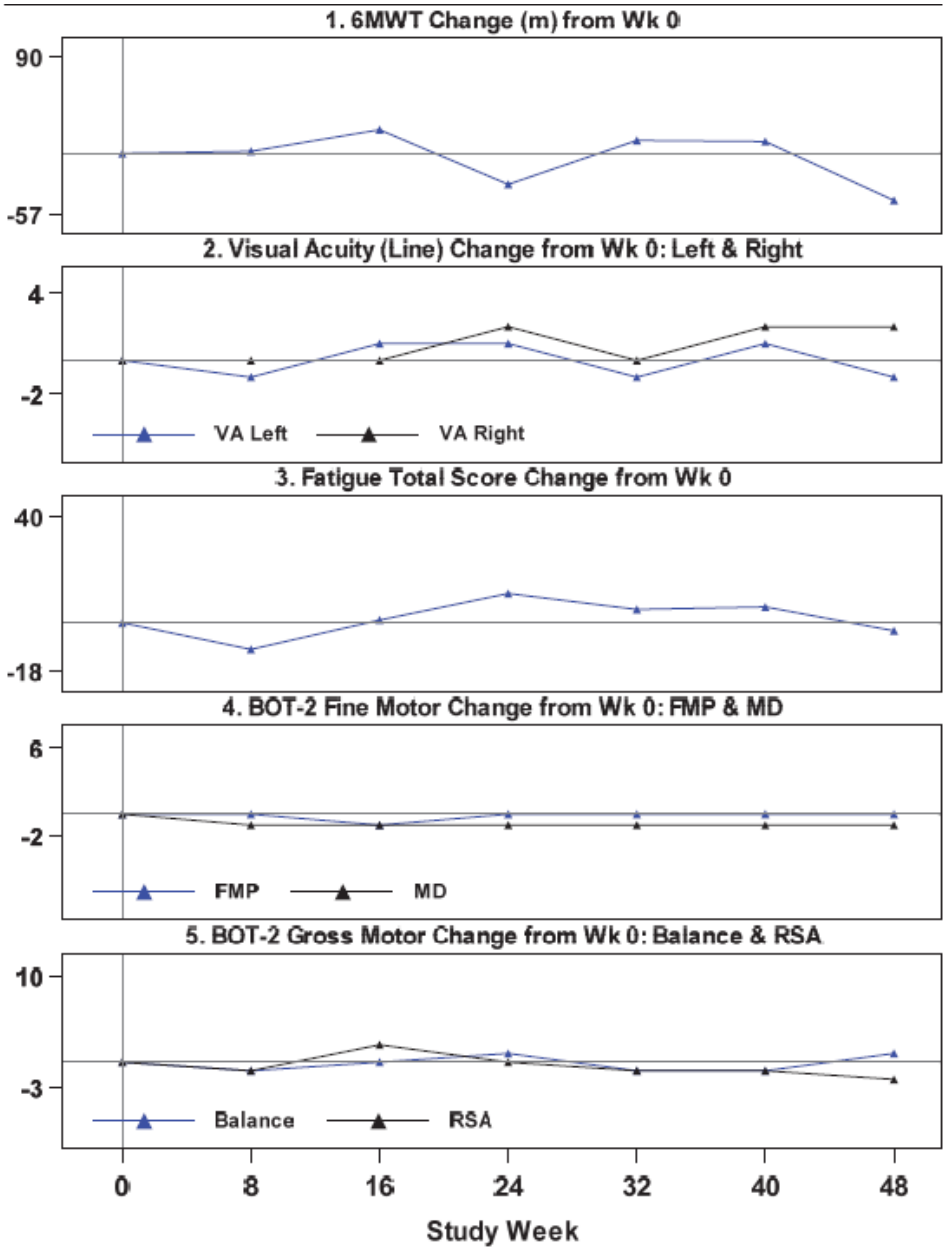
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C3 (0 weeks placebo/48 weeks vestronidase alfa)



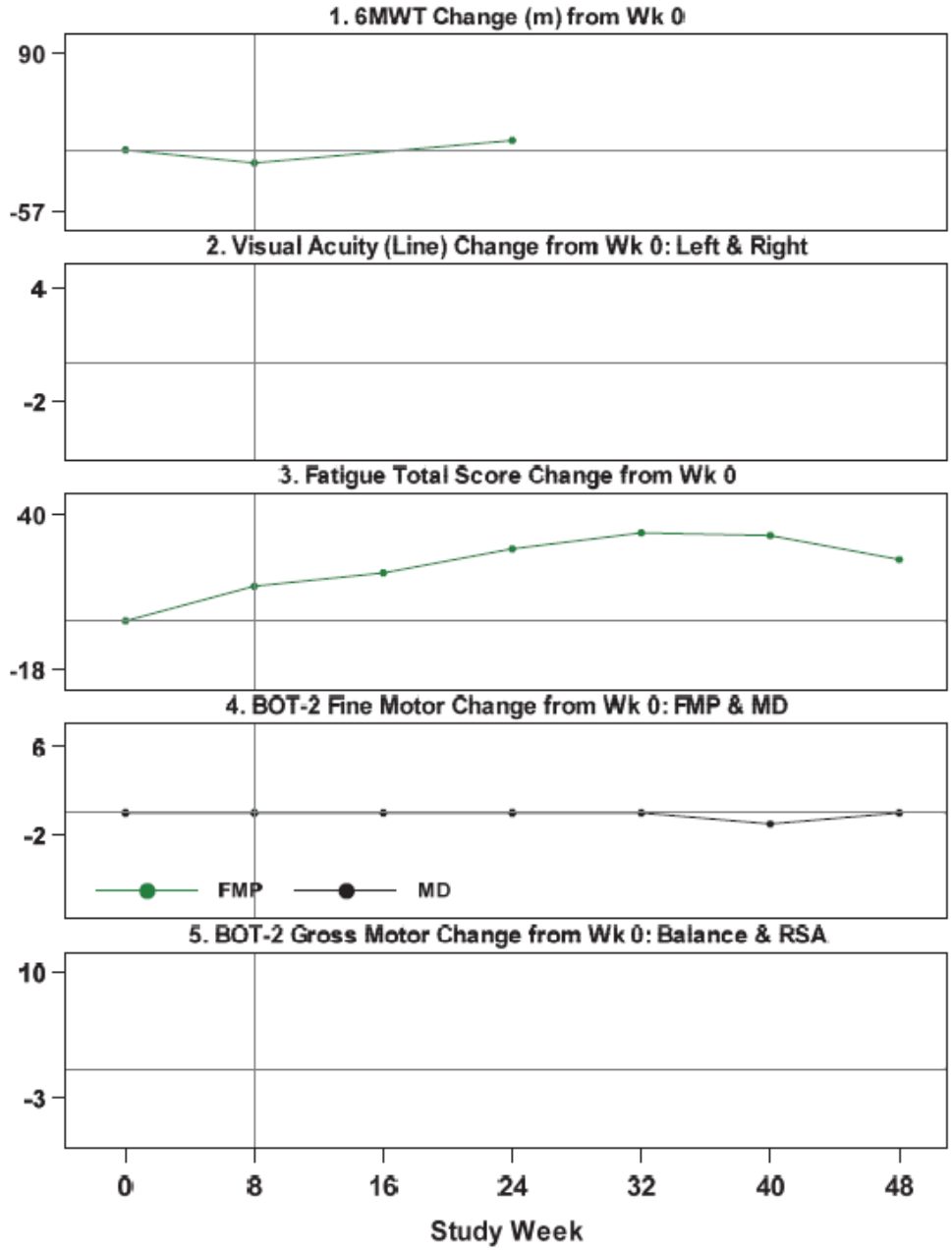
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C12 (0 weeks placebo/48 weeks vestronidase alfa)



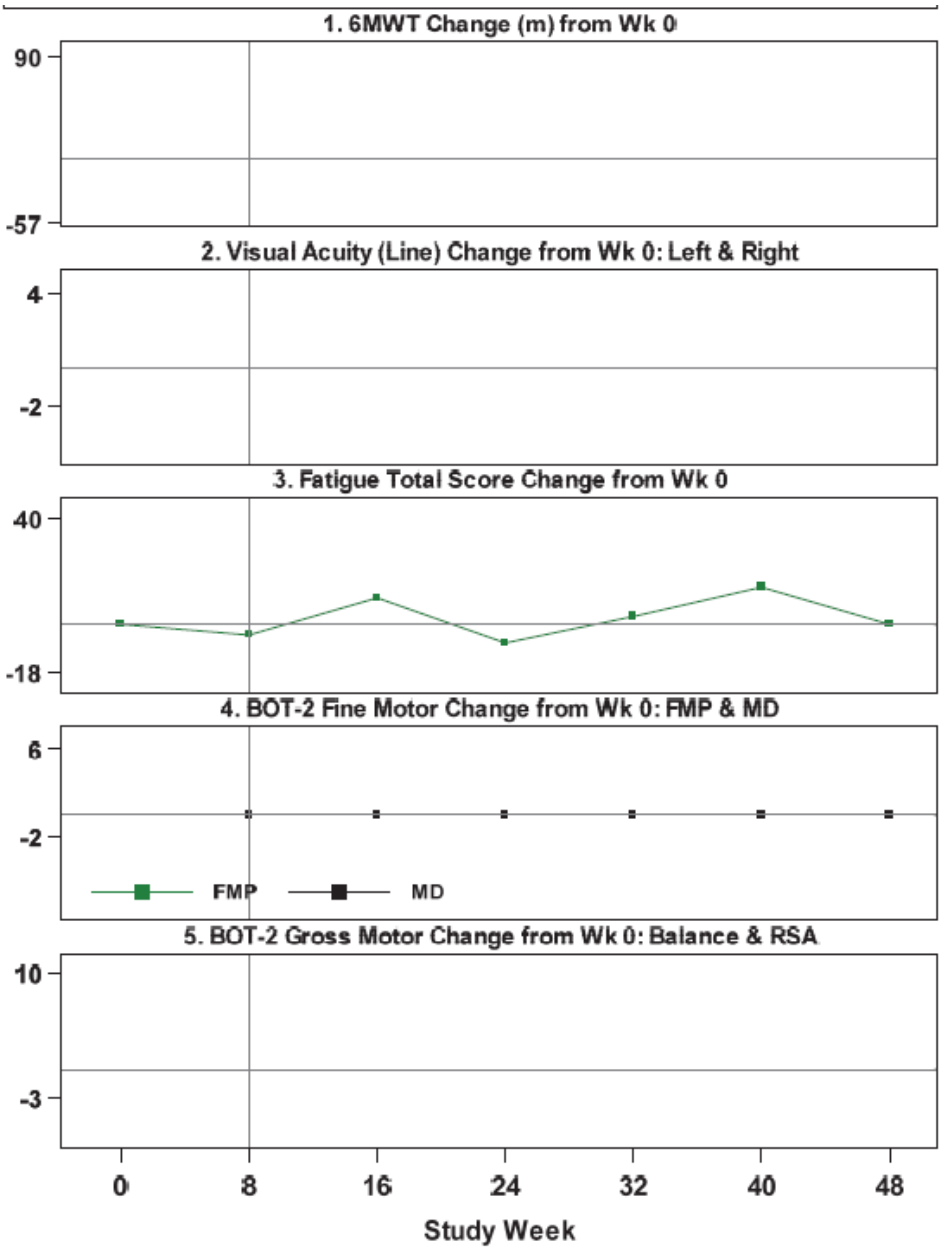
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C2 (8 weeks placebo/40 weeks vestronidase alfa)



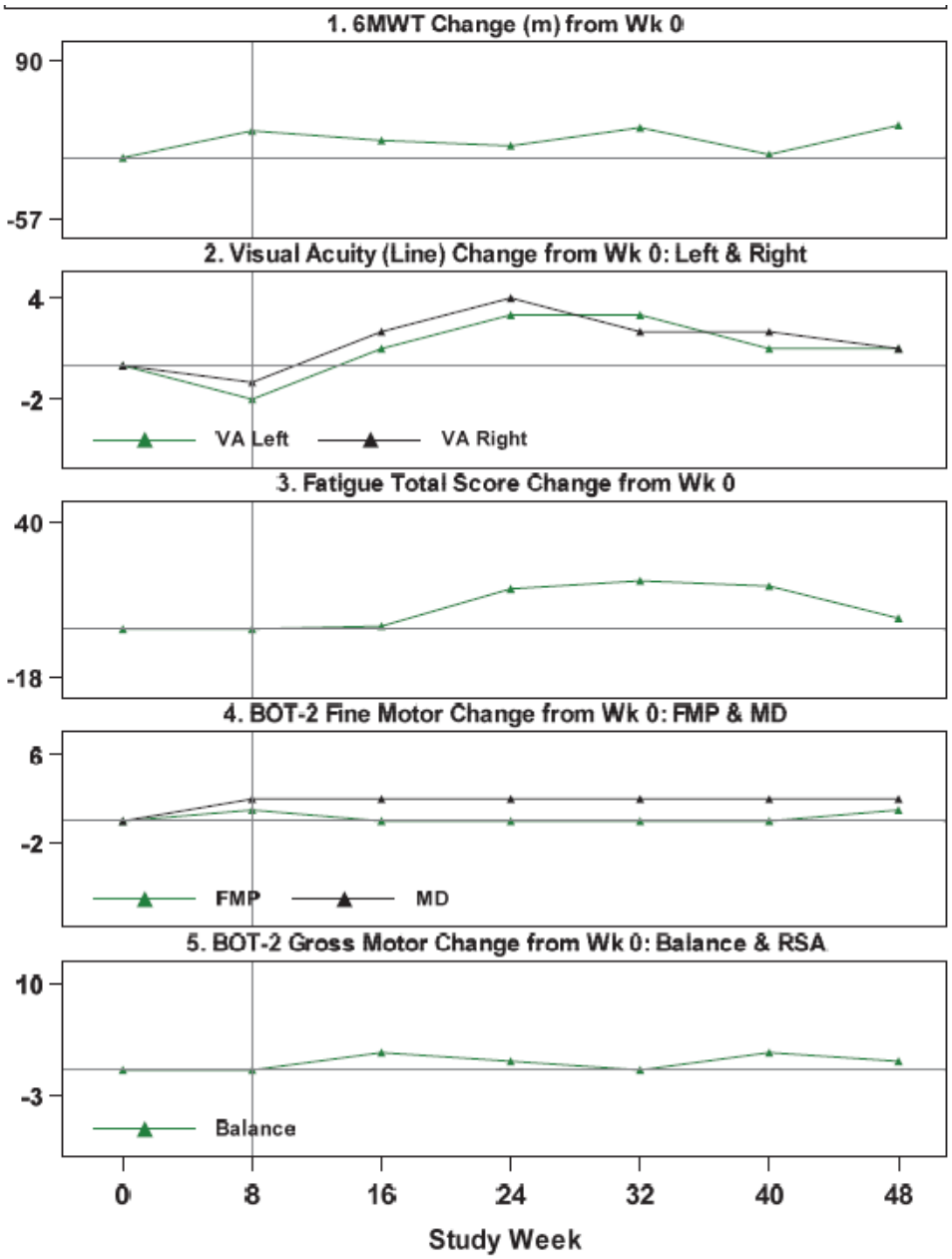
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C4 (8 weeks placebo/40 weeks vestronidase alfa)



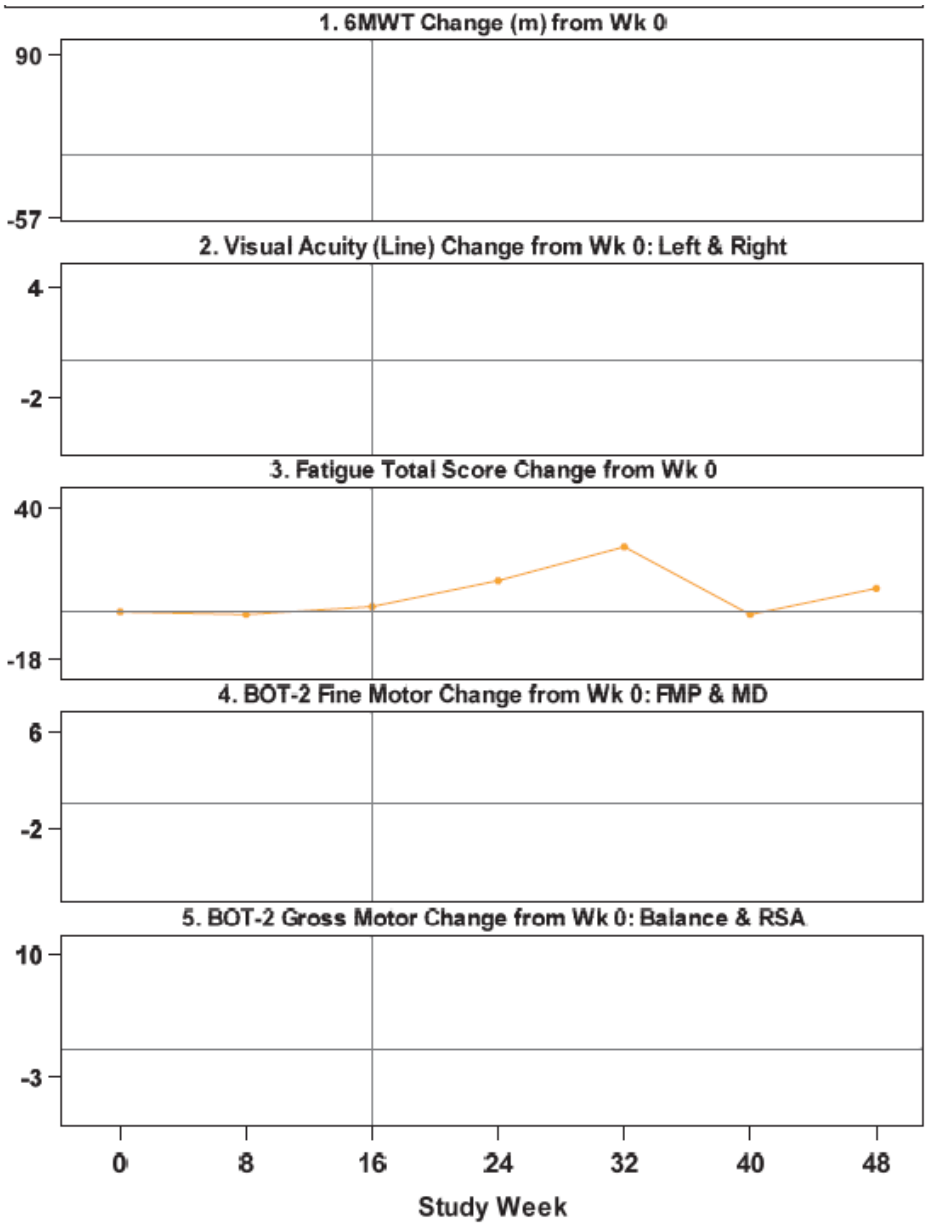
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C11 (8 weeks placebo/40weeks vestronidase alfa)



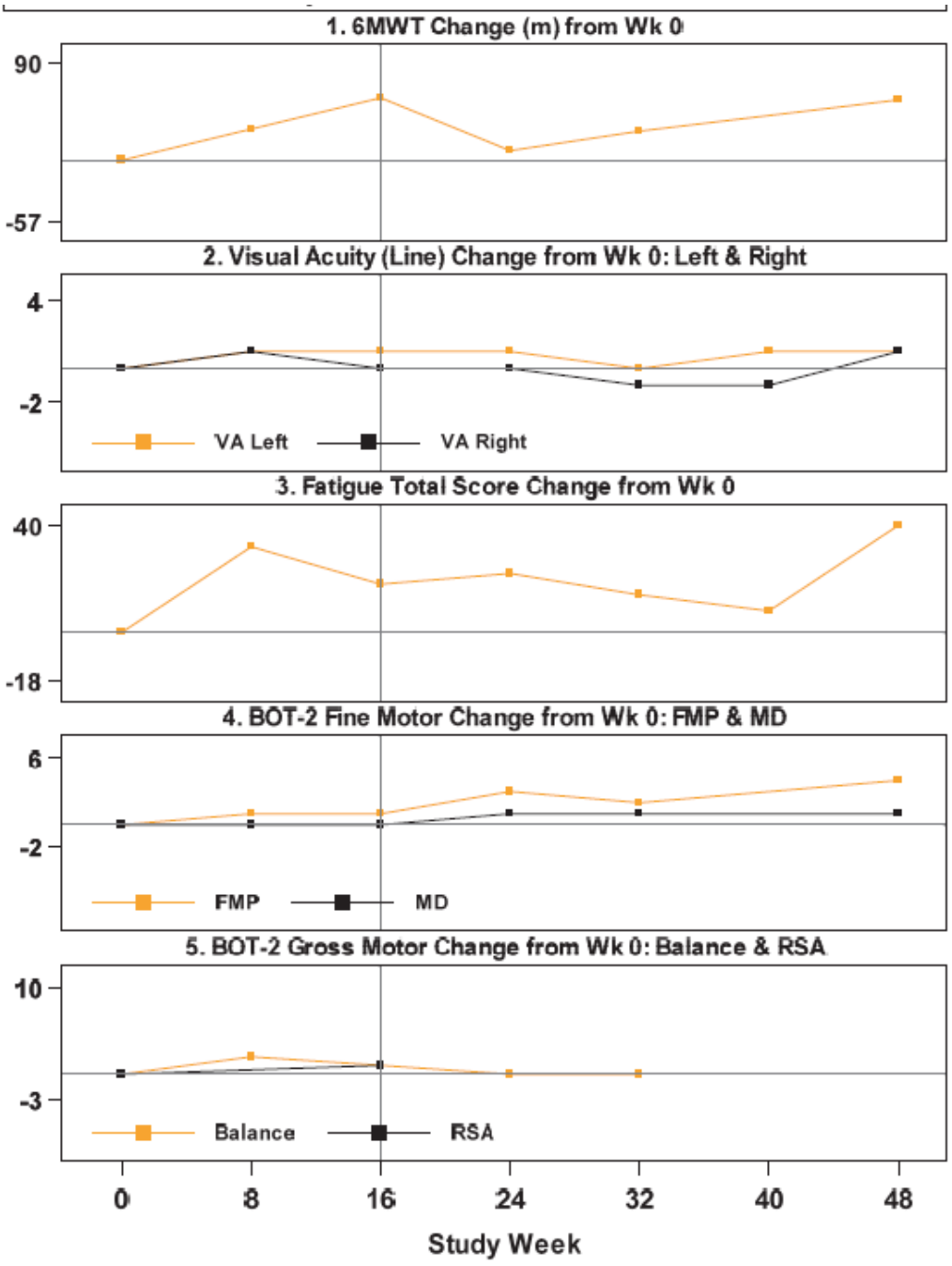
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C6 (16 weeks placebo/32 weeks vestronidase alfa)



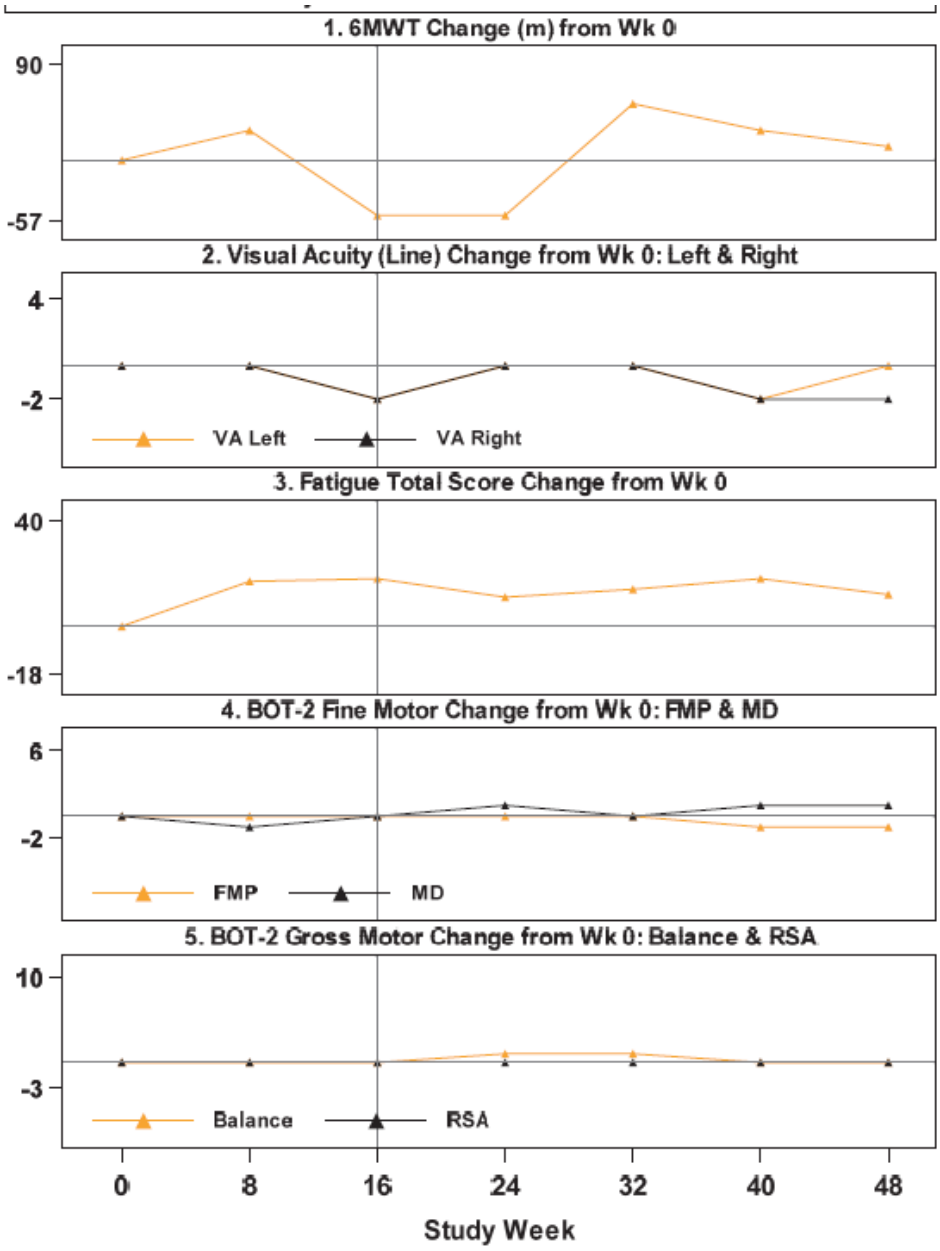
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C9 (16 weeks placebo/32 weeks vestronidase alfa)



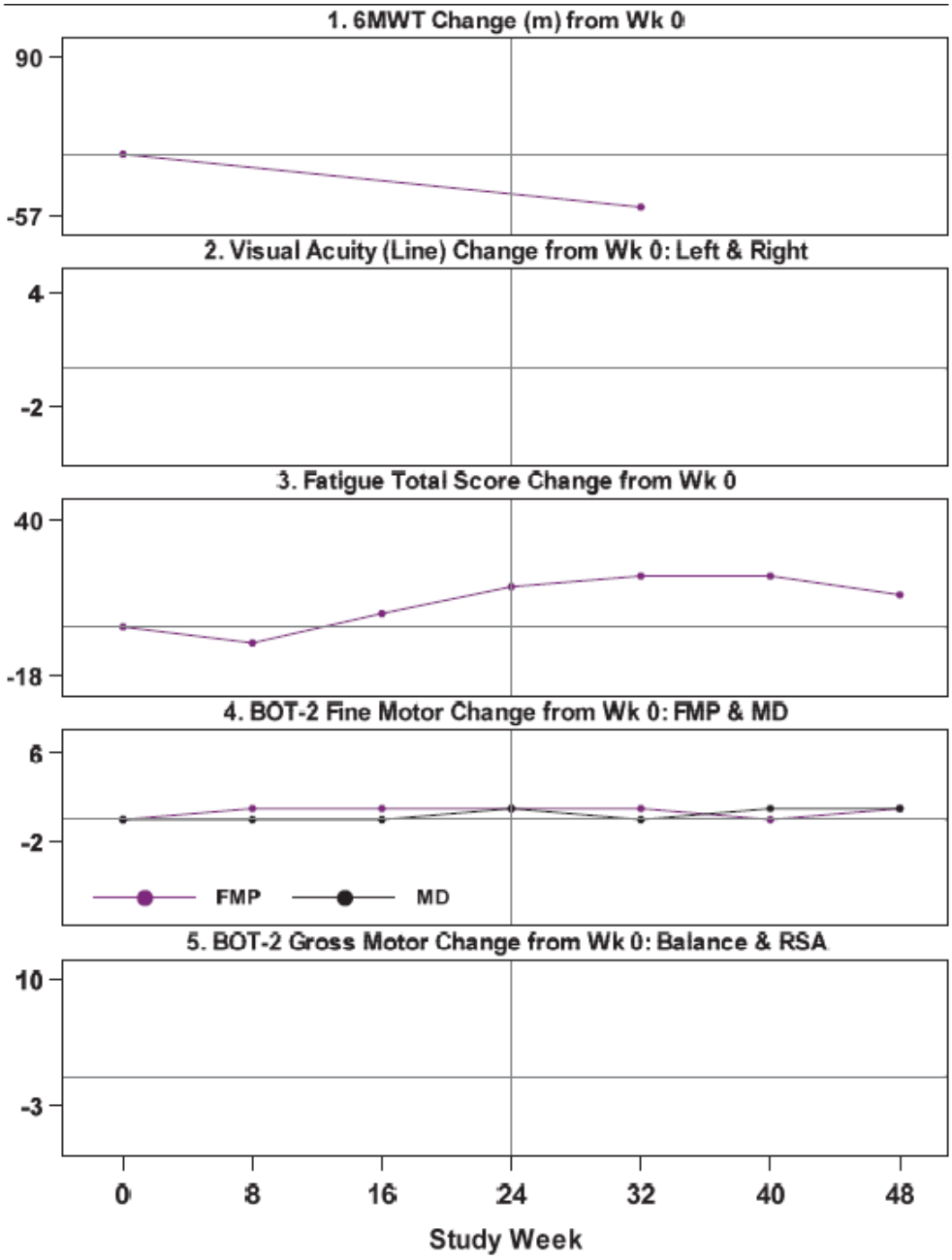
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C10 (16 weeks placebo/32 weeks vestronidase alfa)



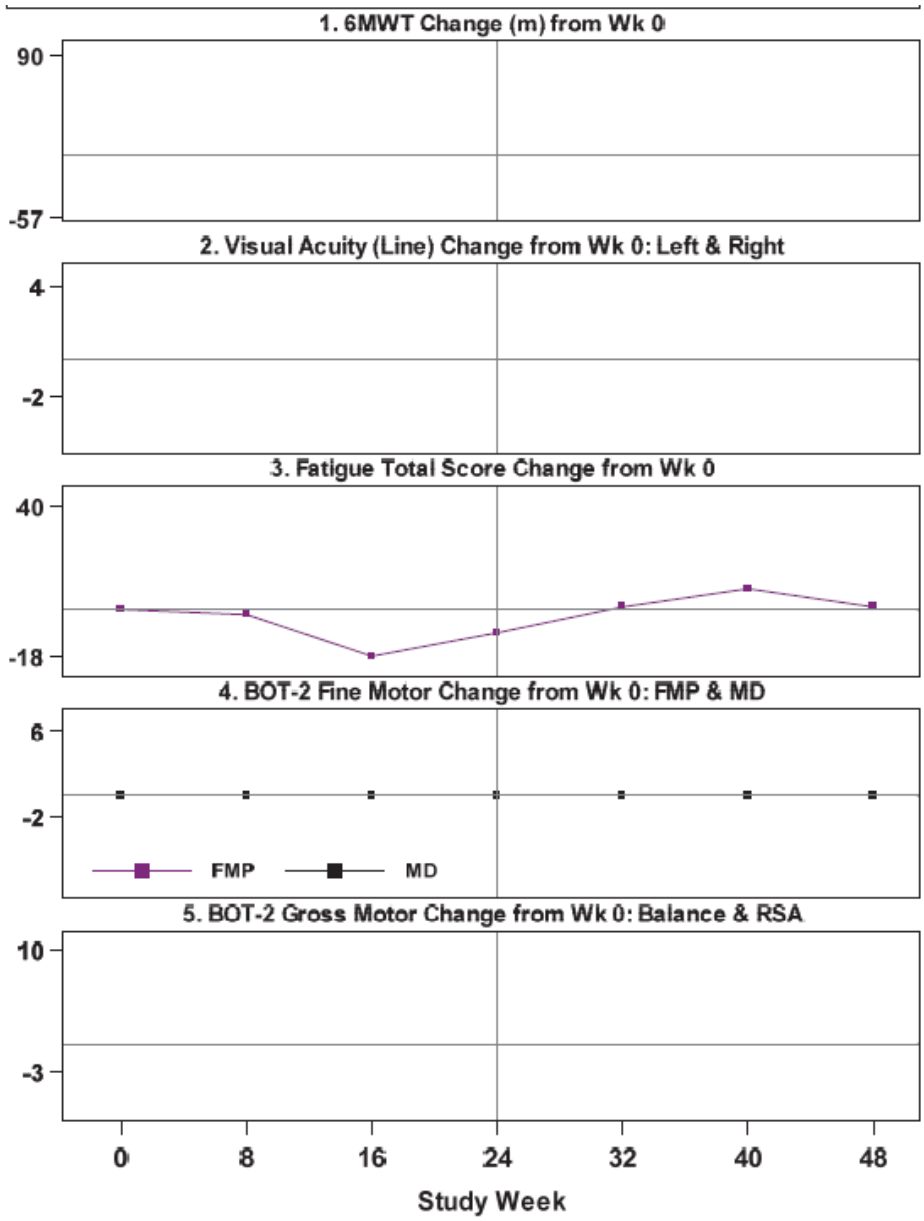
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C5 (24 weeks placebo/24 weeks vestronidase alfa)



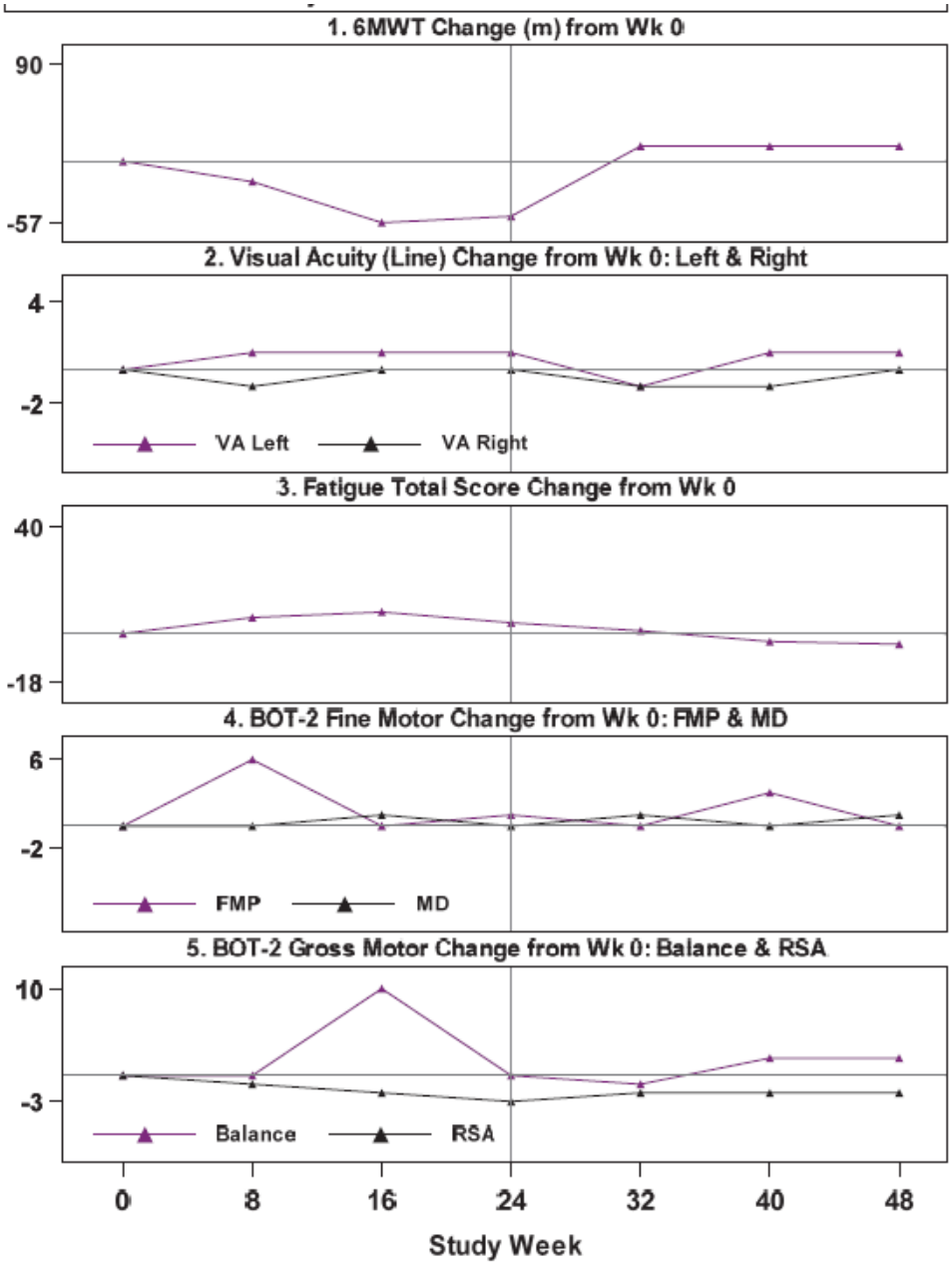
Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C7 (24 weeks placebo/24 weeks vestronidase alfa)



Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

Subject C8 (24 weeks placebo/24 weeks vestronidase alfa)



Source: BLA 761047; submitted by Applicant on 27 Mar 2017 as an IR response

13.3. References

Clarke, L., Wraith, J.E., Beck, M., Kolodny, E.H., Pastores, G.M., Muenzer, J., Papoport, D.M., Berger, K.I., Sidman, M., Kakkis, E.D., Cox, G.F. (2009). "Long-term efficacy and safety of Laronidase in the treatment of Mucopolysaccharidosis I." Pediatrics **123**(1): 229-240.

Do Cao J, et al. (2016). "30 months follow-up of an early enzyme replacement therapy in a severe Morquio A patient: About one case." Mol Genet Metab Rep **9**: 42-45.

Geiger, R., Strasak, A., Treml, B., Basser, K., Kleinsasser, A., Fischer, V., Geiger, H., Loeckinger, A., Stein, J.I. (2007). "Six-minute walk test in children and adolescents." The Journal of Pediatrics **150**(4): 395-399.

Gniadek TJ, et al. (2015). "Cardiovascular pathologies in mucopolysaccharidosis type VII (Sly Syndrome)." Cardiovascular Pathology **25**(5): 322-326.

Loveman, E., Copley, V.R., Colquitt, J., SCott, D.A., Clegg, A., Jones, J., O'Reilly, K.M.A., Singh, S., Bausewein C., and Wells, A. (2015). "The clinical effectiveness and cost-effectivenss of treatments for idiopathic pulmonary fibrosis: a systemic review and economic evaluation." Health Technology Assessment **19**(20).

Montano AM, et al. (2016). "Clinical course of sly syndrome (mucopolysaccharidosis type VII)." Journal of Medical Genetics **53**: 403-418.

Muhlebach MS, et al. (2011). "Respiratory Manifestations in Mucopolysaccharidoses." Paediatric Respiratory Reviews **12**: 133-138.

Sampson HA, M.-F. A., Campbell RL, Adkinson NF Jr, Bock SA, Branum A, Brown SG, Camargo CA Jr, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD Jr, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Connor R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FE, Thomas S, Wood JP, Decker WW. (2006). "Second symposium on the definition and management of anaphylaxis: summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium." J Allergy Clin Immunol **117**(2): 391-397.

Schrover, R., Evans, Kathryn., Giugliani, R., Nobel, I., Bhattacharya, K. (2017). "Minimally clinically important difference for the 6-min walk test: literature review and application to Morquio A syndrome." Orphanet J Rare Dis **12**.

Shankar, G., Arkin, S., Cocea, L., Devanarayan, V., Kirshner, S., Kromminga, A., Quarmby, V., Richards, S., Schneider, C.K., Subramanyam, M, Swanson, S., Verthelyi, D., Yim, S. (2014). "Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides -- harmonized terminology and tactical recommendations." The AAPS Journal **16**(4): 658-672.

Shapiro EG, N. I., Delaney KA, Rudser K, Kovac V, Nair N, Richard CW, Haslett P, Whitley CB (2016). "A prospective natural history stury of Mucopolysaccharidosis type IIIA." J Pediatr **170**: 278-287.

Sly, W. S., et al. (1973). "Beta glucuronidase deficiency: report of clinical, radiologic, and biochemical features of a new mucopolysaccharidosis." J Pediatr **82**(2): 249-257.

Solmazgul E, K. A., Dogru S, Ozalper V, Cetindagli I, Ogun S, Salmanoglu M, Kilic E, Karabaca E, Ozturk S. (2016). "Anaphylactic reactions presenting with hypertension." Springerplus **5**(1): 1223.

Stratford, P. W., Binkley J.M., Riddle J. L (1996). "Health status measures: Strategies and analytic methods for assessing change scores." Physical Therapy **76**: 1109-1123.

Tomatsu S, A.-D. C., Barbosa H, Montano AM, Barrera LA, Shimada T, Yasuda E, Mackenzie WG, Mason RW, Suzuki Y, Orii KE, Orii T (2013). "Therapies of mucopolysaccharidosis IVA (Morquio A syndrome)." Expert Opin Orphan Drugs **1**(10): 805-818.

Wuang, Y., Su, CY (2008). "Reliability and responsiveness of the Bruininks-Oseretsky Test of Motor Proficiency -Second Edition in children with intellectual disability." Research in Developmental Disabilities **30**(5): 847-855.

Yamada Y, et al. (1998). "Treatment of MPS VII (Sly disease) by allogeneic BMT in a female with homozygous A619V mutation." Bone Marrow Transplant **21**(6): 629-634.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DINA J ZAND
11/14/2017

KATHLEEN M DONOHUE
11/14/2017

DRAGOS G ROMAN
11/14/2017

JULIE G BEITZ
11/14/2017

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	C-2017-076
IND/NDA/BLA NUMBER	BLA 761047
REFERENCED IND FOR NDA/BLA	IND 123788
ESTABLISHED NAME/TRADE NAME	UX0003
SPONSOR/APPLICANT	Ultragenyx
INDICATION	Treatment of MPS VII
MEETING TYPE (A/B/C/WRO)	
LETTER DATE/SUBMISSION NUMBER	
PDUFA GOAL DATE	9/16/2017
DATE OF CONSULT REQUEST	3/17/2017
REVIEW COMPLETION DATE	8/16/2017
REVIEW DIVISION	DGIEP
MEDICAL REVIEWER/TEAM LEADER (TL)	Dina Zand/Katie Donohue
REVIEW DIVISION PM	Jenny Doan
COA REVIEWER	Michelle Campbell
COA TL/SECONDARY REVIEWER	
ASSOCIATE DIRECTOR, COA STAFF	Elektra Papadopoulos
INSTRUMENT(S)	PedsQL and BOT-2
COA TYPE	PRO and PerfO
ENDPOINT(S) CONCEPT(S)	Multi-domain responder index
INTENDED POPULATION(S)	Children with MPS VII
Please check all that apply:	☒Rare Disease/Orphan Designation ☒Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology and Inborn Errors Products regarding Biological License Application (BLA) 761047. The applicant has submitted their biological license application of their drug development program. The proposed indication is treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

The applicant implemented the following clinical outcome assessments in their single, pivotal phase 3 clinical trial in patients with Mucopolysaccharidosis VII (MPS VII, Sly syndrome). The focus of this review is on the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) and the Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL- Fatigue).

Instrument name (COA Type)	Concept(s)	Endpoint	Copy of Instrument
6 Minute Walk Test (PerfO)	Gait Speed	Secondary	
BOT-2 (PerfO)	Fine Motor Skills, Balance and Agility	Secondary	Attached
PedsQL-Fatigue (PRO)	Fatigue Quality of Life	Secondary	Attached

(b) (4)

The applicant did not provide validation information to support the use of the BOT-2 and the PedsQL Fatigue in the MPS VII patients.

There are two modes of administration of the PedsQL-Fatigue, parent-report and child-report. We are concerned that both PedsQL-Fatigue are not fit for purpose for this context of use.

Self-report

- Many of the patients in Study CL-301 had "moderate to severe cognitive impairments" as determined by review of medical records; no standardized cognitive testing was conducted as part of the trial. It is unclear from the application whether patients were able to reliably self-report based on discussion with the clinical review team.

Parent-report

- The parent version of the PedsQL Fatigue Scale is not an observer-reported outcome; instead, it uses proxy reporting (reporting by someone who is not the patient, such as a parent or caregiver, responding as if that person were the patient). The items in the PedsQL Fatigue Scale cannot be adequately assessed by observers (e.g., parents or caregivers). Items such as "trouble remember what he/she was just thinking" can only be assessed directly by the patients. The 2009 PRO Guidance discourages the use of proxy reporting

and recommends observer-reported outcomes to be based on observable behaviors a patient may have.
- Supportive information on the measurement properties for both versions of the PedsQL Fatigue Scale in the MPS VII population was not provided.

We also found that the BOT-2 is not fit for purpose in the MPS VII patient population.
- While the BOT-2 is a standardized assessment of motor proficiency is appropriate for use to measure motor performance, a majority of Study CL-301 patients had moderate to severe cognitive impairment with no baseline cognition level assessed. Half of Study CL-301 patients were unable to have a baseline assessment or had missing data from the BOT-2. The CRFs stated that patients were unable to follow the directions.
- Due to the patient population limitations, the BOT-2 is not fit for purpose.

Best Practices When Developing COA Endpoint Measurement Strategy:
For future medical product development, we would encourage sponsors to consider the following:
- We encourage sponsors to have a clear understanding of the natural history of the disease of interest including what are key symptoms that may improve from treatment and what an appropriate length of time would be to see a clinical benefit.
- Prior to the selection of PRO instruments, we would encourage sponsors to establish that the patient population is able to valid and reliable self-report and select a COA measure(s) that takes in to account a spectrum of cognition levels. A data-driven approach to select performance measures that are robust to the cognitive and mobility limitations of the patient population should be utilized.
- When looking to use an observer-reported outcome, we encourage sponsors to determine what observable symptoms or behaviors a parent/caregiver can observe and are relevant to the disease and treatment under study.
- When looking to assess motor performance, we would encourage sponsors to establish a baseline cognition level of the patient population or select a performance outcome measure that take in to account a spectrum on cognition levels.
- Sponsors may want to consider modification of existing measures in cognitively impaired populations. For example, observable symptoms of fatigue in the PedsQLcould be identified and assessed if a patient is living with a consistent caregiver.

B. BACKGROUND

Mucopolysaccharidoses (MPS) are a group of inherited lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of glycosaminoglycans (GAGs). Although many of the characteristics are similar among the MPSs, each disease is a distinct entity arising from deficiency of a specific enzyme and the consequences of storage in different tissues. MPS VII (MPS 7, Sly syndrome) is an ultra-

rare, progressively debilitating and life threatening lysosomal storage disease and one of the rarest of the MPSs [(estimated prevalence < 1/1,000,000 (Orphanet 2016), in which patients are deficient in one specific enzyme, beta-glucuronidase (GUS). Clinical presentation may occur at birth with hydrops foetalis or later in life during adolescence or adulthood with skeletal disease and other manifestations. Varying in severity and progression rate, similar to other MPS diseases, symptoms may include abnormal coarsened facies, pulmonary disease, cardiovascular complications, hepatosplenomegaly, joint stiffness, short stature, cognitive impairment, and the MPS skeletal disease known as dysostosis multiplex (Neufeld et al.2001). Most MPS VII patients die before the second or third decade of life due to complicating medical problems (Montano et al. 2016). The presence and severity of symptoms in MPS VII patients are highly variable.

C. CLINICAL OUTCOME ASSESSMENT REVIEW

Single clinical endpoints may not adequately cover the breadth of MPS VII, which includes many clinical manifestations of disease that can differ by patient. Due to this, the division agreed to a Multi-domain Responder Index (MDRI). The MDRI was included in Study CL-301 to assess efficacy across the broad spectrum of clinical characteristics commonly observed in MPS VII. The intent was to capture the aggregate benefit or decline across multiple domains of clinical function or clinically important change. Six domains were included in the MDRI to assess a range of functions impacted by different body systems: 6MWT, FVC, shoulder flexion, visual acuity, and BOT-2 (fine motor and gross motor). The MID for each domain was defined, and each subject was scored for each endpoint (+1 MID, -1 MID, or 0).

Also the concept of an Individual Clinical Response Results (ICR) was used in Study CL-301. The ICR, is a single clinical measure with the highest impact on the individual subject, was pre-specified in recognition of the small size of the cohort and the expected clinical heterogeneity of the patients. According to the study protocol, the ICR was selected based on, but not limited to: 1)the specific concerns of the subject/parent/caregiver reported; 2) the ability of the subject to reliably complete the assessment; and 3) the extent of impairment measured in the outcome of interest taking in account developmental, cognitive, and behavioral factors observed at both Screening and Randomization visits. The clinical outcome ranked with the highest impact on daily life that could be reliably completed by the subject and met a threshold level of impairment was selected as the ICR for that subject. All of the assessments included in the MDRI along with fatigue, as measured by the PedsQL-Multidimensional Fatigue Scale, could have been selected as a subject's ICR. Ultimately, one assessment was selected based on the subject's individual clinical problem evaluation.

1 CONTEXT OF USE

1.1 Clinical Trial Population

Confirmed MPS VII patients aged 5 to 35 years.

Inclusion criteria:

- Confirmed diagnosis of MPS VII based on leukocyte or fibroblast glucuronidase enzyme assay or genetic testing
- Elevated uGAG excretion at a minimum of 3-fold over the mean normal for age (at Screening)
- Apparent clinical signs of lysosomal storage disease as judged by the Investigator (eg, enlarged liver and spleen
- Joint limitations
- Airway obstruction or pulmonary problems, limitation of mobility while still ambulatory)
- Aged 5 to 35 years, inclusive

Exclusion criteria:

- Subjects who had undergone a successful bone marrow or stem cell transplant or had any degree of detectable chimaerism with donor cells
- Major surgery within 3 months prior to study entry or planned major surgery during the study
- Any hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, placed the subject at increased risk for adverse effects.

1.2 Clinical Trial Design

A multicenter, randomized, placebo-controlled, blind start, single crossover Phase 3 study to assess the efficacy and safety of 4 mg/kg UX003 in MPS VII subjects aged 5 to 35 years.

Figure 1: Study Schema for Study CL-301

Figure 2.1: UX003-CL301 Study Schema

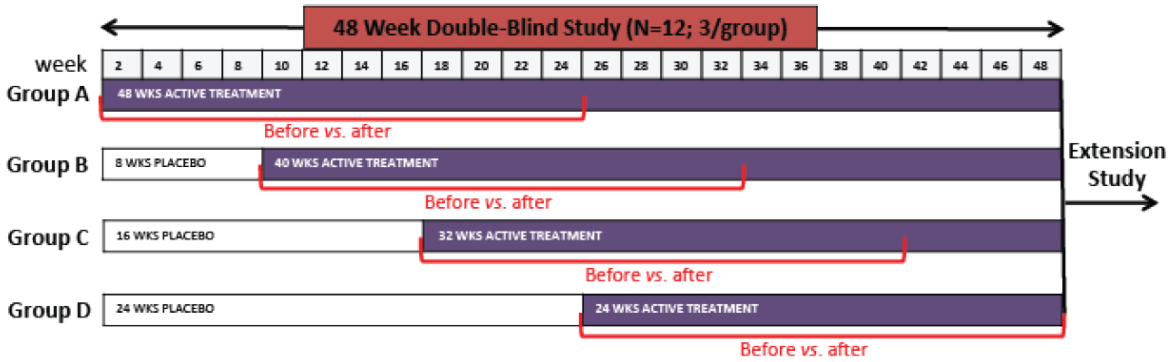


Table 1: Demographics of Study CL-301

Treatment Group	Subject ID	Age/Sex/Race
	(b) (6)	
0WK PBO/UX003		14.7/Female/White
0WK PBO/UX003		13.3/Female/White
0WK PBO/UX003		11.4/Female/White
8WK PBO/UX003		8.4/Female/Other
8WK PBO/UX003		12.7/Female/White
8WK PBO/UX003		16.4/Male/White
16WK PBO/UX003		17.3/Female/Other
16WK PBO/UX003		22.6/Female/White
16WK PBO/UX003		22.4/Female/White
24WK PBO/UX003		10.1/Male/Other
24WK PBO/UX003		10.4/Male/White
24WK PBO/UX003		25.2/Male/White

1.3 Endpoint Hierarchy and Definition

There was no a priori primary endpoint for Study CL-301. The results of Study CL-301 will evaluated by the totality of evidence on a per patient basis.

Secondary Endpoints:

- Percent reduction from baseline over 24 weeks of treatment with UX003 in the specific uGAG analyte (dermatan sulfate [DS] derived fragments) measured by LC-MS/MS. First morning void urine was evaluated for uGAG concentration normalized to urinary creatinine concentration.
- Multi-Domain Responder Index: (6MWT, FVC, shoulder flexion, visual acuity, and Bruininks-Oseretsky Test of Motor Proficiency [BOT-2])
- Pulmonary function testing
- Fatigue (Pediatric Quality of Life Multidimensional Fatigue Scale
- Individual Clinical Response (a single clinical measure with the highest impact on the individual subject), and scoring of impactful clinical problems.

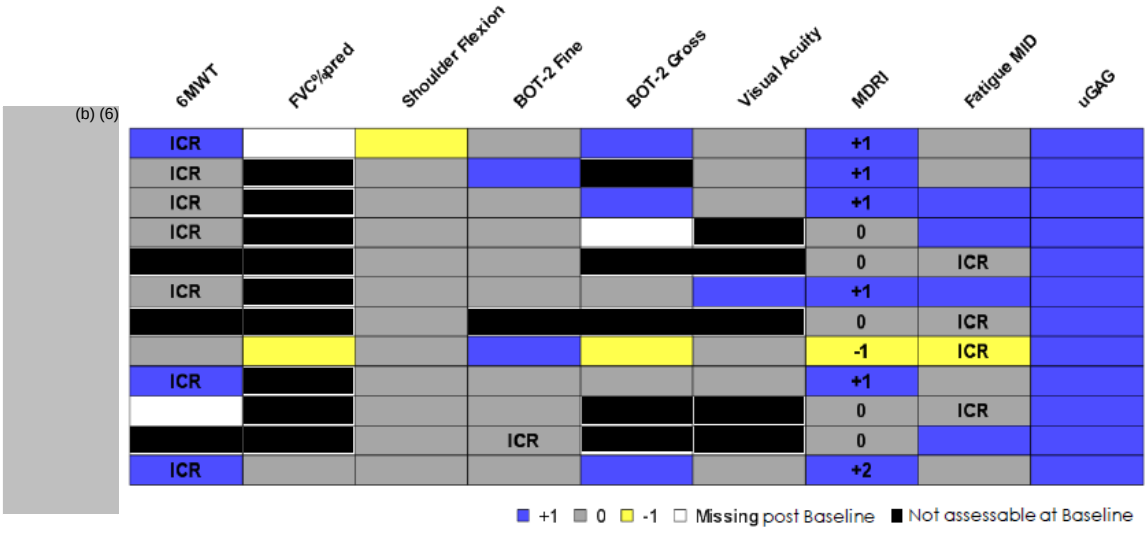
Other Endpoints:

- Additional GAG measures (chondroitin sulfate [CS] and heparan sulfate [HS] uGAG by LC-MS/MS; and non-reducing end [NRE] CS/DS and HS GAG in serum and urine)
- Hepatosplenomegaly
- Cardiac ventricular mass
- 3-Minute Stair Climb Test (3MSCT)
- 2-minute Walk Test (2MWT); growth
- Subject-reported disability and pain

- The MPS Health Assessment Questionnaire (MPS HAQ)
- Childhood Health Assessment Questionnaire (CHAQ) or PROMIS Health Assessment Questionnaire (PROMIS HAQ)
- Physician and Subject/Parent/Caregiver Clinical Global Impression (CGI) scales.

Figure 2: Study Endpoints for Study CL-301

Figure 2.2: Endpoints Defined with MID or Response at UX003 Treatment Week 24



uGAG = uGAG (LC-MS/MS-DS) responder (>=50% reduction)

Adapted from Source: Figure 14.2.2.2.1 and 14.2.2.2
ICR: Individualized Clinical Response for each subject
When any domains are missing for MDRI at UX003 Treatment Week 24, the MDRI domain at UX003 Treatment Week 32, if it exists, is used for imputation. If the MDRI domain at UX003 Treatment Week 32 is missing, then the MDRI domain at UX003 Treatment Week 16, if available, is used. The missing values are counted as 0 to calculate MDRI total score
uGAG responders are subjects who ever reached >= 50% reduction from baseline in uGAG excretion during the first 24 weeks of UX003 treatment.
Not assessable at Baseline: defined as when the subjects could not perform the test at Baseline visit (prior to UX003 treatment) due to the disease and/or age/cognition.
Missing (post baseline): When a subject had baseline evaluation but the domain score at treatment week 24 was missing and could not be imputed

Reviewer's Comment: Figure 2 the outcome assessments measured in Study CL-301. Cells in the chart with the letters ICR were identified to be the patient's individualized response. Blue colored cells represent a positive change, grey colored cells represent no change and yellow colored cells represent a negative change. Black colored cells represent the outcomes

assessment was not assessed at baseline and a white colored cell represent the post-baseline data was missing.

Table 2: Applicant Stated COA Responders in Study CL-301

Table 2: Study UX003-CL301 Respondent by PRO Instrument and Study Visit

			Respondent						
Treatment Group	Subject ID	Instrument	Randomiz-ation	Study Week 8	Study Week 16	Study Week 24	Study Week 32	Study Week 40	Study Week 48
0WK PBO/UX003	(b) (6)	PEDSQL (AGES 13-17)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		PROMIS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		PEDSQL (AGES 13-17)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		PEDSQL (AGES 8-12)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
0WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		PEDSQL (AGES 8-12)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		PEDSQL (AGES 8-12)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		PEDSQL (AGES 13-17)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
8WK PBO/UX003		PROMIS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
16WK PBO/UX003		PEDSQL (AGES 13-17)	Father	Father	Father	Father	Father	Father	Father
16WK PBO/UX003		MPS HAQ	Father	Father	Father	Father	Father	Father	Father
16WK PBO/UX003		PROMIS HAQ	Father	Father	Father	Father	Father	Father	Father

Treatment Group	Subject ID	Instrument	Respondent						
			Randomization	Study Week 8	Study Week 16	Study Week 24	Study Week 32	Study Week 40	Study Week 48
16WK PBO/UX003	(b) (6)	PEDSQL (AGES 18-25)	Subject	Subject	Subject	Subject	Subject	Subject	Subject
16WK PBO/UX003		MPS HAQ	Subject	Subject	Subject	Subject	Subject	Subject	Subject
16WK PBO/UX003		PROMIS HAQ	Subject	Subject	Subject	Subject	Subject	Subject	Subject
16WK PBO/UX003		PEDSQL (AGES 18-25)	Mother and sister	Mother	Mother	Mother	Mother	Mother	Mother and sister
16WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
16WK PBO/UX003		PROMIS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother and sister
24WK PBO/UX003		PEDSQL (AGES 8-12)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		PEDSQL (AGES 8-12)	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		MPS HAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		CHAQ	Mother	Mother	Mother	Mother	Mother	Mother	Mother
24WK PBO/UX003		PEDSQL (AGES 18-25)	Subject	Subject	Subject	Subject	Subject	Subject	Mother
24WK PBO/UX003		MPS HAQ	Subject	Subject	Subject	Subject	Subject	Subject	Mother
24WK PBO/UX003		PROMIS HAQ	Subject	Subject	Subject	Subject	Subject	Subject	Mother

Source: BLA 761047_Response Listing 16.2.6.8.4, Study UX003-CL301 EDC data (Fatigue), and UX003-CL301 CSR Listing 16.2.6.17.1 (MPS HAQ), Listing 16.2.6.18.1.1 (CHAQ) and Listing 16.2.6.19.1 (PROMIS HAQ)

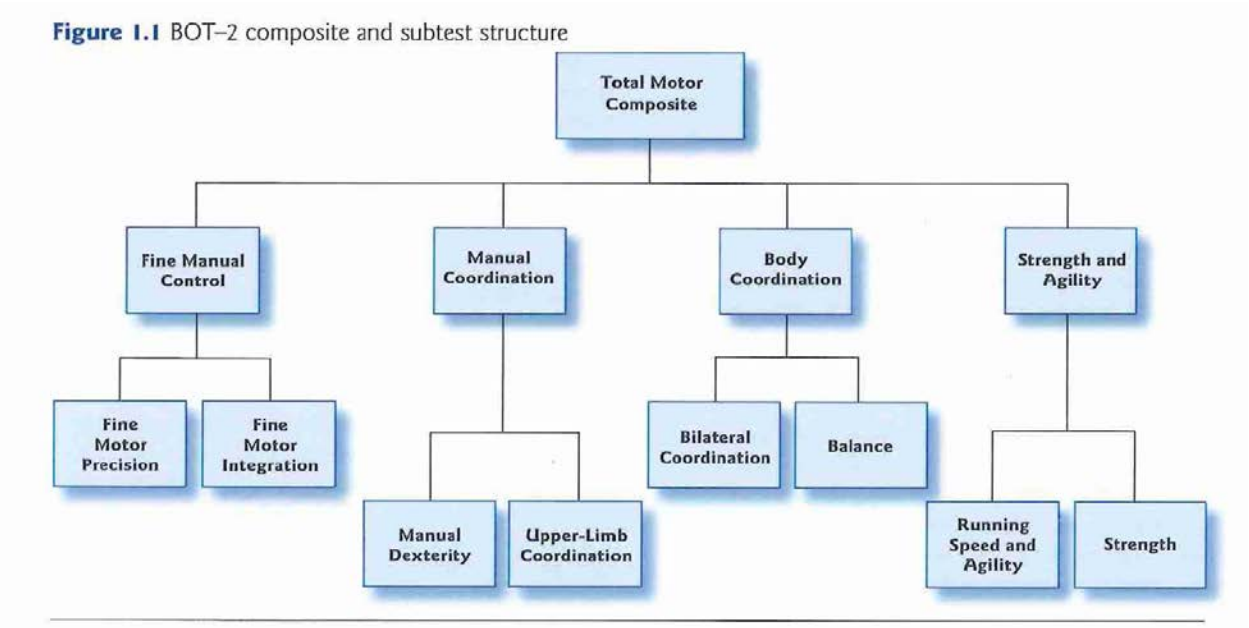
1.4 Labeling or promotional claim(s) based on the COA

The proposed indication is treatment of Mucopolysaccharidosis VII (MPS VII, Sly syndrome).

(b) (4)

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

Figure 3: Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) Framework



Reviewer comments: The applicant administered the following domains in Study CL-301: (1) running speed and agility (2) balance (3) manual dexterity (4) fine motor precision. Table 3, describes what performance items were included in the domain the applicant utilized in Study CL-301.

Table 3: Individual Performance Items for Domains of BOT-2 Utilized in Study CL-301

Filling in Shapes-Circle	Fine Motor Precision	Fine Manual Control (**Fine Motor Precision** and Fine Motor Integration)	Total Motor Composite
Filling Shapes- Star			
Drawing Lines through Paths-Crooked			
Drawing through Paths-Curved			
Connecting Dots			
Folding Paper			
Cutting Out a Circle			
Making Dots in Circles	Manual Dexterity	Manual Coordination (**Manual Dexterity** and Upper-Limb Coordination)	
Transferring Pennies			
Placing Pegs into a Peg Board			
Sorting Cards			
Stringing Blocks			
Standing with Feet Apart on a Line-Eyes Open	Balance	Body Coordination (**Balance** and Bilateral Coordination)	
Walking Forward on a Line			
Standing on One Leg on a Line-Eyes Open			
Standing with Feet Apart on a Line-Eyes Closed			
Walking Forward Heel-to-Toe on a Line			
Standing on One Leg on a Line-Eyes Closed			
Standing Heel-to-Toe on a Balance Beam			
Standing on One Leg on a Balance Beam-Eyes Open			
Standing on One Leg on a Balance Beam-Eyes Closed			
Shuttle Run	Running Speed and Agility	Strength and Agility (**Running Speed/Agility** and Strength)	
Stepping Sideways over a Balance Beam			
One-Legged Stationary Hop			
One-Legged Side Hop			
Two-Legged Side Hop			

Reviewer's Comment: Individual Performance Items for Domains of BOT-2 appear to be well-standardized. However, the BOT-2 was not fit for purpose for the patient population in Study CL-301.

Table 4: Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL) Framework

Items	Domain	General Concept
1. I feel tired	General Fatigue Scale	Total Fatigue
2. I feel physically weak (not strong)		
3. I feel too tired to do the think I like to do		
4. I feel too tired to spent time with friends		
5. I have trouble finishing things		
6. I have trouble starting things		
7. I sleep a lot	Sleep/Rest Fatigue Scale	
8. It is hard for me to sleep through the night		
9. I feel tired when I wake up in the morning		
10. I rest a lot		
11. I take a lot of naps		
12. I spend a lot of time in bed		
13. It is hard for me to keep my attention on things	Cognitive Fatigue Scale	
14. It is hard for me to remember what people tell me		
15. It is hard for me to remember what I just heard		
16. It is hard for me to think quickly		
17. I have trouble remembering what I was just thinking		
18. I have trouble remembering more than one thing at a time		

Reviewer's Comment: The conceptual framework for the parent-report and self-report PedsQL Fatigue is the same.

3 CLINICAL OUTCOME ASSESSMENTS

The BOT-2 is a standardized, norm-referenced test of motor proficiency administered in Study UX003-CL301 to evaluate treatment-related changes in fine and gross motor function. Fine motor function can be impacted by contractures in the shoulder, elbow, wrist and fingers caused by accumulation of GAG in connective tissue. The BOT-2 includes fine motor tests (e.g., drawing lines, folding paper, transferring pennies, cutting with scissors) that simulate activities of daily living requiring the use of arms and hands such as writing, fastening buttons, brushing teeth, eating with utensils, etc. (Bruininks et al. 2005). Gross motor activities that require strength, agility, balance and coordination can be impacted by skeletal abnormalities seen in MPS VII, such as hip dysplasia, contractures of the hip, knee and ankle, and genu valgum. The BOT-2 gross motor tests (e.g., walking forward, walking heel-to-toe on a line, standing on one leg on a line, shuttle run) simulate activities of daily living requiring balance and coordination such as dressing, bathing, transfers, etc. (Bruininks et al. 2005).

The BOT-2 was developed and validated to assess fine and gross motor skills of individuals from 4 to 21 years of age, and it was standardized and normed using a nationally representative US sample across these age groups. Reliability of the BOT-2 was assessed by three tests including inter-rater reliability, test-retest reliability, and internal consistency reliability. Evidence supporting the validity of the BOT-2 was established through assessments of content validity, internal structure of the measure (e.g., item fit and confirmatory factory analysis), clinical group differences and construct validity. The results of all psychometric tests were considered acceptable, and supported the reliability and validity of the measure. Details of the development, standardization, and validation procedures are included in the BOT-2 Manual (Bruininks et al. 2005).

PedsQL-Multidimensional Fatigue Scale: Subject or caregiver-reported fatigue was assessed by the Pediatric Quality of Life Inventory™ (PedsQL)-Multidimensional Fatigue Scale. Fatigue has been documented as a primary clinical manifestation of MPS syndromes including MPS IVA (Hendriksz et al. 2016), and was confirmed as an impactful clinical problem in 1:1 interviews with MPS VII patients/caregivers (UX003-CL002 Summary Report). Fatigue could be a consequence of many of the clinical issues associated with MPS VII including cardiac disease, hepatosplenomegaly, decreased respiratory function, etc. The PedsQL was designed as a symptom-specific instrument to measure fatigue in patients with acute and chronic health conditions, and healthy school and community populations (Varni et al. 2002).

The PedsQL-Multidimensional Fatigue Scale is a specific module of the PedsQL™ designed to measure fatigue in patients aged 2 and above (Varni et al. 1999) (Varni et al. 2001). The 18-item scale is comprised of three dimensions: general fatigue (6 items), sleep/rest fatigue (6 items) and cognitive fatigue (6 items). Each item has a 5-point Likert response scale from 0 (Never) to 4 (Almost always) that is reverse scored and transformed to a 0 to 100 scale with higher scores indicating less fatigue.

Self-report and parent-proxy versions were developed for use in the following age categories relevant to this study: Young Child (5-7 years of age), Child (8-12 years of age), Adolescent (13-18 years of age), Young Adult (18-25 years of age). The subject or caregiver completed the age-appropriate version of the PedsQL on paper, based on the subject's age at baseline. Caregivers were encouraged to complete the PedsQL parent-proxy versions considering the cognitive impairment seen in this patient population, and the same caregiver was expected to complete the PedsQL throughout the study. The version of the PedsQL completed at baseline was to be administered for the duration of the study.

4 CONTENT VALIDITY

The applicant did not provide a COA dossier on any of the COAs used in Study CL-301 including the PedsQL and BOT-2 in patients with MPS VII including a complete content validity for review. It is unclear on how or why the COAs used in Study CL-301 were selected. The selection of the 6MWT is most likely due to prior approvals in other MPS subtypes where 6MWT was an endpoint. Limited qualitative work was conducted through a telephone parent interview with research staff. In these interviews, the patient's parent provided their child's medical history and identified what they perceived as the most impactful symptom of MPS VII for their child. Most parents described that motor function was most impactful. Only a few parents listed fatigue. No patients were interviewed with their parents to confirm this information. These telephone interviews were to determine the individual clinical response (ICR) for each patient. Through an information request, the clinical team was able to review each patients developmental history and in their opinion most participants had moderate to severe cognitive impairment.

Reviewer's Comment: Limited qualitative information was submitted for review, it was identified that motor function is an important aspect of MPS VII lives. However, because no baseline cognition level was assessed and based on individual patient study reports, a majority of Study CL-301 patients had moderate to severe cognitive impairment, which limited their ability to follow instructions and completed many of the outcome assessments including the 6MWT and the BOT-2 (See Figure 2). Additionally, two patients were non-ambulatory and could not perform these tasks. Another patient refused to complete the 6MWT or the BOT-2. A better understanding of the natural history of a rare disease patient population and possible pilot testing of the performance measures in a patient or two would assist in better selection of appropriate performance measures for future studies. Pilot testing would allow for sponsors to see what the 6MWT is appropriate or if a shorter time is a better fit for the patient population, also it would also allow sponsors to see if the lengthy motor proficiency is able to be completed with interpretable data.

The BOT-2 as a standardized assessment of motor proficiency is appropriate for use to measure motor performance. The BOT-2 is a lengthy assessment with patients completing most of the tasks multiple times. It is the opinion of this reviewer that the BOT-2 is not fit for purpose due to the patient population limitations.

This reviewer has the following concerns regarding the PedsQL fitness for purpose:

- *Among patients administered the PRO, is unclear from the application whether patients were able to reliably self-report.*
- *The parent version used proxy reporting. The 2009 "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" discourages the use of proxy reporting. When looking to use an observer-*

reported outcome, we encourage sponsors to determine what observable symptoms or behaviors a parent/caregiver can observe and is relevant to the disease and treatment under study.

- *We also note that there are duplicate items between the three fatigue domains. Duplication of items can add to responder burden in completing the instrument.*

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

No information was provided on the measurement properties of PedsQL or BOT-2 based on the MPS VII population.
The measurement properties of the PedsQL can be found in the literature. The measurement properties for the BOT-2 can be found in the user manual.

Varni, JW, Beaujean, AA, and Limbers, CA. 2013. "Factorial invariance of pediatric patient self-reported fatigue across age and gender: a multigroup confirmatory factor analysis approach utilizing the PedsQL Multidimensional Fatigue Scale." *Qual Life Res* 22 (9):2581-94.

Varni, JW, Burwinkle, TM, Katz, ER, Meeske, K, and Dickinson, P. 2002. "The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module." *Cancer* 94 (7):2090-106.

Varni, JW, Burwinkle, TM, and Szer, IS. 2004. "The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: reliability and validity." *J Rheumatol* 31 (12):2494-500.

Varni, JW, and Limbers, CA. 2008. "The PedsQL Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a University student population." *Qual Life Res* 17 (1):105-14.

Varni, JW, Limbers, CA, Bryant, WP, and Wilson, DP. 2009. "The PedsQL Multidimensional Fatigue Scale in type 1 diabetes: feasibility, reliability, and validity." *Pediatr Diabetes* 10 (5):321-8.

Varni, JW, Limbers, CA, Bryant, WP, and Wilson, DP. 2010. "The PedsQL multidimensional fatigue scale in pediatric obesity: feasibility, reliability and validity." *Int J Pediatr Obes* 5 (1):34-42.

Varni, JW, Limbers, CA, Bryant, WP, and Wilson, DP. 2012. "Assessment of Fatigue in Pediatric Patients With Short Stature Utilizing the PedsQL Multidimensional Fatigue Scale." *Children's Health Care* 41:162-181.

Varni, JW, Seid, M, and Kurtin, PS. 2001. "PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations." *Med.Care* 39 (8):800-812.

Reviewer's Comment: Some patients of Study CL-301 have multiple evaluators of the BOT-2. When asked if inter-rater reliability was established for those patients who had multiple evaluators, the applicant stated that they did not establish inter-rater reliability in MPS VII on the BOT-2 and stated that all evaluators received training at the beginning of the study and that the BOT-2 has established reliability. It is the opinion of this reviewer, for future studies, sponsors should examine the both the inter and intra reliability of the BOT-2 in the specific patient population the BOT-2 is being used in.

6 INTERPRETATION OF SCORES

Table 5: Applicant's Proposed Minimal Important Difference Values for Study CL-301

Table 8.8.5.3.1.1: Definition of the Minimal Important Difference for domains included in the UX003-CL301 multi-domain responder analysis

Domain	Minimal Important Difference (MID)	References
6MWT	23 meter AND 10% change from baseline	(Redelmeier et al. 1997), (Puhan et al. 2008), (du Bois et al. 2011), (Mathai et al. 2012), (Wraith et al. 2004), (Clarke et al. 2009), (Muenzer et al. 2006), (Harmatz et al. 2006), (BioMarin 2013)
$FVC_{\%pred}$	5% absolute change or 10% relative change from baseline in $FVC_{\%pred}$	(Wraith et al. 2004), (Muenzer et al. 2006), (BioMarin 2013)
Shoulder flexion	20 degree change of passive shoulder range of motion	(Wraith et al. 2004), (Harmatz et al. 2006), (Clarke et al. 2009), (Okuyama et al. 2010)
Visual acuity	3 lines (corrected, both eyes)	(Arch-Ophthalmol 1999); (Ferris et al. 1982), (Reeves et al. 1993)
BOT-2 fine motor	Fine Motor Precision: change of 0.72 Manual Dexterity: change of 1.47	(Wuang et al. 2009)
BOT-2 gross motor	Balance: 0.57 Running speed and agility:0.59	(Wuang et al. 2009)

The MIDs for each component of the MDRI are discussed in more detail below:

- For 6MWT distance, the score +1 was assigned when there was $\geq$ 23 meters AND $\geq$ 10% change from baseline observed, while the score -1 was assigned when there was -23 meters and less AND decrease of 10% or more from baseline observed. Otherwise the score for this domain was 0.

- For $FVC_{\%pred}$, the score +1 was assigned when there was a 5% absolute increase or 10% relative increase from baseline, while the score -1 was assigned when there was a 5% absolute decrease or 10% relative decrease from baseline. Otherwise the score for this domain was 0.

- For visual acuity, the score +1 was assigned when both eyes, corrected, had 3 lines or more improvement in visual acuity scales, while the score -1 was assigned when both eyes, corrected, declined 3 lines or more in visual acuity scales. Otherwise the score for this domain was 0. If only uncorrected visual acuity (no corrected visual acuity) was obtained at baseline, changes from baseline were assessed based on the uncorrected visual acuity. If the change from baseline for one eye was missing, the score for visual acuity domain was based on the other eye. If the changes from baseline for both eyes were missing, the score for the visual acuity domain was missing. One line of improvement was defined as -0.10 of change in LogMAR scale.

- For shoulder flexion where there were two tests to evaluate changes from baseline: the score +1 was assigned when at least one side's (left or right) range of motion improve at least one MID or more where the other side did not decline for more than one MID. The score -1 was assigned when both shoulder range of motion decline by more than one MID. Otherwise, the score was set as 0. If the change from baseline for one shoulder was missing, the score for the shoulder flexion domain was based on the other shoulder. If the changes from baseline for both shoulders were missing, the score for the shoulder flexion domain was considered missing.

- For BOT-2 fine motor and gross motor domains where there were two tests to evaluate MID: the score +1 was assigned when at least one test improved at least one MID or more where the other test did not decline for more than one MID. The score -1 was assigned when both tests declined for more than one MID. Otherwise the score was set as 0. If the change from baseline for one test was missing, the score for the domain was based on the other test. If the changes from baseline for both tests were missing, the score for the domain was considered missing. The scale score from BOT-2 was used to evaluate MID.

> The integration of benefit occurred by summing the responses, positive, negative, or zero across all domain variables to derive the subject-specific MDRI.
>
> If a subject was unable to reliably or safely perform a particular assessment at a visit, that domain was scored as 0 for that visit.

Scoring of the BOT -2 was described in the user manual for each domain and was followed during Study CL-301. For the BOT-2, the applicant used the Wuang et al. 2009 article which conducted further psychometric analysis of the BOT-2, and Minimal Important Difference (MID) values. These values were calculated for the subtest scores: Fine Motor Precision (0.72), Manual Dexterity (1.47), Balance (0.57) and Running speed and agility (0.59).

Scoring for the PedsQL has the 5-point Likert response scale from 0 (Never) to 4 (Almost always) reverse scored and linearly transformed to a 0 to 100 scale with higher scores indicating less fatigue. For the PedsQL, the applicant selected a MID for the PedsQL as a 10 point change from baseline in the Total Fatigue Score. This MID is based on an interventional study conducted by Keats et al. 2008.

Reviewer's comment: The BOT-2 MID as pre-specified by the applicant and described in the Wuang (2009) is the group level MID (i.e., it is the difference of the average BOT-2 change scores between the "improved" and "no-change" groups). It was not the within-patient level MID (i.e., the average change score of the patients who have "improved"). Data was not presented in the article to determine what the average within-patient level score change is. Since with-in patient change was not pre-specified the use of the MID provided by the applicant should not be used to interpret meaningful within-in patient change. The PedsQL MID as pre-specified by the applicant does not reflect the article the applicant references. The Keats et al. (2008) article describes a physical activity intervention in pediatric cancer survivors. The article describes a 10-point mean change from baseline to end of intervention not an individual 10-point change.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The Spanish version of the PedsQL was used in Study CL-301. Information on the translation and cultural adaptation of the PedsQL was not provided by the applicant.

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not Applicable

9 REVIEW USER MANUAL

The only user manual submitted for review was for the BOT-2. The user manual for the BOT-2 is appropriate for use to measure fine motor skills, balance, running speed/agility. It also contains the development history and the measurement properties of the BOT-2.

E. APPENDICES (INCLUDE COPY OF INSTRUMENT(S))

Attached is the PedsQL-Fatigue

Basic information on the BOT-2 can be found here:
https://www.pearsonclinical.com/therapy/products/100000648/bruininks-oseretsky-test-of-motor-proficiency-second-edition-bot-2.html

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELLE L CAMPBELL
10/18/2017

ELEKTRA J PAPADOPOULOS
10/22/2017