

28 June 2018 EMA/480950/2018 Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mepsevii

International non-proprietary name: vestronidase alfa

Procedure No. EMEA/H/C/004438/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

3MSCT	3-minute stair climb test
6MWT	6-minute walk test
ADA	Anti-drug-antibody
ADR	Adverse drug reactions
AE	Adverse event
BE	Bioequivalence
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency
CGI	Clinical Global Impression
CIM6PR	Cation-independent mannose 6-phosphate receptor
CL	Clearance
Cmax	Maximum concentration
CMC	Chemistry, Manufacturing, and Controls
CS	Chondroitin sulfate
DART	Developmental and reproductive toxicology
DMP	Drug Monitoring Program
DS	Dermatan sulfate
eIND	Emergency Investigational New Drug [application]
EMA	European Medicines Agency
ER	Exposure response
ERT	Enzyme replacement therapy
EU	European Union
FDA	Food and Drug Administration
FVC	Forced vital capacity
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GUS	Beta-glucuronidase
HS	Heparan sulfate
HSCT	Haematopoietic stem cell transplantation
IAR	Infusion associated reaction

ICH	International Conference on Harmonisation
ICR	Individualized clinical response
IND	Investigational New Drug [application]
IV	Intravenous(ly)
KS	Keratan sulfate
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LFT	Liver function test
LS	Least squares
M6P	Mannose-6-phosphate
M6PR	Mannose-6-phosphate receptor
MAA	Marketing Authorisation Application
MDRI	Multi-domain responder index
MHLW	[Japanese] Ministry of Health, Labor and Welfare
MID	Minimally important difference
MPS	Mucopolysaccharidoses
MPS VII	Mucopolysaccharidosis VII, Sly syndrome
MPS HAQ	Mucopolysaccharidoses Health Assessment Questionnaire
MR	Mannose receptor
ODD	Orphan Drug Designation
PD	Pharmacodynamics(s)
PedsQL	Pediatric Quality of Life Multidimensional Fatigue Scale
PGI-C	Physician Global Impression-Change
PIND	Pre-Investigational New Drug [application]
PIP	Paediatric Investigational Plan
РК	Pharmacokinetic(s)
QOW	Every other week
rh-GUS	Recombinant human GUS
rm-GUS	Recombinant mouse GUS
SAE	Serious adverse event
SOC	System Organ Class
t1/2	Half-life
TEAE	Treatment-emergent adverse event
uGAG	Urinary glycosaminoglycan
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ultragenyx Germany GmbH submitted on 30 March 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Mepsevii, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 April 2016.

Mepsevii was designated as an orphan medicinal product EU/3/12/973 on 21 March 2012 in the following condition: Treatment of mucopolysaccharidosis type VII (Sly syndrome).

The applicant applied for the following indication "Mepsevii is indicated for the treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages".

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Mepsevii as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: <u>ema.europa.eu/Find medicine/Human medicines/European public assessment reports</u>.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, nonclinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0202/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0202/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances and in accordance with Article 14(8) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance vestronidase alfa contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received Protocol assistance from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2342/1/2012/SME/III	21 June 2012	The protocol assistance pertained to non-clinical and clinical aspects of the dossier.
EMEA/H/SA/2342/2/2016/SME/I	1 April 2016	The protocol assistance pertained to quality aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	30 March 2017
The procedure started on	18 May 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 August 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	4 August 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 August 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 December 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	30 January 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 February 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 February 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2018
The Rapporteurs circulated the Joint Assessment Report on the	12 April 2018

responses to the List of Outstanding Issues to all CHMP members on	
The CHMP agreed on a 2 nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 April 2018
The applicant submitted the responses to the 2 nd CHMP List of Outstanding Issues on	25 May 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 June 2018
Ad-Hoc Expert group were convened to address questions raised by the CHMP on	19 June 2018
The CHMP considered the views of the Expert group as presented in the minutes of this meeting.	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	22 June 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Mepsevii on	28 June 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Mucopolysaccharidosis (MPS) VII is a progressively debilitating and life-threatening disease that is caused by a deficiency of the lysosomal enzyme beta-glucuronidase.

2.1.2. Epidemiology

MPS VII (also known as Sly syndrome) is an ultra-rare disease with an estimated prevalence < 1/1,000,000 (Orphanet 2016), and for which the applicant estimates that there are less than 100 living patients worldwide.

2.1.3. Aetiology and pathogenesis

Mucopolysaccharidoses are a group of inherited lysosomal storage disorders caused by a deficiency of one of the enzymes involved in the stepwise degradation of complex carbohydrates known as glycosaminoglycans (GAGs) that include dermatan sulfate (DS), chondroitin sulfate (CS), heparan sulfate (HS) and keratan sulfate (KS).

In MPS VII, the disease is caused by a deficiency in beta-glucuronidase (GUS), resulting in accumulation of GAGs in the lysosomes and subsequent tissue damage, dysfunction and failure of organs and systems throughout the body and ultimately death.

2.1.4. Clinical presentation, diagnosis

Clinical presentation may occur at birth with hydrops foetalis, or not until adolescence or adulthood with skeletal disease and other manifestations. MPS VII symptoms can include a variety of common

MPS disease manifestations such as abnormal coarsened facies, pulmonary disease, cardiovascular complications, hepatosplenomegaly, joint stiffness, short stature, cognitive impairment, and the MPS skeletal disease known as dysostosis multiplex.

The presence, severity and progression of these symptoms in MPS VII patients are highly variable. Most MPS VII patients die before the second or third decade of life due to complicating medical problems although death may also occur in the first year of life due to hydrops foetalis (Montano et al. 2016).

The diagnosis of MPS VII may be confirmed by a thorough clinical evaluation that includes a detailed patient history and specialized tests that measure the level of GUS activity in blood or skin cells. Molecular genetic testing for mutations in the GUSB gene is available to confirm the diagnosis. Prenatal diagnosis is possible through amniocentesis or chorionic villus sampling to measure GUS activity or molecular genetic testing for GUSB gene mutations.

2.1.5. Management

Limited results from 7 patients (Islam et al., 1996; Yamada et al., 1998; Montaño et al., 2016) suggest that HSCT can delay or even prevent further neurological complications, but has little to no effect on the skeletal disease unless it is performed in an early stage.

Currently there is no specific treatment available for MPS VII. Treatment is limited to symptomatic relief and supportive care. Bone deformities and hernias may require surgical correction. Ocular and cardiovascular abnormalities may also be treated surgically. Genetic counselling is recommended for people with MPS VII and their families.

About the product

Vestronidase alfa is a recombinant form of human GUS and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular internalization of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.

The initially claimed indication for Mepsevii was for the treatment of Mucopolysaccharidosis VII (MPS VII; Sly syndrome) for patients of all ages.

During the evaluation, the applicant amended the proposed indication to patients of all ages with Mucopolysaccharidosis VII (MPSVII; Sly syndrome) for the treatment of non-neurological manifestations of the disease.

The recommended dose of Mepsevii is 4 mg/kg of body weight administered by intravenous infusion every two weeks. To minimize the risk of hypersensitivity reactions, a non-sedating antihistamine with or without an antipyretic medicinal product should be administered 30-60 minutes prior to the start of the infusion.

Type of Application and aspects on development

The applicant received Scientific Advice from the CHMP on 21 June 2012 in relation to non-clinical and clinical aspects including the size of the required clinical trial and the selection of appropriate endpoints to evaluate the product in these conditions. The applicant followed the advice received from the CHMP.

The application was submitted as a full application according to Article 8(3) of Directive 2001/83/EC. The applicant requested an exceptional circumstances status.

Exceptional circumstances

The Applicant considered that the grounds for marketing authorisation under exceptional circumstances apply to Mespsevii according to Article 14(8) of Regulation (EC) No 726 /2004 and to Part II.6 of Annex I to Directive 2001/83/EC and provided justification based on the inability to provide comprehensive efficacy and safety data due to rarity of indication.

Mucopolysaccharidosis (MPS) VII is an orphan condition, with an estimated prevalence of approximately < 1/1,000,000, and Mepsevii (also referred to as UX003 in this report, recombinant human beta-glucuronidase) received orphan medicinal product designation in 2012 for the treatment of MPS VII (EU/3/12/973).

At present, there are no orphan medicinal products marketed in the EU for the treatment of MPS VII.

The applicant noted that the presence, severity and progression of symptoms in MPS VII patients are highly variable, which in addition to its extreme rarity, made the clinical development program of Mepsevii uniquely challenging.

Given the very small heterogeneous patient population, a single Phase 3 study, was designed as a randomized, placebo-controlled, double-blind, Blind-Start, single crossover study of UX003 that incorporated several innovative elements to make efficient and safe use of a small number of subjects and leverage the extensive existing data and lessons learned from previously approved ERTs. The novel study design addressed the development challenges associated with extremely rare and life-threatening diseases by allowing all subjects to be assessed for efficacy on active treatment, while still retaining some evaluation objectivity through the use of a placebo control run-in period.

Due to the rarity of MPS VII, eligibility criteria could not be applied to assure that subjects were able to perform all the clinical assessments or meet certain levels of disease severity, and therefore essentially all comers had to be enrolled in the study, unlike prior MPS Phase 3 studies with selected populations. Consequently, the study population had highly variable disease manifestations and various physical and/or cognitive limitations.

2.2. Quality aspects

2.2.1. Introduction

The finished product, also referred to as drug product (DP) by the applicant, is presented as a concentrate for solution for infusion containing 2 mg/ml of vestronidase alfa as active substance. Other ingredients are: sodium phosphate, sodium chloride, histidine, polysorbate 20 and water for injections. The product is available in a colourless glass vial (Ph. Eur. Type I) with a rubber stopper with fluoro-resin coating and an aluminium over seal with a plastic flip-off cap. Each vial contains an extractable volume of 5.0 ml.

2.2.2. Active Substance

General Information

Vestronidase alfa is a recombinant human beta-glucuronidase (rhGUS) glycoprotein enzyme produced in a genetically engineered stable Chinese Hamster Ovary (CHO) cell line. The protein is expressed as a 651 amino acid precursor with an N-terminal signal sequence of 22 amino acids, which is cleaved intracellularly.

The translated protein is post-translationally modified by glycosylation. The glycans of rhGUS contain mannose 6-phosphate (M6P), which is required for target cell uptake and internalization into the lysosome by the cation independent mannose-6-phosphate receptor (CI-MPR), also known as M6P/IGF2 receptor.

The secreted mature enzyme intracellularly forms a homotetramer after glycosylation. Each rhGUS monomer consists of 629 amino acids; the calculated isotope average molecular mass of each non-glycosylated peptide chain is 72,562 Dalton.

Manufacture, characterisation and process controls

Rentschler Biopharma SE, Laupheim Germany (Rentschler) is the site responsible manufactureand batch release of the active substance.

Description of the manufacturing process and process controls

The manufacturing process of the active substance, vestronidase alfa, has been adequately described. The main steps are upstream processing, comprising cell culture in fed batch mode, followed by harvest using depth filtration, and downstream processing comprising recovery, purification by four chromatography steps, a low pH virus inactivation step, cation exchange chromatography, viral filtration and a final ultra-diafiltration and formulation of bulk active substance. A batch numbering system has been defined for all manufacturing steps.

In response to a Major Objection (MO1) requesting the control strategy to be sufficiently substantiated by process evaluation data especially for the downstream process, the description of the manufacturing process, critical steps, and associated process development was extensively updated during the procedure with newly introduced controls. The control strategy is considered appropriate; parameters, critical process parameters (CPPs) and critical in-process controls (IPCs), and associated ranges (normal operating ranges and/or proven acceptance ranges) are sufficiently supported. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity, adventitious agents and endotoxin, are described for each step. Actions taken if limits are exceeded are specified. The active substance manufacturing process is considered acceptable.

Vestronidase alfa is stored in sterilised bags equipped with filling and outlet ports. Tests carried out demonstrate that the bag meets Ph. Eur. 3.1.7 requirements.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. The history and details of cell line establishment are provided, including the construction of the expression plasmid, clonal selection and isolation of the production clone. A two tiered cell banking system is used. Cell banks preparation are appropriately described and consist of a Master Cell Bank (MCB), a Working Cell Bank (WCB) and end of production cells (EPC). Sufficient information is provided regarding testing of the MCB, WCB and release of future WCBs. Genetic stability has been demonstrated for cells at and beyond the limit of cell age. The limit for in vitro cell age has been calculated. A stability program for the MCB has been provided. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell banks.

Process validation

The manufacturing process of vestronidase alfa active substance has been validated adequately. Consistency in production has been shown on three full scale batches manufactured using the proposed commercial process. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled, demonstrating that the purification process consistently produces vestronidase alfa active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Several important changes have been introduced during the development of the manufacturing process. As the active substance used in the non-clinical studies was not derived from the proposed WCB, upon request, data for batches used in non-clinical studies have been provided and indicate that these batches represent a worst case of the commercial product, as they contain higher levels of impurities.

Characterisation

The vestronidase alfa active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods. The analytical results are consistent with the proposed structure. Process-related and product-related impurities have been characterised. The impurities are controlled in routine, either at release or during production. The specified impurities have been present in product used in clinical studies. In addition, forced degradation studies were performed. Upon request, to resolve MO2, raised to highlight the incompleteness of the characterisation exercise and the scarcity of the critical quality attributes identified, the characterisation of vestronidase alfa was extended with additional data on homotetramer structure and charge variants and additional explanations on peptide mapping, N-linked glycosylation and cellular uptake; additionally some product-related impurities were re-classified from non-critical to critical quality attributes in the course of the procedure. As a consequence, sections 3.2.S.4 (Control of Drug substance), 3.2.S.5 (Reference Standard) and 3.2.S.7 (Stability) have been updated accordingly. The enzymatic activity and cellular uptake of vestronidase alfa is measured using an artificial substrate 4-methylumbelliferyl-glucuronide (4-MUG), which is cleaved into fluorescent 4methylumbelliferone (4-MU) and glucuronic acid by vestronidase alfa enzyme. The amount of cleaved 4-MU, and thus the corresponding activity of vestronidase alfa, is subsequently quantified using fluorometric determination.

Specification

Vestronidase alfa specification contains the tests for appearance and description, identity, content, activity/potency, purity and impurities, endotoxins, bioburden, polysorbate 20 content, pH and osmolality. Most of the methods used in characterization studies to determine the purity/impurity profile of the finished product Mepsevii as well as activity and content are included in the specification of the active substance.

Potency is measured by two methods. As described under Characterisation, the enzymatic activity is measured by quantifying cleaved 4-MU. The bioassay uptake method measures the enzymatic activity of rhGUS after internalisation.

The Applicant is recommended to develop a new method.to control charge heterogeneity. Although the specification of the active substance is considered sufficient at for the authorisation of the product, it is expected that based on manufacturing experience, the acceptance criteria for several parameters should be revised.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. However, several recommendations have been given related to the analytical methods.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference standards

A one-tier reference standard has been established for the control of the commercial vestronidase alfa active substance and finished product. The current reference standard was qualified by release tests and characterisation tests. During the course of the procedure, the qualification protocol for future reference standards was withdrawn as it was considered as not sufficient to ensure a batch-to-batch consistency. The applicant has proposed to submit a revised protocol, including both release and additional characterization testing, in a post-approval variation. This has been accepted. The stability program for the current and future reference standards, to confirm the shelf-life, has been updated by tightening the acceptance criteria of several parameters and by including additional parameters.

Stability

A shelf life at a long-term storage condition, protected from light, is proposed for the the active substance.

The stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life when stored refrigerated in the proposed container.

Real time, real condition stability data on three batches of active substance from a manufacturing process representative of the commercial process under long term storage conditions and under accelerated conditions according to the ICH guidelines were provided. The container used for the stability studies is representative of the active substance storage container closure systemwith regards to the material of construction.

During the review, the acceptance limits have been adjusted to justified levels. The applicant is recommended to inform the EMA immediately if trends or out of specification results are obtained for bioassay uptake during the stability program for commercial batches. The forced degradation study showed the active substance is degraded under light exposure. Therefore a photostability study was requested on the finished product in vials and in-use conditions. In conclusion, the stability results indicate that the active substance is sufficiently stable and justify the proposed shelf life.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Vestronidase alfa finished product (Mepsevii) is a concentrate for solution for infusion containing 2 mg/ml of vestronidase alfa active substance. The excipients used in the finished product formulation are: sodium phosphate, sodium chloride, histidine (all chemical stabilisers) and polysorbate 20 (physical stabiliser) in water for injection. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The development of the finished product

is reflected by the description of the development of the formulated bulk active substance (see active substance). During development, the excipients have been demonstrated compatible with vestronidase alfa and suitable for their intended functions.

Each vial is filled to a target volume of 5.4 ml, which allows the withdrawal of 5.0 ml of deliverable volume containing 10 mg of vestronidase alfa. There are no overages in the formulation of the finished product. Prior to administration, the finished product is diluted with preservative free sterile saline solution for injection (0.9%). The diluent is not supplied with the finished product.

The content of 10 mg per vial is not suitable for the dosing regimen of 4 mg/Kg every other week, especially for children and adults. As an example, a 20 Kg patient would receive a total of 8 vials per administration, and a 70 Kg patient 28 vials. However, taking into consideration that the product will be administered at clinical infusion sites familiar with MPS ERT therapies, and that MPS VII is an ultra-rare disease, the development of another presentation with a larger volume of concentrate per vial is not currently requested.

Manufacture of the product and process controls

Rentschler Biopharma SE (Rentschler), Laupheim, Germany is responsible for manufacture of the finished product. Manufacture of the finished product comprises six process steps: equilibration of stored active substance to room temperature; formulation; sterile filtration, filling and stoppering, capping and visual inspection.

Description of the manufacturing process including where materials enter the process, the operational parameters and critical parameters of the process inputs and the performance parameters of the process outputs for each step, are provided. The process performance qualification was performed by process validation upon three finished product batches covering the proposed batch size range manufactured using the commercial process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Container closure system

The primary packaging is colourless glass vial (Ph. Eur. Type I) with a rubber stopper with a fluororesin coating, and an aluminium over seal with a plastic flip-off cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The suitability of the containerclosure components has been demonstrated. However, the leachable study will be available in the future. One of the extractables is above the PDE in infants and should therefore be controlled in each batch if the PDE is exceeded in the leachable study.

Product specification

The finished product specification includes tests for appearance and description, identity, content activity/potency, purity and impurities, safety, excipients and general tests.

As required by ICH Q3D a risk assessment was used to evaluate the finished product manufacturing process, beginning with final ultrafiltration/diafiltration (UF/DF) and all stages of the finished product, where relevant equipment, consumables, packaging materials, raw materials and utilities were considered. The finished product manufacturing process has no impact on the product related impurity profiles.

Justification of specification

Upon request, a number of acceptance criteria were tightened or justification for the proposed criterion was improved.

Analytical methods

The methods used for testing active substance are also applicable to the finished product. Analytical procedures that are specific to testing the finished product attributes are the compendial methods for testing visible and sub-visible particles, extractable volume, sterility and container closure integrity. The analytical methods used have been adequately described and noncompendial methods appropriately validated in accordance with ICH guidelines.

Batch analyses

Batch analysis data from a umber of finished product batches, manufactured from a number of active substance batches, including a number of batches manufactured using the proposed commercial process and scale, were presented. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used to test the finished product is the same as that used for testing vestronidase alfa active substance.

Stability of the product

Based on available stability data, the shelf-life of 30 months in the refrigerator $(2^{\circ}C - 8^{\circ}C)$, stored in the original package in order to protect from light, as stated in the SmPC are acceptable. Real time/real condition stability data of four primary stability batches using active substance manufactured at the commercial scale of finished product and under accelerated conditions according to the ICH guidelines were provided. The batches of vestronidase alfa finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

No significant changes have been observed during long term storage conditions for the quality attributes. Accelerated stability data show insignificant or no change for most quality attributes. A photostability study was conducted as part of the forced degradation study. The summary of product characteristics (SmPC) was updated to include the statement "Store in the original package in order to protect from light" in Section 6.4 special precautions for storage.

After dilution: Chemical and physical in-use stability has been demonstrated for up to 36 hours under refrigeration at $2^{\circ}C - 8^{\circ}C$ followed by up to 6 hours at room temperature up to a maximum of $25^{\circ}C$.

From a microbiological safety point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user, but should normally not be longer than 36 hours at $2^{\circ}C - 8^{\circ}C$ followed by up to 6 hours at room temperature up to a maximum of $25^{\circ}C$.

In accordance with EU GMP guidelines (6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union), any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Comparability exercise for Finished Medicinal Drug Product

The applicant has sufficiently substantiated their conclusion that the material derived from the development and commercial process are comparable.

Adventitious agents

The only animal derived materials from TSE-relevant species used late in the development of the cell banks is provided with an EDQM certificate of suitability and is sourced from a geographical location with a negligible TSE/BSE risk. No other animal-derived materials are used in the manufacture of the active substance and finished product manufacturing processes. Additional media components, are manufactured without use of animal-derived materials. None of the excipients are of animal or human origin.

The packaging material component used throughout the process contain stearates and/or other additives derived from bovine tallow. These tallow derivatives have been processed at temperatures and pressures that are consistent with the requirements of EMA/410/01 rev 3 "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" and the European Pharmacopoeia. Tallow derivatives manufactured according to these conditions are unlikely to present any TSE risk and shall therefore be considered compliant with EMA/410/01 rev 3. A manufacturer's statement on BSE/TSE risk is provided and is deemed acceptable.

In general, the viral safety of vestronidase alfa is well addressed. The cells banks were assayed for adventitious and endogenous agents according to ICHQA5 guideline. No viral particles were observed other than retroviral-like particles normally seen in the MCB and EPC cell types.

An assessment was conducted for all raw materials used in the development of cell lines. Virus validation studies have been performed to meet the CPMP/BWP/268/95 guideline. Global reduction factors were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.

GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

During the review two MOs were raised; the first MO was related to the control strategy which needed to be sufficiently substantiated by the process evaluation, especially with regard to selection of parameters/CPPs/critical IPCs, and associated ranges (NORs and/or PARs). MO2 was related to the characterisation exercise and its incompleteness. Upon request, the applicant extensively improved the active substance dossier sections on characterisation, manufacturing process, and control strategy (including specifications/release testing), comparability during development, and the cell banking system. However, several recommendations on reviewing the active substance methods and limits, when additional experience is gained, have been agreed with the applicant. The information on development, manufacture and control of the active substance and finished product is now considered satisfactory. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Conclusions on the chemical, pharmaceutical and biological aspects

Module 3 of the CTD of Mepsevii is now of reasonable quality; however, eight recommendations have been identified and agreed with the applicant.

2.2.4.1. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

UX003 is a recombinant protein developed as an enzyme replacement therapy (ERT) for MPS VII. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular internalization of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated glycosaminoglycans (GAGs) in affected tissues.

2.3.2. Pharmacology

The applicant submitted one *in vitro* study, and one *in vivo* primary pharmacodynamic (PD) study to confirm the pharmacological effect of UX003 in the MPS VII mouse model. The nonclinical pharmacology of recombinant GUS, including recombinant mouse (rm-GUS) and multiple recombinant human versions of GUS (rh-GUS) was further supported by published *in vitro* and *in vivo* studies in murine models of MPS VII.

Three GLP safety pharmacology studies were conducted to assess potential effects on the central nervous system (CNS), and on cardiovascular (CV) and respiratory parameters.

Primary pharmacodynamic studies

In vitro studies

The kinetics of UX003 transport (internalization) into β -glucuronidase-deficient fibroblasts were investigated in the presence of M6P, which functioned as a competitive inhibitor of the extracellular receptor. Uptake increased rapidly with increasing UX003 enzyme concentration and achieved a saturated level of uptake consistent with receptor-mediated uptake. The overall concentration of enzyme giving half-maximal uptake (K_{uptake}) determined from different UX003 lots was approximately 0.8 – 1.8 nM.

Half-life of UX003 in MPS VII fibroblasts (study UGNX-013)

Human MPS VII fibroblasts were incubated with UX003 at 1, 2 or 4 μ g/ml for 19-22h. After a recovery period, to allow for the enzyme to be delivered to the lysosomes, cells were harvested at various time points between 2-42 days, and the half-life of GUS enzymatic activity was measured in fibroblast extracts (**Figure 1**).

Figure 1. Half-life of UX003 in human MPS VII fibroblasts



In vivo studies

A naturally occurring mouse model for MPS VII, has morphologic, genetic, and biochemical characteristics that closely mimic those of human MPS VII. Progressive lysosomal GAG storage in MPS VII mice affects all organs, including the brain, eye, skeleton, liver, spleen, heart, kidney, skin, and circulating granulocytes. In order to confer immune tolerance to human GUS and allow longer-term preclinical trials in MPS VII mice, a transgenic mouse model (MPS VII/E540A^{TG}) was developed by Sly et al (2001), retaining the clinical, morphological, biochemical and histopathological characteristics of the original MPS VII (gus^{mps}/gus^{mps}) mouse but being immunologically tolerant to human GUS (by expressing an inactive version of the rhGUS cDNA). This has allowed for studies with up to 13 weeks treatment with rhGUS, without the confounding occurrence of immune responses.

Studies conducted with rmGUS and different versions of rhGUS, including UX003 are summarized in **Table 1**, and a selection of these are further described below.

 Table 1. Overview of enzyme replacement studies with recombinant GUS in murine MPS VII models

Reference	Test Article (Mouse strain)	Age at Treatment	N	IV Dose* (mg/kg)	Frequency	Time to Sacrifice Post-Treatment	Effects
UX003-PC001	UX003 (MPSVII/ E540A ^{TG})	10-12 wks	6/group	0, 0.1, 0.25, 1, 4, 20	Once weekly for 8 weeks	72 hr (0-4 mg/kg groups) 1 week (20 mg/kg group)	Reductions of disease-specific biomarkers observed in serum and urine were complimented by proportionally decreased cytoplasmic vacuolization in various tissues evaluated histologically
		4-5 weeks	2 or 3/ group	0.3, 1, 2.5, or 5	Weekly x 3	1 week	Moderate decrease in meningeal storage
(Vogler et al. 2005)	rhGUSª (MPSVII/ E540A ^{TG})	8-12 weeks	4 or 5/ group	1, 2, or 4	Weekly x 13	1 week	Clearance in meninges and parietal, neocortical and hippocampal neurons + glia. Reduced GAG storage in liver and kidney; reduced GAG excretion in urine.
		15-16 weeks	2	20 or 40	3 doses in 1 week	3 days	No change in lysosomal storage in CNS except meninges
		15-16 weeks	2	20	Weekly x 4	1 week	Decreased neuronal, glial and meningeal storage.
(Sly et al. 2006)	rhGUS (MPSVII/ E540A ^{TG})	Not reported	3	(1)	Weekly x 3	1 wk	Both MR and CIM6PR uptake of GUS in a variety of tissues affected by MPS VII. The MR contributes to rapid clearance of enzyme from the circulation; lower total amount of residual enzyme in MR [*] / liver at 7 days.
(Sands et al. 1994)	rmGUS (gus ^{mps} /gus ^{mps})	Newborn	5	28,000 U (3.5-0.28)	Weekly x 6	1 week	Reduced or prevented GAG storage in most tissues, including neurons. Difficult to distinguish from normal mice at 6 weeks. Effects prolonged with extended lifespan.
	10 10 1	5 weeks	5	28,000 U (0.28)	1 x	1 week	Reduced GAG in fixed tissue macrophages. No clinical effects.

Reference	Test Article (Mouse strain)	Age at Treatment	Ν	IV Dose* (mg/kg)	Frequency	Time to Sacrifice Post-Treatment	Effects	
(Vogler et al. 1996) mGUS		Newborn	8	28,000 U (3.5-0.28)	Weekly x 6	Two mice at 14, 29, 85 150 days	Reductions in lysosomal storage at 14, 29 days in spleen, liver, bone marrow and brain. Effects gone by day 85 except in cortical and hippocampal neurons.	
	(gus ^{mps} /gus ^{mps})	/gus ^{mps})		28,000 U (3.5-0.28)	Weekly x 6	391 days	Milder MPS VII symptoms: more alert, more normal gait and coats. Body weights 93.2% of normal; bone lengths 91.5% of normal.	
		Newborn	11	28,000 U (3.5-0.28)	Weekly x 6; monthly x 11	Two mice from each	Mice from these 2 groups were difficult to	
(Sands et al. 1997)	rmGUS (gus ^{mp;} /gus ^{mp;})	mGUS Newborn		28,000 U (3.5-0.28)	Weekly x 5 then syngeneic BMT	group were sacrificed at age day 185. The remainder at 1 week after last treatment	significant increases in bone length and survival. Lysosomal storage was significantly decreased in these groups.	
		5 weeks	10	28,000 U (0.28)	Monthly up to 1 year		Treatment starting at 5 weeks had less phenotypic effect and less effect on lysosomal storage.	
(O'Connor et al. 1998)	rmGUS (gus ^{mps} /gus ^{mps})	Newborn	22 MPSVII 21 Normal	28,000 U (3.5-0.28)	Weekly x 6	Mice not sacrificed; subjected to Morris Water Maze Test	Less severe phenotype and improvements in histopathology in the brain and ear. Significant improvements in learning and auditory tests	
(Vogler et al. 1999)	rmGUS (gus ^{mp:/} gus ^{mp:})	Newborn-2 weeks	17	16,000 U/g (4.0)	1, 2, 3, 4, 5, or 6 weekly (N=2 or 3) starting at 0, 1, 2, 3, 4, 5 or 6 weeks	Day 42, except 3 mice treatment started at wk 5: killed Day 77	Treatment from birth to 6 weeks led to reduced lysosomal storage in brain. Treatment started at 2 weeks did not reduce lysosomal storage in brain. Leptomeningeal, osteoblast, RPE lysosomal storage not as sensitive to age at start of treatment.	

* Doses were calculated using a specific activity of 4000 U/µg for rh-GUS.

^a The enzyme in this study was produced from the same master cell bank that is used to produce material for Ultragenyx sponsored nonclinical and clinical studies, by comparable traditional purification method.

RPE = retinal pigment epithelium

UX003 primary pharmacodynamic bio-distribution study to confirm relationship between uGAG and tissue pathology (Study UX003-PC001)

Male and female transgenic MPS VII/E540A^{TG} mice received UX003 by IV injection once weekly for up to 8 consecutive weeks at doses of 0 (vehicle control), 0.1, 0.25, 1, 4, or 20 mg/kg. A recovery group at the 4 mg/kg dose level remained on study for a 1-week non-treatment recovery evaluation.

Rh-GUS activity in tissues

UX003 levels, measured as GUS activity, were found in a variety of tissues. In the majority of tissue samples collected approximately 48 hours following the final dose in Week 8, a dosedependent increase in tissue levels of UX003 was observed (see also Section 2.3.3 of this report under *Distribution*).

At 20 mg/kg/week, the highest levels of activity were noted in the liver (~900 U/mg), spleen (~600 U/mg), and adrenal gland (~400 U/mg); the lowest levels were noted in brain tissue (~0.7 U/mg). Tissue activity levels in animals that received UX003 at 4 mg/kg were maintained following the 1-week recovery period. Low levels of activity were reported in serum, heart, brain, and prostate of the control group animals suggesting that some endogenous GUS production capability remains in this mouse strain.

Serum and urinary GAG

Analysis of GAG based on technology to assay the non-reducing ends (NRE) of released disaccharides from the GAGs for specific chemistry derived from lysosomal exposure in UX003-treated mice is shown in (**Figure 2**).





Dose-related effect on cytoplasmic vacuolization

Vacuolization was not observed in tissue samples examined from the adrenal gland, epididymis, quadriceps muscle, or prostate in control or UX003-treated MPS VII/E540ATg mice. In tissues with vacuolization, treatment with UX003 appeared to result in a dose-dependent reduction in cytoplasmic vacuolization in most tissues and tissue elements (**Figure 3**).



Relation between urinary GAG (NRE) and tissue pathology scores

A consistent pattern of a reduction in pathology score was observed with reductions in urinary GAG levels for both dermatan sulfate (DS) and heparan sulfate (HS), GAG structures that are unique to the lysosomal enzyme deficiency found in MPS VII patients (**Figure 4**).

Figure 4. % reduction in urinary GAG vs pathology score in kidney tubular epithelium (upper panels) and heart valvular and epicardial stromal cells (lower panels)



<u>Rh-GUS leads to enzyme activity and reduced lysosomal storage in the brain and other tissues</u> (Vogler et al. 2005, CRL 20022037-1, 20022037-2)

Adult MPS VII/E540A^{TG} mice were treated with IV bolus rh-GUS using once weekly or every-otherday schedules for up to 13 weeks. The brain from mice receiving 4 mg/kg rh-GUS weekly for 13 weeks contained, on average, 1.38% of wild-type GUS activity 7 days after the last of 13 weekly doses. This group also showed clearance in meninges, parietal neocortical and hippocampal neurons and glia, in addition to liver, kidney, and urine. The mice treated with 20 mg/kg once weekly for 4 weeks, had even higher enzyme levels in brain, with an average of 2.5% of wild-type activity, as well as decreased neuronal, glial, and meningeal storage. No change was observed in hippocampal neurons. The brains of mice treated with up to 5 mg/kg once weekly for 3 weeks, had much lower levels of enzyme and only moderate reduction in meningeal storage with no change in neocortical or hippocampal neurons. Thus, the increased enzyme levels and reduction in lysosomal storage in brain correlated with both dose and duration of treatment.

The pathology slides from this study were available and obtained by the applicant for a blinded reevaluation (study reports CRL 20022037-1 and 20022037-2, **Figure 5**).

Figure 5. Correlation of dose with histopathological scores from 13-week rhGUS ERT treatment in MPS VII/E540A^{TG} mice



rmGUS distributes to multiple tissues and reduces lysosomal storage (Sands et al. 1994)

MPS VII mice received either six weekly IV injections of rmGUS beginning at birth or a single IV injection at 5 weeks of age. One week following the single and sixth weekly injection, rmGUS was detected in the liver, spleen, kidney and brain. Tissue activity levels following the sixth weekly injection were 28% (liver), 3-5% (spleen), 3-5% (kidney), and 7% (brain) of normal. Tissue activity levels following the single injection were 35% (liver), 3-5% (spleen), 3-5% (kidney), and 7% (brain) of normal. Tissue activity levels following the single injection were 35% (liver), 3-5% (spleen), 3-5% (kidney), and 1% (brain) of normal. Enzyme activity was undetectable in control MPS VII mice and no detectable increase in activity was seen in the tissues of normal mice, with the exception of the brain.

Clinically, MPS VII mice treated from birth with six weekly enzyme injections were difficult to distinguish from normal 6-week old mice; they had nearly normal body weights and reduced facial dysmorphism. However, mice receiving only a single enzyme injection at 5 weeks of age were phenotypically identical one week later to untreated MPS VII mice of the same age.

rmGUS prolongs survival and improves growth (Vogler et al. 1996)

MPS VII mice received six weekly IV bolus injections of rmGUS beginning at birth. Four untreated mice were used as controls. Following six weekly IV bolus injections of rmGUS, GUS activity was demonstrable for at least 14 days in the fixed tissue macrophage system. The subsequent disappearance of GUS activity and the compensatory rebound in elevations of alpha-galactosidase and beta-hexosaminidase correlated with the appearance of lysosomal storage in the fixed tissue macrophage system.

By 29 days after the last enzyme injection, lysosomal storage material in bone was not different from that seen in untreated MPS VII mice. By 85 days, the fixed tissue macrophage system, meninges, and brain glia had also accumulated storage comparable to that seen in untreated controls. One year after treatment, lysosomal storage was similar to that of untreated MPS VII mice in all sites except cortical neurons, where there was still a slight reduction.

Mice treated for 6 weeks lived longer, were larger, and had milder facial and skeletal deformities than untreated MPS VII mice. Although phenotypically still distinguishable as MPS VII mice, these long-term survivors were more alert with a more normal gait and coat texture. Their body weight was 93.2% of normal, and bone lengths were 91.5% of normal 1 year after discontinuation of treatment. In comparison, adult untreated MPS VII animals up to 218 days of age have body weights 1.2% of normal and bone length 85.2% of normal. Both body weight and bone length were markedly improved in treated MPS VII mice as compared to adult untreated MPS VII mice (p < 0.01 for body weight; p < 0.025 for bone length).Although bone accumulated lysosomal storage to the same extent as in untreated MPS VII mice by 29 days after the last injection, the short course of therapy markedly improved bone growth, and morphologic evidence of dysplasia was reduced for as long as the 1 year time point.

rmGUS leads to improvements in phenotype, behaviour and auditory function (O'Connor et al. 1998)

Following six doses of treatment with rmGUS (28,000 U; 7 μ g), the MPS VII phenotype, characterized by dwarfism and flattened facial profile, did not develop to the same extent in treated mice as compared to untreated mice. The treated MPS VII mouse was larger, the bone lengths were greater, and the facial dysmorphism was less severe than in the untreated MPS VII mouse. The more normal phenotype was still apparent at the end of the study when the mice were ~12 weeks of age.

MPS VII mice treated with enzyme from birth had histological evidence of reduced lysosomal storage in many tissues, including neurons of the brain. Lysosomal distension and storage material was reduced or absent in neocortical neurons in treated MPS VII mice when compared with untreated MPS VII mice

The reduced lysosomal storage in the brain was associated with improved mental function as measured by improved spatial leaning in the Morris Water Maze test. Although lysosomal storage material was not completely eliminated from the CNS after enzyme replacement therapy, lysosomal storage was reduced in neocortical neurons of treated MPS VII mice.

Mice with MPS VII have severe histopathologic abnormalities in the ear, associated with a profound hearing loss. In treated MPS VII mice there was a substantial improvement in auditory function after treatment and a corresponding improvement in the histopathology of the ear (reduced malformations of the ossicles, less middle ear inflammation and mucosa thickening, thinner tympanic membranes), when compared with the untreated MPS VII mice.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were submitted as in accordance with the ICH S7A Guideline, Safety Pharmacology Studies for Human Pharmaceuticals, the product is a recombinant form of a naturally occurring human protein, and its mechanism and site of action (degradation of GAGs of dermatan sulfate, chondroitin sulfate and heparan sulfate in cellular lysosomes) does not suggest any effect or risk that is unrelated to its therapeutic target.

Safety pharmacology programme

The core battery of GLP-compliant safety pharmacology studies was conducted with UX003, in accordance with ICH S7A. These studies consisted of an evaluation of respiratory effects in SD rats, and an evaluation of central nervous system (CNS) and cardiovascular (CV) system effects as part of a GLP single-dose toxicity study in SD rats and a GLP repeat-dose toxicity study in cynomolgus monkeys, respectively. The studies are summarised in **Table 2**, and are further described below.

Table 2. Overview of safety pharmacology studies with UX003

Study Type /Sponsor Study No. / Study Title	Species	Route of Admin.	Regimen & Duration	Dose (mg/kg)	Sex/No. Animals	Findings
Respiratory UX003-PC004 A Pharmacological Assessment of the Effect of UX003 on the Respiratory System of the Sprague Dawley Rat following Intravenous Administration	SD Rat	IV infusion, 2 hr	Single dose on Day 1	Group1=0 Group2=6 Group3=20	Group1=6 males Group2=6 males Group3=6 males	 Plethysmography data: no significant UX003-related effects were observed on the ventilatory parameters (tidal volume, respiratory rate, and derived minute volume) up to 240 hours post dose Body Weights (BWs): There were no UX003-related effects Clinical observations: There were no UX003-related effects Animals were euthanized the day after derivations
Central Nervous System (CNS) ^a UX003-PC002 A Single-dose Toxicity, Toxicokinetic and CNS Safety Pharmacology Study in SD Rats	SD Rat	IV infusion, 2 hr	Single dose on Day 1	Group1=0 Group2=6 Group3=20	Group1=6/sex Main study animals + 4/sex TK Group2=6/sex Main study animals + 4/sex TK Group3=6/sex Main study animals + 4/sex TK	 CNS (Functional Observational Battery of Tests): There were no UX003-related effects BWs: There were no UX003-related effects Clinical observations: There were no UX003-related effects

Study Type /Sponsor Study No. / Study Title	Species	Route of Admin.	Regimen & Duration	Dose (mg/kg)	Sex/No. Animals	Findings
Cardiovascular (CV) ^b UX003-PC003 A 26-Week Toxicity, Toxicology and Cardiovascular Safety Study of UX003 by Intravenous Infusion Administration in Young Cynomolgus Monkeys with a 4-Week Recovery Period	Cynomolgu s monkey (juveniles 1.5-2 yrs of age)	IV infusion, 2 hr	QOW x 26 weeks plus 4-week recovery	Group1=0 Group 2=2 Group3=6 Group4=20	Group1= 5 males (3 Main study + 2 Recovery animals) and 5 females (3 Main study + 2 Recovery animals) Group2= 3 males + 3 females Group3= 3 males + 3 females Group4= 5 males (3 Main study + 2 Recovery animals) and 5 females (3 Main study + 2 Recovery animals)	 Electrocardiogram recordings on Days 1, 85, 155, and during the last week of recovery (for a 24-hour period): There were no UX003-related effects BWs and food consumption: There were no UX003-related effects Clinical observations: There were no UX003-related effects Physical exams: There were no UX003-related effects

* The single-dose toxicity and TK study in rat was conducted in combination with the CNS safety pharmacology assessment

b. The 26-week chronic toxicity and TK study in cynomolgus monkey was conducted in combination with the CV safety pharmacology assessment

Pharmacodynamic drug interactions

No pharmacodynamics drug interaction studies were submitted as the applicant considered that the product as an enzyme replacement therapy will not interact with the pharmacodynamics of other drugs.

2.3.3. Pharmacokinetics

Characterization of the pharmacokinetic properties of IV administered UX003 was determined as part of the toxicokinetics (TK) assessments in the single-dose combined toxicity and CNS safety pharmacology GLP study in rats (UX003-PC002) and the 26-week combined GLP repeat-dose toxicity and CV safety pharmacology study in cynomolgus monkeys (UX003-PC003). Limited TK sampling was also performed in the IV developmental and reproductive toxicity (DART) studies, UX003-PC007 and UX003-PC008 in rats and UX003-PC006 and UX003-PC009 in rabbits. The PK and tissue distribution profile of UX003 in male rats was assessed further in a non-GLP single-dose study (UX003-PC005).

Additional nonclinical PK and bio-distribution information on rm- and rhGUS is summarized below based on several publications.

Absorption

Single dose PK in SD rats (study UX003-PC002, GLP)

Sprague-Dawley (SD) rats were administered single iv infusions of UX003 at 0 (vehicle control), 6 and 20 mg/kg for 2 hours via pre-implanted catheter. Serum samples for toxicokinetic analysis were collected prior to dose and various time points post dose on Day 1.

Peak GUS activity was reached at 2.03 hours post start-of-infusion for the treated groups. GUS activity exposure ($AUC_{[0-t]}$ and C_{max}) was dose proportional for females and slightly greater than dose proportional for males between 6 and 20 mg/kg. Exposure was slightly lower in females when compared to males.

Single dose PK in male SD rats (study UX003-PC005, non-GLP)

Rats received ~ 2 mg/kg of either UX003 or a research grade lot of rhGUS via iv infusion for 2 hours. Serum samples for pharmacokinetic analysis were collected pre-dose and pot-infusion start and end.

Although T_{max} was similar for both groups, the mean C_{max} for animals dosed with UX003 was approximately 3-4-fold higher than the mean C_{max} for GUS 43/44. This 3-4-fold difference was also evident in the mean exposure (measured by AUC) between the two groups. The mean half-life was similar (about 1 hour) between animals dosed with UX003 or GUS 43/44.

Repeat-dose PK in a 26-week toxicity study in juvenile monkeys (study UX003-PC003, GLP)

Monkeys (1.5-2 years of age) were administered UX003 (at 0 (vehicle, control), 2, 6 or 20 mg/kg every other week by IV infusion every other week for 2 hours via catheter for 26 weeks.

The 10-fold dose increase between 2 and 20 mg/kg, resulted in an AUC_(0-t) increase up to 99.6-fold and C_{max} increase up to 64-fold. GUS activity doubled between Day 1 and Day 169 except for females from the 2 mg/kg group where exposure remained relatively unchanged. Accumulation ratios for GUS activity ranged from 0.856 to 2.23 for AUC_(0-t). There were no notable sex-related differences in GUS activity exposure except at 2 mg/kg on Day 169 where exposure was approximately 40% lower in females than males. Female/male ratios ranged from 0.580 to 1.52 for C_{max} and from 0.548 to 1.67 for AUC_(0-t).

In total 16 of 32 animals (2/10 control, 4/6 at 2 mg/kg, 4/6 at 6 mg/kg, and 6/10 at 20 mg/kg) screened positive for ADAs at one or more time points during the study. However, 6 of these animals screened positive for ADA prior to dosing.

Distribution

Bio-distribution Study in MPS VII mice (UX003-PC001)

In the majority of tissue samples collected approximately 48 hours following the final dose in Week 8, a dose-dependent increase in tissue levels of UX003 was observed (**Table 3**).

Table 3: rh-GUS enzyme activity in MPS VII mice after ERT for 8 weeks with UX003 48 hours following the final dose-Study UX003-PC001

Tissuo					
Tissue	0	1	4	20	WT B6 mice
Adrenal Gland	0.18	96	303	1131	267
Liver	0.01	86	285	2848	221
Spleen	0.01	120	462	1948	398
Brain	0.02	0.1	0.2	0.7	17
Lung	0.02	5.8	17	58	61
Testis	0.02	0.6	4.4	54	81
Bone	0.04	20	29	25	149
Muscle	0.00	1.0	3.5	4.2	4.39
Thymus	0.13	1.2	4.1	22	203
Ovary/Uterus	0.04	2.8	4.8	52	166
Thyroid	0.07	2.0	5.1	32	64
Heart	0.14	1.9	13	63	7.0
Kidney	0.02	1.9	6.7	103	229
Prostate	0.06	0.5	3.2	11	180
Serum(u/ml)	0.35	0.7	1.9	13	45.3

Tissue activity levels (see also Section 2.3.2 under *Primary pharmacodynamic studies*) in animals that received UX003 at 4 mg/kg were maintained following the 1-week recovery period. Low levels of activity were reported in serum, heart, brain, and prostate of the control group animals.

<u>Tissue distribution of UX003 in male SD rats after administration via a single two-hour intravenous</u> infusion (study UX003-PC005)

At approximately 24 hours following dosing of 0 (saline, control) or 2 mg/kg UX003 or rh-GUS to male rats, tissue samples from brain, lungs, liver, spleen, kidneys, and heart were collected. Tissue extracts were prepared and assayed for GUS activity and protein. The level of GUS in rats infused with UX003 and rh-GUS was higher than the saline infused rats in most tissues. Highest levels of GUS were seen in the liver, spleen and kidney.

Published bio-distribution studies with recombinant GUS in MPS VII mice models

Sands et al. 1994

MPS VII mice received rm-GUS as a single IV injection of 28,000 U at 5 weeks of age, or as six weekly IV injections of 28,000 U beginning at birth. One week following the single and sixth weekly injection rmGUS activity was detected in the liver, spleen, kidney and brain. MPS VII mice that received a single injection had 35% (liver), 3-5% (spleen), 3-5% (kidney) and 1% (brain) of normal GUS levels.

Vogler et al. 1993

The tissue distribution of rh-GUS was evaluated in newborn MPS VII mice following a single IV administration of 3.5 mg/kg (28,000 units). One hour after dosing, GUS levels were equal to or greater than normal in every organ evaluated with exception of the brain, where 31% normal activity was present. Enzyme was detectable histochemically in the major sites of pathology for MPS VII including bone, brain, heart and fixed tissue macrophages. The half-life of rhGUS in various organs was 1.5 to 4.5 days.

Vogler et al. 2005

Adult MPS VII/E540A^{TG} mice were treated with rh-GUS at varying dose schedules with IV doses up to 20 mg/kg. The activity of rh-GUS was measured in tissues 7 days after the last injection. Dose dependent enzyme levels were seen in brain, liver, spleen, heart, kidney, bone, muscle and eye 1 week after the last injection.

Grubb et al. 2008a

MPS VII mice were administered rh-GUS via tail vein with enzyme at dose of 4 mg/kg, and the activity of rh-GUS was measured in tissues 48 hours after the injection. Enzyme activity was detected in brain, liver, spleen, heart, kidney, lung, muscle, bone and eye at levels ranging from 1.4 % to 482% of the levels seen in the wild-type mice.

Sly et al. 2006

The activity of rh-GUS in a variety of tissues from MPS VII/E540A^{TG} mice was assessed following treatment with rh-GUS at doses of 0.4, 1.5 or 6.4 mg/kg. Twenty-four hours after a single bolus IV infusion, dose-dependent levels of GUS activity were detected in the brain, liver, spleen, heart, kidney, lung, muscle and bone.

Placental transfer - single dose study with rhGUS in mouse (Grubb et al. 2008b)

The PK profiles of rh-GUS and a chimeric rh-GUS-Fc fusion protein were evaluated following IV injection of 3-5 mg/kg into pregnant MPS VII mice. When rh-GUS was infused into $MR^{+/+}$ mice, it was cleared from the plasma with a $t_{1/2}$ of 1.7 min. The clearance was slower in the $MR^{-/-}$ mouse ($t_{1/2}$ 19 min). The clearance of GUS-Fc (a fusion protein of GUS with the Fc receptor of an immunoglobulin) was substantially slower than that of GUS in both the $MR^{+/+}$ and $MR^{-/-}$ mice ($t_{1/2}$ = 36 and 72 min, respectively).

The transplacental transfer of plasma GUS activity following IV administration of GUS or GUS-Fc, or PerT-GUS (periodate-treated rh-GUS which cannot be taken into the cell by the mannose receptor or mannose-6-phospate receptor) to MPS VII MR^{+/+} and MR^{-/-} mice was also evaluated in this study. Both MR^{+/+} and MR^{-/-} pregnant females, which were infused with GUS-Fc, produced MPS VII^{-/-} pups that contained high levels of GUS activity in plasma. By contrast, plasma GUS levels of pups from mothers infused with untagged GUS were not above the low residual levels seen in MPS VII^{-/-} pups of mothers who received buffer only.

Metabolism

No metabolism studies were performed, as in accordance with ICH S6 (R1) guidance, the expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids.

Excretion

No excretion or mass balance studies were submitted, as due to the large molecular size (~332 kDa homotetramer) of the product, the applicant considered that is unlikely to be renally excreted. The end products (amino acids) from its catabolism would be expected to be incorporated into the endogenous cellular amino acid pool with a portion of it being excreted.

Pharmacokinetic drug interactions

No PK drug interaction studies were performed, as the product is a recombinant form of a naturally occurring human enzyme which is not metabolized by cytochrome P450 enzymes, and therefore no P450 mediated drug-drug interactions are anticipated.

2.3.4. Toxicology

The nonclinical toxicology of UX003 was characterized in a single dose toxicity study SD rats, a 26week chronic toxicity study in juvenile cynomolgus monkeys, in an 8-week (with 1-week recovery) bio-distribution study in MPS VII/E540A^{TG} mice, and in reproductive toxicity studies in SD rats and NZW rabbits.

Single dose toxicity

The results from the single-dose toxicity, toxicokinetic and CNS safety pharmacology study in SD rats (study UX003-PC002 are described in Sections 2.3.2 and 2.3.3 of this report.

Repeat dose toxicity

26-week toxicity, toxicology and cardiovascular safety study of UX003 by intravenous infusion administration in young cynomolgus monkeys with a 4-week recovery period (study UX003-PC003, <u>GLP</u>)

Animals were also evaluated for clinical observations, ECG, body weight, food consumption, ophthalmic observations, haematology, clinical chemistry, urinalysis and gross necropsy. Histopathological evaluation was only performed on the control and high dose groups.

There were no toxicologically significant findings related to the administration of UX003 in clinical observations, food consumption, body weights, veterinary physical examinations and physiological measurements. There were no effects of UX003 on haematology, coagulation and urinalysis parameters measured during the 26-week study. Effects were limited to mild, transient increase in bilirubin in females on Day 4, which were reversible and not considered adverse. There were no target organ toxicities identified at the dose levels tested. All dosing formulations tested were within acceptance criteria, and enzyme activity results indicated that the enzyme was active after the formulation process.

Repeat dose toxicity data was also investigated in the bio-distribution study to confirm relationship between uGAG and tissue pathology (study UX003-PC001).

Unscheduled deaths occurred in both control and UX003-treated animals (2/6, 1/6, 0/6, 1/6, 1/12 and 3/6 animals at 0, 0.1, 0.25, 1, 4 and 20 mg/kg/week, respectively). The cause of death in the control animals was not determined but may be associated with the age of the animals, the MPS VII disease and/or extensive animal handling while on study. In the UX003 treatment groups, all mortalities observed at doses ≥ 1 mg/kg occurred post dose administration in Week 3. The cause of deaths in the treated animals was not determined.

No significant adverse clinical observations related to UX003 were noted during the study. There were no apparent adverse changes in the serum chemistry parameters evaluated.

The histologic findings included irregular thickening of the heart valve(s) noted in all untreated, control group animals with valves present. This finding was also noted in some of the UX003-treated animals, but generally with reduced severity as compared to the control animals suggesting the finding was already present prior to the initiation of treatment. Other findings such as minimal to mild inflammation of the liver and eosinophilic crystalline pneumonia of the lung were considered to be background or incidental lesions not associated with UX003.

Published Repeat-Dose Studies in the MPS VII Mouse Model for 3 and 13 Weeks (non-GLP)

Repeat-dose studies with rh-GUS and rm-GUS have been conducted in MPSVII/ E540A^{TG} mice to assess biodistribution, lysosomal clearance and efficacy (Vogler et al. 1996, 1999, 2005). None of the studies were conducted as formal GLP toxicology studies.

In order to confirm the absence of significant pathologic findings in MPS VII tolerant mice, a blinded reassessment of all available histological slides from Vogler et al. (2005, see also Section 2.3.2).

Histopathological observations, such as inflammation, were uncommon, minimal in severity, and considered to be unrelated to treatment with rh-GUS. No histopathologic findings attributable to rh-GUS treatment were observed following treatment at weekly IV doses up to 5 mg/kg for 3 weeks or 4 mg/kg for 13 weeks.

Genotoxicity

Genotoxicity testing was not conducted, as it is a recombinant form of a naturally occurring human protein, whose mechanism and site of action (degradation of GAGs in cellular lysosomes) does not suggest any genotoxic risk. Being a large protein, the applicant considered that product is not expected to enter the nucleus, interact with DNA (deoxyribonucleic acid) or chromosomes.

Carcinogenicity

No carcinogenicity studies were conducted with UX003 based on a number of factors as cited in ICH S1A "Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals". Per ICH S1A Guidelines, "carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (i.e., physiological levels), particularly where there is previous clinical experience with similar products. The product belongs to a class of pharmaceuticals, ERTs, where there is previous clinical experience. Furthermore, UX003 is recombinant human GUS, which endogenously exists in the body; therefore it is not expected to be carcinogenic.

Reproduction Toxicity

The reproductive and developmental toxicity studies with UX003 are presented in Table 4.

Study ID (GLP)	Species (strain) n	Dose (mg/ kg/dose)	Dosing period	Major findings	NOAEL (mg/kg)			
Combined fertility and embryo-foetal development								
UX003-PC008 (GLP)	Rat (SD) 23/sex/gr	0, 0+DHP, 2, 6, 20	Males: once/week for 4 weeks prior to mating Females: once/week for 2 weeks prior to mating, and on GD 6, 9, 12, 15, 18	0+DHP: 1M died (study day 43) 2 mg/kg: 1M died (at end of 4 th dosing) 6 mg/kg: 1F with multiple clinical observations (denuded tail, convulsions shortly prior to dosing, head bobbing, hypoactivity). 20 mg/kg: 1M and 1F died (at end of 3 rd dosing). ↓body weight and weight gain (M). Hypoactivity (3M). ↑fetal skull and rib variations, ↓centra variations	Paternal: 20 Maternal: 20 Fertility: 20 Fetal: 20			
Embryo-foetal development								
UX003-PC007 (non-GLP)	Rat (SD) 4F/gr	0, 2, 6, 20	GD 6, 9, 12, 15 and 18		Maternal: 20 Fetal: 20			
UX003-PC006 (non-GLP)	Rabbit (NZW) 3F/gr	0, 2, 6, 20	Daily, from GD 6-18		Maternal: 20 Fetal: 20			
UX003-PC009 (GLP)	Rabbit (NZW) 23F/gr	0, 2, 6, 20	GD 6, 9, 12, 15 and 18		Maternal: 20 Fetal: 20			

Table 4. Reproductive toxicity studies with UX003

In the Combined Fertility and Embryo Fetal Development Toxicity of UX003 in Rats (study UX003-PC008), fertility, mating performance, outcome (pregnancy), sperm parameters (motility, count and morphology) and male organ weights were unaffected by treatment with UX003. Overall, no treatment related differences in litter viability were detected. The percent pre- and post-implantation loss, were similar across groups. Average number of corpora lutea, live, total implants and non-live (resorptions) was similar across groups. The average range for resorptions was ~0.3-0.7 and no dead foetuses were observed in any of the litters. The percent of live foetuses ranged from 95-99%. No statistical significance difference was seen between the UX003 treated groups and control group in litter viability data.

Average litter weights were similar across all groups. No evidence of developmental anomalies or malformations, as determined by foetal evaluations (gross external evaluation including litter weights, cephalic, visceral or skeletal examinations). Skeletal variations included misshapen (dumbbell, bipartite) centra in the controls and incomplete ossification of the skull (14%) and/or wavy ribs (9%) in the high dose foetuses. Observations noted in both the skull and rib were significantly above the concurrent control but similar to that seen in control fetuses in a historical control study (11% and 8%, respectively).

In the dose-range finding Study with UX003 in Pregnant Rats (study UX003-PC007) UX003 did not produce any maternal toxicity, and no significant differences in maternal food consumption, body weight, body weight gain, uterus weights and foetal body weights were seen between the treated and control groups. Gross external examinations of the foetuses were unremarkable. Total body weight corrected for uterus weight was similar across groups.

Overall, no treatment-related differences in litter viability were detected. The average number of corpora lutea, live and total implants was similar across groups, although the number of live implants was slightly higher in the treated groups. No dead foetuses were observed, and number of

resorptions was similar across groups. Average foetal weights were similar across all groups and no gross external abnormalities were noted in any of the foetuses. Eleven of the 20 dams had a positive response for ADA prior to treatment initiation on GD 6.

In the actual study, these pre-study ADA positives were randomly distributed across the groups (2-3/group), including controls. However, animals which had a positive response on GD 6 remained positive on GD 21. All rats in the UX003 treated groups (2, 6 and 20 mg/kg groups) were ADA positive by GD 21 and the magnitude of the response was greater on GD 21 compared to their response on GD 6. In addition, litters from the UX003 treated dams also displayed a highly positive ADA response. The levels seen in the litters were likely due to maternal antibody transfer to the foetus. A positive ADA response was also seen in the control dams (Vehicle alone or Vehicle + DHP) on GD 6; however, the response was not magnified on GD 21, nor was the response of their litters elevated in the same manner as the litters from the UX003 treated dams.

In the dose-range finding study with UX003 in pregnant rabbits (study UX003-PC006) serum levels of UX003 (GUS) on GD 29 were higher than endogenous levels seen prior to treatment initiation on GD 6 in all groups including the controls. GUS levels in foetal blood were lower than endogenous levels seen prior to treatment on gestation day 6 in the dams. This was suggestive of no exposure of the foetus to UX003 on GD 29.

Some dams had a positive response for ADA prior to treatment initiation on GD 6. These were randomly distributed across the groups, including controls. Animals which had a positive response on GD 6 remained positive on GD 29; however, a dose related-increase was seen in the dose given 6 and 20 mg/kg on gestation day 29. A positive ADA response was also seen in the litters from dams treated with 6 and 20 mg/kg treated groups.

No adverse treatment-related clinical signs were noted in any of the dams during the study, and no evidence of a hypersensitivity reaction was noted in any of the dams. No obvious treatment-related difference in litter viability was seen between the dams treated with 2, 6 or 20 mg/kg of UX003 as the number of corpora lutea, implants and average litter size was similar in the treated and control groups. Pre- and post-implantation loss were similar across groups and unaffected by treatment.

Gross external anomalies were unremarkable and all foetuses were normal. Foetal examinations failed to reveal any treatment-related effects, and mean litter body weights of the treated groups were comparable to controls; as such UX003 did not adversely impact foetal growth.

In the embryo-foetal development toxicity of UX003 in rabbits (UX003-PC009), no adverse treatment-related clinical signs were noted in any of the does during the study, and no evidence of a hypersensitivity reaction was noted in any of the doses. No treatment related differences were observed in litter viability, pre- and post-implantation loss, average number of corpora lutea, total implants, live foetuses or litter viability. Litter (average foetal) body weights were similar across groups and unaffected by treatment with UX003.

Toxicokinetic data

Toxicokinetic data are presented in Section 2.3.3. Additional TK data were collected through the reproduction toxicity studies.

Repeat-dose PK in a combined iv fertility and developmental toxicity study in SD rats (study UX003-PC008, GLP)

Animals were administered UX003 at 0 (vehicle control), 2, 6 or 20 mg/kg/dose via intravenous infusion for 30 minutes. All male rats were dosed for 6 weeks. Female rats were dosed once a week for 2 weeks prior mating and every third day during pregnancy.

Systemic exposure of UX003 after weekly IV infusion were substantially greater than dose proportional in male and female rats (**Table 5**).

Repeat-dose PK in an embryo-foetal development study in NZW rabbits (study UX003-PC009, GLP)

Pregnant rabbits were administered UX003 at 0 (vehicle control), 2, 6 or 20 mg/kg on GD 6, 9, 12, 15 and 18 by iv infusion for 30 minutes. Blood for TK and ADA was collected prior to treatment initiation and periodically during the study as well as on GD 29 from the does and litters (pooled foetal blood). TK parameters at gestation day 18 are presented in **Table 5**.

Local Tolerance

No dedicated nonclinical local tolerance studies for UX003 were conducted. However, no gross or histopathological abnormalities attributed to UX003 were observed at the IV infusion sites in the single dose rat toxicity study or the 26-week repeat-dose toxicity study in juvenile cynomolgus monkeys (UX003-PC002 and UX003-PC003, respectively).

In the single dose rat study (UX003-PC002), minimal or mild, chronic inflammation, endothelial hyperplasia, and/or thrombosis were observed at the administration site (jugular vein) of some control and UX003-dosed animals which were attributed to the presence of the indwelling jugular catheter.

$AUC_{0,t}(hr^*\mu g/mL)$								
Dose (mg/kg)	Stu	Rats (DART) ^a dy No. UX003-PC00	Rabbits (DART) ^b Study No. UX003-PC009					
2 ···· (····a···a)	Mc	\mathbf{F}^{d}	F ^e	\mathbf{F}^{f}				
2	0.800 + 45.6	7.30 + 24.2	0.725 + 30.3	3.62 + 62.1				
6	20.3 + 59.2	35.4 + 16.6	10.2 + 92.8	58.8 + 10.4				
20	258 + 8.6	191 + 3.5	91.7 + 83.2	604 + 48.4				
C _{max} (µg/mL)								
Dose (mg/kg)	Stu	Rats (DART) ^ª dy No. UX003-PC00	Rabbits (DART) ^b Study No. UX003-PC009					
	M ^c	\mathbf{F}^{d}	F	$\mathbf{F}^{\mathbf{f}}$				
2	1.23 + 58.6	12.5 + 20.3	1.07 + 43.8	4.65 + 73.0				
6	39.1 <u>+</u> 59.1	58.8 <u>+</u> 26.2	19.3 <u>+</u> 97.4	64.3 <u>+</u> 18.5				
20	386 <u>+</u> 8.2	314 <u>+</u> 7.8	134 <u>+</u> 81.0	372 <u>+</u> 45.4				
T _{max} (hr)								
Dose (mø/kø)	Stu	Rats (DART) ^a dy No. UX003-PC00	Rabbits (DART) ^b Study No. UX003-PC009					
	M ^c	\mathbf{F}^{d}	F	$\mathbf{F}^{\mathbf{f}}$				
2	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500				
6	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500				
20	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500 <u>+</u> 0.0	0.500				
t _{1/2} (hr)								
Dose (mg/kg)	Stu	Rats (DART) ^a dy No. UX003-PC00	Rabbits (DART) ^b Study No. UX003-PC009					
2000 (mg/ng)	M°	\mathbf{F}^{d}	Fe	$\mathbf{F}^{\mathbf{f}}$				
2	5.15 <u>+</u> 28.3	1.01 <u>+</u> 9.5	4.77 <u>+</u> 15.0	1.74 <u>+</u> 27.5				
6	0.96 <u>+</u> 25.0	0.754 <u>+</u> 37.9	1.75 <u>+</u> 76.5	0.461 <u>+</u> 8.4				
20	0.362 <u>+</u> 2.0	0.516 <u>+</u> 48.0	3.54 <u>+</u> 143.3	0.856 <u>+</u> 35.3				

Table 5. Overview of toxicokinetic data from development and reproductive toxicity studies with UX003

^a DART: Developmental and Reproductive Toxicity; Study Title: Combined Intravenous Fertility and Developmental Toxicity study (Segment I and II) of UX003 in Rat

^b DART: Developmental and Reproductive Toxicity; Study Title: Definitive Intravenous Developmental Toxicity Study (Seg II) of UX003 in Rabbits

^c N= 3 Male Rats on Study Day 22 (4th weekly dose)

^d N= 3 Nulliparous Non-gestational Female Rats on Study Day 8 for Females (2nd weekly dose)

^e N= 3 Gestational Female Rats on Gestation Day 18

^fN= 3 Female Rabbits on Gestation day 18/ group/ timepoint. All values are rounded to 3 significant figures

Other toxicity studies

Not applicable.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant provided a justification for not submitting any environmental risk assessment studies based on the fact that UX003 is a protein and therefore unlikely to pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The levels of Rh-GUS activity observed in the different tissues in the primary PD study conducted by the applicant were comparable to that observed in the prior (Vogler et al. 2005) study, for the same dose levels.

In the same study, a substantial, dose-related and consistent reduction of serum and urinary GAG in UX003-treated mice was demonstrated. Treatment with UX003 also resulted in a dose-dependent reduction in cytoplasmic vacuolization in most tissues. This reduction started at the lowest dose tested in well-perfused tissues, including tissue macrophages or endothelium. Less well-perfused tissues, such as the renal tubules, connective tissues, or neurons, required higher doses of UX003 to reduce storage. The effect on the brain neurons indicates that small amounts of rh-GUS may cross the blood-brain barrier as has been suggested in the past (Vogler et al. 2005).

Other tissues such as heart valvular and epicardial stromal cells may be considered partially resistant to treatment. It should be noted, however, that there also appears to be reduced cytoplasmic vacuolization in these tissues as well

The reduction in urinary GAG corresponded to a reduction in several tissue pathology scores. In tissues such as kidney tubular epithelium, bone osteocytes, bone surface lining cells, and heart normal pathology was achieved only when urinary GAG levels are reduced by 50% or more. Thus far, all subjects treated with the intended therapeutic dose of 4 mg/kg every other week have achieved at least a 50% sustained reduction in urinary GAG.

IV bolus injection of a fixed-dose of rm-GUS initiated at birth have shown reduced pathological evidence of disease and prevented some of the learning, memory, and hearing deficits in the MPS VII mouse (Sands et al. 1994, Vogler et al. 1996, O'Connor et al. 1998), but only if treatment begun before or during the second week of life. After that age, no therapeutic effect was seen in the neocortical and hippocampal pyramidal neurons in the CNS.

Similarly, results from Sands et al. 1994 and Vogler et al.1996, have shown the importance of early treatment with GUS in order to achieve GAG degradation in the rapidly growing skeleton which could have an impact on bone development.

Vogler et al 2005, have shown that reduction of lysosomal storage in the brain is related to dose and duration of treatment. Slides from this study were available and re-evaluated by the applicant. This analysis showed that treatment with rh-GUS resulted in a dose-dependent reduction in lysosomal storage in the majority of tissues, including CNS (neurons, glial cells, cerebellar perivascular cells and meningeal cells). Finally, O'Connor et al. 1998, provided evidence to suggest that that some of the learning, memory, and hearing deficits can be prevented in MPS VII mice if enzyme replacement therapy is initiated early in life.

The non-clinical safety pharmacology of IV administered UX003 has been characterized in GLP *in vivo* studies, conducted at dose levels up to 20 mg/kg in the SD rat (single dose) and in the juvenile cynomolgus monkey (combined 26-week repeat dose toxicity/TK/CV study). No UX003-related effects were seen on the respiratory system (study UX003-PC004) or the CNS (evaluated by FOB endpoints in study UX003-PC002) in SD rats, or on cardiovascular parameters in cynomolgus monkeys (study UX003-PC003).

No pharmacodynamics drug interaction studies were performed, and this was considered acceptable as it is not expected that enzyme replacement therapy would pharmacodynamically interact with the other drugs.
Pharmacokinetics

In the pivotal reproductive toxicity study in rats (study UX003-PC008), the systemic exposures of UX003 after weekly IV infusion were substantially greater than dose proportional in male and female rats. Overall, the estimated clearance (CL) decreased when the dose increased, independently of sex. Mean serum UX003 half-life ($t_{1/2}$) in males was inversely related to dose on Day 22 (Dose 4), ranging from 5.15 to 0.362 hours at 2 mg/kg and 20 mg/kg dose, respectively. Female rats showed a more modest range of serum $t_{1/2}$ values from 1.01 to 0.516 hours (non-gestational) or from 4.77 to 3.5 hours (gestational).

Serum levels of UX003 were substantially reduced at end of dosing in high-dose pregnant females, attributed to the development of ADA. However, while ADA was confirmed present in both males and females, similar reduction in serum UX003 levels were not seen in males or non-pregnant females. The mid- and high-dose males appeared to achieve a similar C_{max} levels at the beginning and end of the study (Day 1 and Day 29, respectively). It is acknowledged that the pregnant females were dosed for a longer period and a higher dosing frequency than the males and non-pregnant females. This might lead to higher ADA titres in pregnant females at gd18, than in the males at dosing day (D29) and non-pregnant females (D15), leading to reduced exposure levels.

The systemic exposure of UX003 in gestational rabbits was greater than dose proportional. There was little or no change in mean C_{max} (same as EOI concentration) on GD 9, 12 and 15 across all UX003 dose groups; however, individual low and mid-dose animals had variable reductions in C_{max} on GD 12 and/or 15, with GD 18 mean concentrations at EOI reduced by roughly 70% at the low dose. At the mid-dose, mean C_{max} was reduced by roughly 20% on GD 18 versus GD 15, and at the high dose, only 1 of 3 animals had a lower C_{max} (roughly 65%) on GD 18 compared to GD 15. The presence of ADA in adult (and fetal) samples in UX003-treated animals on GD 18 and 29 (terminal), suggest a likely impact of ADA on exposure on GD 18, most notably at the low dose.

Enzyme activity levels were dose-related following repeated dosing for 8 weeks, and enzyme activity levels remained above vehicle control levels one week after end of dosing. In most tissues the enzyme activity levels at end of recovery were reduced relative to the activity level at end of treatment (34-88%), however, in some tissues the activity levels were increased (104-142%).

Even though placental transfer of UX033 has not been studied, Grubb et.al have shown that transplacental transfer of rhGUS is limited in MPS VII mice.

As per ICH S6 (R1) guidance, the expected metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the CHMP agreed that classical biotransformation studies were not necessary for UX003.

Because of the large molecular size, UX003 is unlikely to be renally excreted. The end products (amino acids) of its catabolism are expected to be incorporated into the endogenous cellular amino acid pool. Therefore the absence of excretion or mass balance studies was considered acceptable.

Finally as UX003 represents a recombinant form of a naturally occurring human enzyme no P450 mediated drug-drug interactions are anticipated.

Toxicology

No significant adverse clinical observations related to UX003 were noted in any of the toxicology studies. This is consistent with published repeat-dose studies with recombinant mouse and human GUS.

Intravenous infusion of UX003 every 2 weeks for 26 weeks at dose levels up to 20 mg/kg was well tolerated by juvenile cynomolgus monkeys.

Unscheduled deaths were observed in the primary pharmacodynamic study (Study UX003-PC001). Cause of death was not determined in the animals receiving UX003 but may be due to test article-related immune responses to UX003 despite immune toleration. Immune allergic reactions are expected and commonly observed in ERT studies in animal models.

No major findings were reported in the combined fertility and embryo fetal development toxicity of UX003 in rats. Litter viability was unaffected by treatment with UX003 at doses up to 20 mg/kg/day and there was no evidence of UX003-related developmental anomalies or malformations, as determined by foetal evaluations (gross external evaluation including litter weights). The higher incidence of incomplete ossification of the skull and wavy ribs in the animals treated with the highest dose of UX003 were not considered adverse since such variants are known to occur in control/untreated animals, are reversible and were not associated with any condition or pattern that would be indicative of frank malformations or teratogenesis. However, as the applicant did not submit a Developmental and Perinatal/Postnatal Reproduction Study as stipulated in ICH S6 (R1) guidance, the conduct of such a study in rats is recommended to detect any potential effects of Mepsevii in offspring development.

Similarly, no findings were reported in the dose-range finding studies with UX003 in pregnant rats and rabbits, other than a high number of ADA positive responses prior to treatment. This high rate of false positives may be related to the assay cut point that was used. However, the applicant provided a validation report which demonstrated that the assay was robust and may be used to reliably compare pre- and post-treatment results to interpret, as an initial screen, whether anti-rhGUS antibodies may have developed in rabbits or rats treated with the therapeutic.

UX003 is a large protein molecule which is not expected to cross the nuclear or mitochondrial membrane and interact directly with DNA or other chromosomal material. Furthermore, is a recombinant form of the naturally occurring human GU with a mechanism of action that does not suggest any genotoxic or carcinogenic risks. Therefore the lack of genotoxicity and carcinogenicity studies with UX003 was considered acceptable.

In accordance with Guideline on the Environmental Risk Assessment of Medicinal Product for Human Use (EMEA/CHMP/SWP/4447/00 corr 2), the applicant did not submit any environmental risk assessment studies as UX003 is a protein and therefore unlikely to pose a significant risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of vestronidase alfa have been adequately characterised from a non-clinical perspective. A Developmental and Perinatal/Postnatal Reproduction study in rats is recommended to further characterise the potential reproductive toxicity effect of vestronidase alfa in line with the ICH S6 (R1) guidance.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

• Tabular overview of clinical studies

Study Identifier	Objectives	Study Design (Countries)	Number of subjects	Treatment duration	Status
UX003-CL301	Primary Objective (region-specific): US: Efficacy of UX003 based on totality of data on a per subject basis. No primary endpoint is declared. EU and rest of world (secondary in US): Efficacy of UX003 as determined by percent reduction uGAG excretion following 24 weeks UX003 Secondary Objectives: Safety and tolerability following up to 48 weeks UX003; efficacy following 24 weeks UX003 as measured by MDRI and positive ICR outcome; effects of UX003 on clinical outcomes (eg, pulmonary function, walking distance, shoulder flexion, fine and gross motor function following	Phase 3, Randomized, Placebo controlled, blind-start, single crossover, efficacy and safety (US)	12	24-48 weeks	Completed Final CSR
UX003-CL201	Primary Objectives: Safety and tolerability of UX003; efficacy of UX003 as determined by reduction in uGAG excretion Secondary Objectives: Determination of optimal UX003 dose and effect of UX003 on walking capacity (6MWT), stair climbing capacity (3MSCT), pulmonary function (FVC, FEV1, and MVV), growth velocity, shoulder range of motion	Phase 1/2, Open-label, uncontrolled, safety, efficacy, and dose exploration (UK, Spain, Turkey)	3	Up to 240 weeks	Completed Final CSR
UX003-CL203	Primary Objectives: Safety; efficacy as determined by reduction in uGAG excretion Secondary Objectives: Effect of UX003 on growth velocity and hepato- splenomegaly	Phase 2, Open label, uncontrolled, safety, and efficacy (US, Spain, Portugal)	8	Up to 240	Ongoing Interim CSR data cut-off date: 13 July 2017 ^a

3MSCT = 3-minute stair climb; 6MWT = 6-minute walk test; ADA = anti-drug antibody (anti-rhGUS antibody); BOT-2 = Bruininks-Oseretsky Test of Motor Proficiency; ERT = enzyme replacement therapy; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GAG = glycosaminoglycan; ICR = individualized clinical response; IV = intravenous(Iy); MDRI = multi-domain responder index; MPS = mucopolysaccharidosis; MPS HAQ =Mucopolysaccharidosis

Health Assessment Questionnaire; MVV = maximum voluntary ventilation; N/A = not applicable; PGI-C = Physician Global Impression of Change [scale]; PK = pharmacokinetics; QOW = every other week; uGAG = urinary glycosaminoglycan; UK = United Kingdom; US = United States

^aThe interim UX003-CL203 CSR includes data for 8 subjects of which 5 (62.5%) completed the Week 48 visit and entered the optional Continuation Period up to the Week 96 visit. The remaining 3 subjects completed at least the Week 24 visit.

2.4.2. Pharmacokinetics

The pharmacokinetic profile of vestronidase alfa were evaluated in a total of 19 MPS VII patients including 15 paediatric patients and 4 adults from 3 clinical trials (UX003-CL201, 203 and 301). No data were obtained in healthy volunteers.

Absorption

Analysis included PK parameters from the pivotal Phase 3 Study UX003-CL301 (excluding the PK parameter results from the first dose) as they were considered to provide a more appropriate description of vestronidase alfa PK after repeated dosing of 4 mg/kg/QOW in this study.

Table 6. Vestronidase alfa summary statistics of pharmacokinetics parameters after RepeatedDosing of 4 mg/kg/QOW, Study UX003-CL301

	AUC _{0-t} (µg*h/mL)	C _{max} (µg/mL)
Mean	57.4	20.0
SD	23.9	8.1
Min	18.8	6.6
Max	97.0	34.9

Distribution

After repeated dosing of 4 mg/kg every other week in MPS VII patients in Study UX003-CL301, the mean \pm standard deviation of the total volume of distribution (Vss) was 0.26 \pm 0.13 L/kg (range: 0.10 to 0.60 L/kg).

Elimination

After repeated dosing of 4 mg/kg every other week in MPS VII patients in Study UX003-CL301, the mean \pm standard deviation of the total clearance (CL) was 0.079 \pm 0.045 L/h/kg (range: 0.038 to 0.20 L/h/kg); the mean \pm standard deviation of the elimination half-life (t1/2) was 2.6 \pm 0.6 hours (range: 0.9 to 3.6 hours).

Dose proportionality and time dependencies

Dose proportionality

Pharmacokinetic parameters following repeat vestronidase alfa administration in study UX003-CL201 are presented in **Table 7**. **Table 7.** Pharmacokinetic variables (n=3) following infusion of vestronidase alfa at a dose of 1, 2and 4 mg/kg/QOW (study UX003-CL201)

week	dose	C _{max}	AUCt	AUCinf	CL	t _{1/2}	Vdss
		(µg∕ml)	(µg.h/ml)	(µg.h/ml)	(l/h/kg)	(h)	(l/kg)
0	2	2.2 ± 0.6	8.2 ± 2.1	8.2 ± 2.1	0.25 ± 0.06	1.5 ± 0.07	0.75 ± 0.30
12	2	3.6 ± 1.5	11.3 ± 5.4	12.6 ± 6.0	0.18 ± 0.08	1.6 ± 0.23	0.52 ± 0.29
20	1	2.3 ± 1.1	7.1 ± 2.6	7.6 ± 2.8	0.15 ± 0.07	1.4 ± 0.08	0.31 ± 0.10
28	4	13.3 ± 4.1	41.3 ± 12.7	44.0 ± 12.5	0.10 ± 0.03	1.3 ± 0.26	0.19 ± 0.07
36	2	4.8 ± 0.3	14.5 ± 3.2	16.0 ± 3.8	0.13 ± 0.03	1.5 ± 0.68	0.23 ± 0.04
84*	4	8.2 ± 2.1	28.9 ± 1.3	30.5 ± 1.6	0.13 ± 0.01	1.9 ± 0.36	0.38 ± 0.04

*n=2

Time dependency

The mean post-treatment vestronidase alfa serum concentration-time profiles by visit for subjects in Studies UX003-CL201 and CL301 are shown in **Figure 6**.

Figure 6. Mean vestronidase alfa serum concentration versus time post-treatment by visit- Study UX003-CL201 (left panel) and UX003-CL301 (right panel)



Special populations

Paediatric population

In the ongoing open-label Phase 2 study UX003-CL203, MPS VII patients of less than 5 years old, received 4 mg/kg vestronidase alfa by slow infusion (4h). Due to the young age of the study participants, the blood sampling scheme for this study only included 2 samples to be taken postend of infusion, and thus only Cmax, tmax and AUCO-t are reported. Pharmacokinetics were evaluated at week 0 and 24 and the results are shown in **Table 8**.

	subject	week	Dose	C _{max} (µg∕ml)	AUCt (µg.h∕ml)
	А	0	4	5.5	16.7
	В	0	4	25.0	84.4
	С	0	4	4.9	22.5
	D	0	4	6.6	21.9
m	ean		10	.5 ± 9.7	36.4 ± 21.1
	А	24	4	7.1	33.8
	В	24	4	35.7	153
	С	24	4	11.6	43.2
_	mean			18.1 ± 15.4	76.5 ± 66.0

Table 8. Individual and vestronidase alfa pharmacokinetic parameters after 4 mg/kg QOW dosing at week 0 and 24 in pediatric patients aged < 5 years of age (study UX003-CL203)</th>

Impaired renal function

No data were submitted regarding evaluation of vestronidase alfa pharmacokinetics in patients with impaired renal function.

Impaired hepatic function

No data were submitted regarding evaluation of vestronidase alfa pharmacokinetics in patients with impaired hepatic function.

Gender and race

Potential covariate effects of subject demographics on vestronidase alfa pharmacokinetics were assessed by pooling all available results from the studies. The potential effect on vestronidase alfa pharmacokinetics from the categorical covariates sex and race are shown in the box plots in **Figures 7** and **8** respectively.



Figure 7. Relationship of vestronidase alfa (UX003) pharmacokinetics (CI and Vss) vs. sex

Note: 0=male, 1=female; number of subjects in brackets.

Race

Figure 8. Relationship of vestronidase alfa (UX003) pharmacokinetics (CI and Vss) vs. race



Note: number of subjects in brackets.

Age and body weight

Potential covariate effects of subject demographics on vestronidase alfa pharmacokinetics were assessed by pooling all available results from the studies. The two primary and independent parameters, clearance (CI) and distribution volume (Vss) were available from study UX003-CL201 and study UX003-CL301.

The relationship of vestronidase alfa body weight normalized CL and Vss at steady-state following multiple dosing versus subjects' age and body-weight are shown in **Figures 9** and **10** respectively.

Figure 9. Relationship of vestronidase alfa (UX003) steady-state body-weight-normalized CI and Vss vs. subjects' body-weight







The allometric relationship between vestronidase alfa pharmacokinetics and body weight was further explored by performing a linear regression of whole-body CI and Vss versus body weight

after logarithmic transformation of values (data not shown). The allometric scalars for vestronidase alfa clearance and volume were estimated to be 0.33 (90% CI: 0.094 - 0.57) and 0.36 (90% CI: 0.078 - 0.64), respectively.

Pharmacokinetic interaction studies

No pharmacokinetic drug interaction studies were submitted, as the applicant considered that the product as an enzyme replacement therapy would not interact with other drugs.

Antibodies

In **Study UX003-CL301**, 5 of the 12 subjects in the study had no or negligible titers (\leq 1:40). In six subjects, the formation of antibodies was treatment emergent (no pre-existing ADA) and one subject had pre-existing background antibodies. Of the seven ADA positive subjects, two had low to moderate ADA titer (<1:5,000) and five had moderate titers (>1:5,000). Subjects tested ADA positive after 8 to 16 weeks of treatment with vestronidase alfa and their titers peaked between 8 and 40 weeks of treatment.

Neutralizing activity (NAb) was detected in five of the ADA positive subjects in the *in vitro* cellbased assay at one or more time points. A comparison of vestronidase alfa clearance and disposition subjects who tested positive for neutralizing anti-UX003 antibody (NAb) at any time point in the treatment course, and those who tested negative for Nab is shown in **Figure 11**.

Figure 11. Box plots comparing clearance (CI) and disposition half-life (t1/2) in subjects tested positive or negative for neutralizing anti-drug antibody



In **Study UX003-CL201**, the two subjects developed anti-rhGUS antibodies and were treatment emergent (no pre-existing ADAs) and there was no pattern of dose-dependency.

One subject developed ADAs following 8 weeks of treatment and the peak titer (1:10,240) was reached at week 60. The ADA titer reduced to 1:40 at the last two assessed time points, weeks 96 and 108. Neutralizing antibody activity was only detected at a single time point (week 72) when the subject was receiving 2 mg/kg vestronidase alfa QOW.

The other subject developed ADAs following approximately 22 weeks of treatment with the highest titer reached (1:5,120) at the week 36 and 60 time points. ADA titer was reduced to 1:80 at the last assessed time point, week 120. No neutralizing antibody activity was detected for this subject.

There was no correlation between the percent change in uGAG and ADA titer with either subject (data not shown).

One subject included in the study did not have a confirmed positive titer at any assessment.

In **Study UX003-CL203**, antibodies specific for rhGUS were detected in 2 of the 4 subjects. The anti-rhGUS antibodies were negative in the neutralizing activity assay for all subjects and at all time points tested.

2.4.3. Pharmacodynamics

Mechanism of action

Vestronidase alfa is a recombinant form of human GUS and is intended to provide exogenous betaglucuronidase for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to cell surface receptors, leading to cellular internalization of the enzyme, targeting to lysosomes and subsequent catabolism of accumulated GAGs in affected tissues.

Primary and Secondary pharmacology

A summary of the effect of vestronidase alfa treatment on uGAG (DS) levels across the 3 clinical studies is presented in **Table 9**.

Table 9. Percent Change from Baseline in uGAG DS Excretion across All Vestronidase alfa Studies

UX003-CL301 Week 24 (N=12) LS Mean (SE)	UX003-CL201 Week 30 (N=3) Mean (SD)	UX003-CL203 Week 12 (N=4) Mean (SD)
-64.82% (2.468)	-63.49 (6.889)	-68.95% (20.937)
p <0.0001 ^a	NA	NA

^a P-value is from Generalized Estimating Equation (GEE) model including baseline value, and the post vestronidase alfa Treatment Week as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

Figure 12 illustrates the pattern of long-term reduction in both CS and DS in Study UX003-CL301.





Percent change from baseline in uGAG DS (A) and CS (B) excretion by vestronidase alfa Treatment Week (by LC-MS/MS, GEE)

Relationship between plasma concentration and effect Dose response

In study UX003-CL201, dose levels of 1 mg/kg, 2 mg/kg, and 4 mg/kg QOW were evaluated. Vestronidase alfa serum exposures increased with increasing doses, and exceeded the concentrations required for tissue uptake starting from 1 mg/kg QOW and considered to have reached the point of saturation at 4 mg/kg QOW with observed mean Cmax and time-averaged concentrations of vestronidase alfa at many-fold of Kuptake. The vestronidase alfa PD biomarker, the change in uGAG dermantan sulfate (UGAG DS), showed rapid, sustained and apparently dose-dependent reduction from baseline (**Figure 13**).

Figure 13. Mean percent change in uGAG DS excretion at the end of each dosing interval (study UX003-CL201)



Note: The end of each dosing interval corresponds to the first visit when a dose level change occurred: Weeks 14, 22, 30 and 38.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Vestronidase alfa (UX003) is a recombinant form of the human enzyme beta-glucuronidase and is to be administered once every 2 weeks at a dose of 4 mg/kg. After repeated dosing of 4 mg/kg every other week, the maximal serum concentration (Cmax) was $20.0 \pm 8.1 \mu g/mL$.

In MPS VII patients, after end of infusion, vestronidase alfa serum concentrations fell rapidly, followed by a mean elimination half-life of about was 2.6 ± 0.6 hours (range: 0.9 to 3.6 hours).

Clearance was 0.079 \pm 0.045 l/h/kg. Decrease in clearance after multiple dosing is expected to be the result of saturation of uptake into lysosomes and elimination. The lack of specific excretion studies to investigate the elimination of vestronidase alfa was considered acceptable as it is a protein which is expected to be degraded similarly as the endogenous enzyme to smaller proteins and amino acids.

The mean vestronidase alfa Vss in patients receiving 4 mg/kg/qow ranged from 0.03 - 0.19 l/kg, indicating that vestronidase alfa is not distributed beyond the plasma and extracellular water volumes. Plasma protein binding studies were considered not applicable for vestronidase alfa, as it is a protein and not expected to significantly interact with plasma proteins.

Descriptive pharmacokinetic data from doses of 1, 2, and 4 mg/kg/qow in a limited number of patients indicate a more or less dose proportional pharmacokinetics at steady state. Interindividual variability in clearance was about 20 - 35%.

Vestronidase alfa showed time independent pharmacokinetics.

After multiple dosing, no effect of gender and race on the clearance and Vdss of vestronidase alfa was observed. Limited data suggest that vestronidase alfa serum clearance decrease less than proportionally with decreasing body weight, but the serum levels of vestronidase alfa are still well above the saturation levels of the estimated Kuptake value of 0.3 μ g/ml, and therefore there is no expected impact in the younger age group.

No data were submitted regarding evaluation of pharmacokinetics in patients with renal or hepatic impairment. This was considered acceptable considering that vestronidase alfa is a protein and therefore no clinically relevant effect of renal or hepatic impairment is expected.

Across the 3 clinical studies, approximately half of the subjects developed ADAs on vestronidase alfa therapy, approximately half of whom further developed NAb at some time points, but not consistently over time. Antibody titers were generally low to moderate and not associated with an impact on the levels of uGAG.

Pharmacokinetic drug interaction studies were not performed for vestronidase alfa. Vestronidase alfa is a protein and pharmacokinetic interactions with co-administered drugs subject to cytochrome P450-dependent metabolism are unlikely to occur.

Pharmacodynamics

All 19 treated subjects in the studies with evaluable PD data achieved at least a 50% sustained reduction in uGAG with continuous administration of vestronidase alfa at the proposed commercial dose of 4 mg/kg QOW. This reduction was achieved regardless of disease severity or baseline uGAG. Maintenance of uGAG reduction is dependent on ongoing rhGUS treatment effect and is not a result of prior depletion of uGAG stores.

2.4.5. Conclusions on clinical pharmacology

The available pharmacokinetic data even though limited are considered sufficient, given the type of product and limited use of the pharmacokinetics of this product to predict efficacy and safety.

A sustained pharmacodynamic effect of vestronidase alfa in reducing baseline uGAG in MPS VII patients has been demonstrated.

2.5. Clinical efficacy

2.5.1. Dose response study

Study UX003-CL201: An Open-Label Phase 1/2 Study to Assess the Safety, Efficacy and Dose of vestronidase alfa rhGUS Enzyme Replacement Therapy in Patients with MPS VII

The study design is depicted in **Table 10**.

Table 10. Study UX003-CL201 design

				_		Long-term Extension
	First Phase					Phase
	Initial					Long-term
	Treatment				Continuation	Extension
	Period (14	Forced-d	ose Titratio	on Period	Period (up to	Period (up to
	weeks ^{a,b})	(24 weeks ^b) 36 w		36 weeks ^b)	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

^a The Initial Treatment Period was referred to as a 12-week period in the protocol though exposure to vestronidase alfa 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 through Week 12; therefore, duration of treatment is 14 weeks).

^c Dosing was IV QOW throughout the study.

Five (5) subjects were planned and 3 were ultimately enrolled in this study due to limited patient availability.

Inclusion criteria included: Confirmed diagnosis of MPS VII based on leukocyte or fibroblast glucuronidase enzyme assay or genetic testing confirming diagnosis; elevated uGAG excretion at a minimum of 2-fold over the mean normal for age.

Exclusion criteria included: Subjects who had undergone a successful bone marrow or stem cell transplant or had any degree of detectable chimaerism with donor cells; any known hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, placed the subject at increased risk for adverse effects.

The primary efficacy variable was total uGAG excretion normalized to urinary creatinine concentration. The secondary efficacy variables included 6MWT, 3MSCT, pulmonary function testing (spirometry) (FVC, FEV1, and MVV), PGI-C scale, visual acuity, hepatosplenomegaly, and cardiac ventricular mass (echocardiogram).

Five major protocol deviations were reported in the study. Three were reported under "Treatment Compliance", and one each was categorized as "Other" or "Procedure Not Done". All major protocol deviations were reported after the forced-titration period of the study.

MPS VII was diagnosed based on enzyme activity level in leukocytes for all 3 subjects; genetic testing was not performed. Other than symptomatic care, no subject had been treated for MPS VII prior to the study and no subject had a family history of MPS VII.

All three subjects had manifestations of MPS VII in their medical history. Prior medications reported were limited.

Outcomes and estimation

There was a rapid reduction in uGAG excretion (DS and CS) in all three subjects after treatment initiation at 2 mg/kg QOW. Dose-responsive changes in DS and CS were observed during the Forced-dose titration Period with mean of 42.18% reduction in DS at 1 mg/kg QOW, 61.76% reduction at 4 mg/kg QOW, and 52.4% reduction at 2 mg/kg QOW. The mean CS excretion was reduced by 47.7% at 1 mg/kg QOW, 58.97% reduction at 4 mg/kg QOW, and 54.76% reduction at 2 mg/kg QOW.

The changes in levels of DC excretion per subject over time are presented in Figure 14.

Figure 14. Percent Change in uGAG DS Excretion From Week 0 (Baseline) to Week 120 by Subject, Study UX003-CL201



DS = dermatan sulphate; Note: One Subject (shown in orange diamond) completed dosing through Week 118 with an incomplete dose at Week 86 (2.5% completion) and with missed doses at Weeks 88, 90, and 92. The 2nd Subject (shown in grey circle) completed dosing through Week 132 with missed doses at Weeks 74, 96, 118, and 122. The 3rd Subject (shown in light pink square) completed dosing through Week 124 with missed doses at Weeks 112 and 116.

Secondary endpoints

Six minute walking test

One subject walked 285 m (35.9% predicted based on age and sex) at baseline. Variable results and several missed assessments were seen between Weeks 6 and 96. An improvement of 105 m from baseline was reported at Week 120 (distance walked = 390 m; 49.6% predicted)but this was likely due to additional medicial procedure performed over the same time.

Pulmonary Function

At baseline and throughout the study, only one subject was able to complete pulmonary function testing, showing an improved pulmonary function on vestronidase alfa treatment with 21% increase in FVC and 36% increase in MVV from baseline to Week 120. There was no appreciable change in FEV. The other two subjects were not able to follow testing instructions due to age and cognitive impairment.

Other secondary endpoints

A reduction in liver size to normal was seen in the two subjects with baseline hepatomegaly. Modest improvement was seen in fine motor function on the BOT-2 assessment for one subject. Two subjects reported improvement on the MPS HAQ Self-care and Mobility composites, and the majority of domains. Improvement in the Caregiver Assistance score was also reported for these two subjects.

All three subjects were reported to have more endurance/less fatigue on the PGI-C.

2.5.2. Main study

Pivotal Study UX003-CL301: A Multicentre, Randomized, Placebo-controlled, Blind-Start, Singlecrossover Phase 3 Study.

Methods

Figure 15 provides a schematic of the overall study design.

Figure 15. UX003-CL301 Study Schema



Study Participants

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, including at least one of the following: enlarged liver and spleen, joint limitations, airway obstruction or pulmonary problems, limitation of mobility while still ambulatory;
- Aged 5 to 35 years, inclusive;
- Willing and able to provide written informed consent, or in the case of subjects under the age of 18 (or 16 years, depending on the region), provide written assent (if required) and written informed consent by a legally authorized representative after the nature of the study has been explained, and prior to any research-related procedures;
- Sexually active subjects must have been willing to use acceptable highly effective methods of contraception while participating in the study and for 30 days following the last dose;

- Females of childbearing potential must have had a negative pregnancy test at Screening and be willing to have had additional pregnancy tests during the study. Females considered not of childbearing potential included those who had not experienced menarche, or had had tubal ligation at least 1 year prior to Screening, or who had had total hysterectomy;
- Naïve to treatment with UX003.

Exclusion criteria:

- 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 that may not have allowed safe participation in the study;
- Presence or history of any hypersensitivity to rhGUS or its excipients that, in the judgment of the Investigator, placed the subject at increased risk for adverse effects;
- Pregnant or breastfeeding at Screening or planning to become pregnant (self or partner) at any time during the study;
- Use of any investigational product (drug or device or combination) within 30 days prior to Screening, or requirement for any investigational agent prior to completion of all scheduled study assessments;
- Presence of a condition of such severity and acuity that, in the opinion of the Investigator, warranted immediate surgical intervention or other treatment or may not have allowed safe participation in the study;
- Concurrent disease or condition, or laboratory abnormality that, in the view of the Investigator, placed the subject at high risk of poor treatment compliance or of not completing the study, or would have interfered with study participation or introduced additional safety concerns.

Treatments

Subjects were dosed QOW for 48 weeks (dosed through Week 46). All groups received a minimum of 24 weeks of treatment with 4 mg/kg vestronidase alfa QOW. Group assignments were coded and blinded to the Sponsor, Investigators, observers, and subjects.

- **Group A** received 4 mg/kg vestronidase alfa QOW from Week 0 through Week 48 (dosed through Week 46)
- **Group B** received placebo QOW for the first 8 weeks (dosed through Week 6) followed by 4 mg/kg vestronidase alfa QOW from Week 8 through Week 48 (dosed through Week 46)
- Group C received placebo QOW for the first 16 weeks (dosed through Week 14) followed by 4 mg/kg vestronidase alfa QOW from Week 16 through Week 48 (dosed through Week 46)
- Group D received placebo QOW for the first 24 weeks (dosed through Week 22) followed by 4 mg/kg vestronidase alfa QOW from Week 24 through Week 48 (dosed through Week 46)

Objectives

The primary objectives of the study were to evaluate the following:

• Efficacy of vestronidase alfa in MPS VII subjects as determined by the percent reduction of uGAG excretion after 24 weeks of treatment relative to the pre-treatment baseline.

Secondary objectives of the study were to evaluate:

- Safety and tolerability following up to 48 weeks of vestronidase alfa exposure
- Efficacy of vestronidase alfa in MPS VII subjects as measured by a multi-domain clinical responder index following 24 weeks of vestronidase alfa exposure
- Efficacy following 24 weeks of treatment as determined by the proportion of subjects achieving a positive individualized clinical response (ICR) outcome
- Clinical effects including pulmonary function, walking distance, shoulder flexion, fine motor function, and gross motor function following 24 weeks of vestronidase alfa exposure

Other objectives of the study were to evaluate the following changes after 24 weeks of treatment from the last measurement before crossover:

- Measures of lysosomal storage including GAG substrate serum levels and hepatosplenomegaly
- Measures of other clinical and functional outcomes
- Physician and subject or parent/caregiver global assessment of change and impact on activities of daily living
- Pharmacokinetic (PK) parameters

Outcomes/endpoints

The primary efficacy analysis tested the mean percent change in uGAG DS excretion over 24 weeks of treatment for significant reduction from the pre-treatment baseline (defined as the average of all assessments prior to beginning UX003 treatment).

This primary assessment was supported by multiple secondary and tertiary variables. This included a novel MDRI which was intended to capture the aggregate benefit or decline across multiple domains of clinical function: 6MWT, FVC, shoulder range of motion, visual acuity, and BOT-2 fine motor and gross motor function.

For each MDRI domain, a minimally important difference (MID) was established based on data for other related diseases (**Table 11**). To compute the MDRI, changes over time (e.g. from before treatment to 24 weeks after treatment) in each domain variable were scored based on the MID. An improvement or decline equal to or greater than the MID was scored either a +1 or -1 respectively, and a change less than the MID was scored as a zero. The integration of benefit occurred by summing the responses, positive, negative or zero, across all domain variables to derive the subject-specific MDRI score. If a subject was unable to reliably or safely perform a particular assessment, that domain was scored as 0 for that subject.

Table 11. Definition of the Minimal Important Difference for domains included in the UX003-CL301

 multi-domain responder analysis

Domain	Minimal Important Difference (MID)	References	
		(Redelmeier et al. 1997), (Puhan et al. 2008), (du	
6 N A) A / T	23 meter AND 10% change from	Bois et al. 2011), (Mathai et al. 2012), (Wraith et	
OIVIVVI	baseline	al. 2004), (Clarke et al. 2009), (Muenzer et al.	
		2006), (Harmatz et al. 2006), (BioMarin 2013)	
EV/C9/ prod	5% absolute change or 10% relative	(Wraith et al. 2004), (Muenzer et al. 2006),	
FVC%pred	change from baseline in FVC%pred	(BioMarin 2013)	
Shouldor flovion	20 degree change of passive shoulder	(Wraith et al. 2004), (Harmatz et al. 2006),	
	range of motion	(Clarke et al. 2009), (Okuyama et al. 2010)	
	2 lines (corrected both succe)	(Arch-Ophthalmol 1999); (Ferris et al. 1982),	
visual acuity	3 lines (corrected, both eyes)	(Reeves et al. 1993)	
POT 2 fine motor	Fine Motor Precision: change of 0.72	(Muang et al. 2000)	
BOT-2 TITLE MOLOI	Manual Dexterity: change of 1.47	(Wuang et al. 2009)	
	Balance: 0.57 Running speed and		
BUT-2 gross motor	agility:0.59	(wuang et al. 2009)	

The Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL-Multidimensional Fatigue Scale) was administered to evaluate treatment-related changes in fatigue. A change of 10 points of total score was considered an MID.

For each subject, an Individualized Clinical Response Endpoint (ICR) was determined as a single clinical measure with the highest impact on the individual subject was selected by the investigator from possible clinical endpoints based on the specific concerns of the subject, parents, and caregivers that were reported during the Clinical Problem Evaluation. The percent of patients achieving a response in their pre-specified ICR after 24 weeks of treatment with UX003 was calculated.

Sample size

Based on modelling of the Blind Start design, and given prior information on the degree of reduction, the expected sample size of 12 subjects provides an 88% chance of rejecting the hypothesis of no change from baseline in the uGAG excretion when the true mean change is equal in magnitude to the standard deviation of change.

These 12 subjects with MPS VII were planned, enrolled, and treated in the study. All enrolled subjects completed the study and were analysed.

Randomisation

Subjects were randomized in a 1:1:1:1 ratio to Groups A, B, C, or D and assigned to a treatment sequence group via an Interactive Web Randomization System (IWRS). There was no stratification.

Blinding (masking)

The study was conducted as a randomized, blind start, single crossover, placebo-controlled study. Blinded conditions were established so that neither the sponsor (with the exception of a single dedicated person who was responsible for managing study treatment assignment), nor subject, nor site personnel involved in study conduct knew the group to which the subjects were randomized.

Statistical methods

Statistical tests were 2-sided at the alpha=0.05 significance level. All p-values were presented as nominal p-values. Continuous variables were summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables were summarized by counts and by percentages of subjects in corresponding categories.

The primary analysis method applied for percent reduction ([(uGAG- Baseline uGAG)/Baseline uGAG] x100) from baseline uGAG used a general estimating equation (GEE) model (Hanley et al. 2003), at 24 weeks of treatment. In general, baseline was defined as the last assessment prior to or on the date of initiation of treatment with vestronidase alfa. For uGAG, baseline was defined as the average of all assessments prior to or on the date of initiation of treatments prior to or on the date of initiation of treatments prior to or on the date of initiation of treatment with vestronidase alfa.

The model for percent change from baseline of uGAG included baseline and the post UX003 initiation time points as a categorical variable. The covariance structure within subjects was assumed to be exchangeable.

In general, missing data was treated as missing unless otherwise specified. When a change from baseline was assessed, only subjects with a baseline and at least one post-baseline measurement were included in the analysis. Using the GEE approach to analysis, missing data were not be replaced; all available data were used and the model parameters are simultaneously estimated using all of the observed data. Descriptive summary statistics were provided where the GEE procedure could not be performed because of the limitation of available sample sizes.

GEE modelling was the primary analysis method for all repeated measures endpoints. All the key secondary endpoints are measured every 8 weeks throughout the study (week 0 to week 48). The last assessment for each patient prior to or on the date of UX003 treatment initiation will be used as baseline.

The multi-domain responder index, the main secondary endpoint was tested first at the 0.05 level. No adjustment for multiplicity was performed to the rest of the secondary endpoints due to the small size of this study.

Results

Participant flow

A total of 12 subjects were enrolled and completed the 48-week study. There were no deaths or AEs leading to treatment discontinuation and no withdrawals from study.

Recruitment

Study Start: 02 Dec 2014

Study Finish: 04 May 2016

Conduct of the study

There were ten major protocol deviations reported in the study, including two of each categorized as "procedure not done" or "treatment compliance" and the remaining six categorized as "other", including five study entry criteria waivers. These patients did not meet the inclusion criterion #2, which required elevated uGAG excretion at a minimum of 3-fold over the mean normal for age. The

rationale for granting these waivers was based on the accumulating scientific information on the accuracy of the method used during the screening phase of the study.

Back-up screening samples from the five subjects granted waivers in the UX003-CL301, were retested using the more precise LC-MS/MS method that was developed after the study had enrolled the patents (and validated for use in assessing the primary endpoint of the study) This assay confirmed all five subjects had substantially elevated uGAG DS and uGAG (CS) levels 14- to 22-fold and 10- to 27-fold over the normal range for their age, respectively, thereby confirming that the DMB assay may not be reliable for the MPS VII patient population.

Baseline data

Demographics of the trial population are presented in **Table 12**.

 Table 12. Baseline demographic characteristics in Study UX003-CL301

Demographic Parameter	0 Week Placebo/ UX003	8 Week Placebo/ UX003	16 Week Placebo/ UX003	24 Week Placebo/ UX003	Total (N=12)
Age at Informed Consent (years)					
Ν	3	3	3	3	12
Mean (SD)	13.13 (1,656)	12,50 (4.004)	20.77 (3.004)	15.23 (8.633)	15.41 (5.492)
Median	13.30	12.70	22.40	10.40	14.00
Min, Max	11.4, 14.7	8.4, 16.4	17.3, 22.6	10.1, 25.2	8.4, 25.2
Sex, n (%)					
Male	0 (0.0)	1 (33.3)	0 (0.0)	3 (100.0)	4 (33.3)
Female	3 (100.0)	2 (66.7)	3 (100.0)	0 (0.0)	8 (66.7)

All 12 subjects had abnormalities in their medical history. The SOCs that were reported in more than 50% of subjects were: Musculoskeletal and connective tissue disorders (91.7%); nervous system disorders (83.3%); cardiac disorders (75.0%); congenital, familial, and genetic disorders (75.0%); general disorders and administration site conditions (75.0%); infections and infestations (75.0%); respiratory, thoracic and mediastinal disorders (75.0%); hepatobiliary disorders (66.7%); skin and subcutaneous tissue disorders (66.7%); investigations (58.3%); surgical and medical procedures (58.3%); and gastrointestinal disorders (50.0%). Skeletal deformities were present in nearly all subjects and included kyphoscoliosis, hip and knee dysplasia, short stature, pectus carinatum, odontoid hypoplasia, cervical spinal stenosis, genu valgum, claw hand, painful gait, joint and bone pain, frequent orthopaedic surgeries and restricted mobility. Four subjects used a wheelchair or walking aid more than 50% of the time.

Notably nearly all subjects had cognitive disabilities manifesting as developmental delay, language delay and intellectual impairment which affected their abilities to complete certain clinical assessments. More than a quarter of subjects had cardiac valve disorders at Baseline: aortic valve incompetence and aortic valve sclerosis at 25% each; mitral valve incompetence (33%); and mitral valve stenosis (25%).

Because of the rarity of the disease, selection criteria for subjects able to do all the Clinical outcome assessments or meeting certain disease level targets could not be applied and essentially, all comers had to be enrolled in the study. Therefore, the subjects enrolled in the study had highly variable disease manifestations and various physical and/or cognitive limitations. As expected, there were a number of non-assessable clinical outcomes at Baseline for some subjects: 6MWT

(three subjects that could not walk); FVC (nine subjects too young or cognitively impaired to perform this complex test); BOT-2 fine motor (one subject); BOT-2 gross motor (five subjects); visual acuity (five subjects could not understand the eye chart test).

A total of eight subjects (66.7%) had a history of prior medication use. The highest reported use was in the anti-inflammatory and anti-rheumatic class of medications (such as naproxen [three subjects, 25%]). The other classes of medications were: anti-epileptics, medications for obstructive airway diseases, muscle relaxants, nasal preparations, and other respiratory system products.

Numbers analysed

The efficacy analyses were based on the full analysis set. Safety analyses were based on the safety analysis set. The full analysis set was defined as all subjects who were randomized (ITT population), and received at least 1 dose of study drug or placebo. The safety analysis set was defined as all subjects who were randomized and receive at least 1 dose of study drug or placebo. All 12 (100%) subjects who were enrolled in the study were included in both efficacy and safety analyses sets.

Outcomes and estimation

Primary Efficacy Endpoint

Overall, a rapid, marked, and sustained reduction in uGAG DS was observed at treatment week 24 (Figure 16).

Figure 16. Percent Change from Baseline in uGAG DS Excretion at vestronidase alfa Treatment Week 24 (by LC-MS/MS, GEE) in Study UX003-CL301

UX003 Treatment Week 24 Statistics	UX003 (N=12)
LS mean (SE)	-64.82 (2.468)
95% CI	-69.66, -59.98
P-value (a)	<0.0001

At Week 2, the percentage reduction LS means (SE) was -54.30% (2.813%) and statistically significant (p<0.0001). From Week 4 through Week 22, uGAG DS excretion showed a LS means percentage change from baseline of at least -60.0% (p<0.0001 at each treatment week).

Individual uGAG DS response (% change from baseline)

The individual subject uGAG DS response to vestronidase alfa treatment is displayed in as percent change from Baseline for each subject (**Figure 17**). At Baseline, the levels of uGAG DS were 27.5 (SD=7.74) fold above the upper limit of normal. At vestronidase alfa Treatment Week 24, the levels of uGAG DS were 9.95 (SD=1.69) fold above the upper limit of normal.

Figure 17. Percent Change from Baseline in uGAG DS Excretion by Visit and Subject (by LC-MS/MS) in Study UX003-CL301



Of note, during the placebo dosing period, one subject in group D was accidently dosed with active treatment instead of placebo on one occasion at study week 18 (6 weeks prior to planned first vestronidase alfa dose). The subject's uGAG levels were rapidly reduced upon active treatment (indicated by the arrow in **Figure 17**). The levels returned once resuming placebo again; after crossover to the active treatment period, uGAG levels were consistently reduced.

Additional Analyses of uGAG

uGAG Responder Analysis (LC-MS/MS-DS)

The proportion of responders i.e. subjects with \geq 50% decrease in uGAG excretion (µg/mg creatinine)) during the first 24 weeks of vestronidase alfa treatment was assessed. All 12 subjects (100%) reached at least a 50% reduction from Baseline in uGAG DS sometime during the first 24 weeks of vestronidase alfa treatment (95% CI, 0.718, 1.000)

The percentage change from Study Week 0 in uGAG DS by study week is provided in **Table 13**.

Table 13. uGAG Response (% Change from Study Week 0) per Treatment Group in Study UX003-CL301

uGAG (LC-MS/MS-DS) %Change from Week 0	Group A: Week 0 Placebo∕ vestronidase alfa (N=3)	Group B: Week 8 Placebo/ vestronidase alfa (N=3)	Group C: Week 16 Placebo/ vestronidase alfa (N=3)	Group D: Week 24 Placebo/ vestronidase alfa (N=3)			
Study Week 8							
Treatment	Vestronidase alfa	Placebo	Placebo	Placebo			
Mean (SD), %	-67 (5.9)	-8 (10.1)	6 (15.4)	-10 (9.8)			
Study Week 16							
Treatment	Vestronidase alfa	Vestronidase alfa	Placebo	Placebo			
Mean (SD), %	-65 (11.2)	-68 (3.8)	6 (4.3)	-14 (10.3)			
Study Week 24							
Treatment	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa	Placebo			
Mean (SD), %	-66 (10.5)	-69 (12.9)	-76 (2.8)	-5 (15.2)			
Study Week 32							
Treatment	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa			
Mean (SD), %	-67 (8.8)	-66 (12.0)	-72 (6.4)	-63 (6.9)			
Study Week 40							
Treatment	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa			
Mean (SD), %	-75 (0.1)	-69 (4.1)	-68 (5.4)	-68 (1.1)			
Study Week 48	Study Week 48						
Treatment	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa	Vestronidase alfa			
Mean (SD), %	-69 (8.8)	-68 (2.6)	-79 (4.8)	-61 (3.4)			

Key Secondary Efficacy Endpoints

MDRI

Treatment response as assessed by MDRI at vestronidase alfa Treatment Week 24 was positive with a mean score (\pm SD) improvement of +0.5 (\pm 0.8) domains (t-test p=0.0527. Of the 12 subjects, six had a MDRI score of +1 or more. Five subjects had a score of 0 (indicating no change), indicative of no worsening of this progressive disease (**Figure 17**). One subject with -1 MDRI score had an acute viral illness on (blinded) vestronidase alfa Treatment Week 24 visit.





📕 +1 🔲 0 🔲 -1 🗌 Missing post Baseline 🔳 Not assessable at Baseline

When any domains are missing for MDRI at vestronidase alfa Treatment Week 24, the MDRI domain at vestronidase alfa Treatment Week 32, if it exists, is used for imputation. If the MDRI domain at vestronidase alfa Treatment Week 32 is missing, then the MDRI domain at vestronidase alfa Treatment Week 32 is missing, then the MDRI domain at vestronidase alfa 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 vestronidase alfa treatment.

Not assessable at Baseline: defined as when the subjects could not perform the test at Baseline visit (prior to vestronidase alfa 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.

Week 24 was the pre-specified assessment visit for the MDRI; however, an additional analysis was performed examining subjects with clinically important changes in 1 or more domains at any time point during treatment (**Table 14**).

Table 14.	Summary of	Completer	Subjects	who Met	Pre-defined	MID by	Clinical Domain
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Clinical Parameter	MID Criteria	MID= +1 at Week 24/Completers (%)	MID= +1 Anytime /Completers (%)
6MWT	23 meter and 10% change from baseline	3/7 (42.9%)	3/7 (42.9%)
FVC	5% absolute change or 10% relative change from baseline in FVC $_{\rm \% pred}$	O§	1/2 (50%)
Shoulder Flexion	20 degree change of one shoulder range of motion	0*	1/12 (8.3%)
	Fine Motor Precision:		
Bot-2 Fine	change of 0.72 Manual Dexterity: change of 1,47	2/11 (18.2%)	3/11 (27.3%)
Bot-2 Gross	Balance: 0.57 Running speed and agility:0,59	3/6 (50%)	5/6 (83.3%)
Visual Acuity	3 lines (corrected**, both eyes)	1/7 (14.3%)	1/7 (14.3%)
Fatigue	10 points of total score	4/12 (33.3%)	9/12 (75%)

Completer is defined as being able to perform the test adequately on 2 or more different assessment visits during vestronidase alfa treatment.

When any domains are missing for MDRI at vestronidase alfa Treatment Week 24, the domain at vestronidase alfa Treatment Week 32, if exists, is used for imputation. If the domain at vestronidase alfa Treatment Week 32 is missing, then the domain at vestronidase alfa Treatment Week 16, if available, is used.

§ non-assessable at Treatment Week 24 for 11 of 12 subjects

*no clinically significant impairment observed at baseline.

**when corrected visual acuity measurements are not available, the uncorrected visual acuity measurements were used

To assess the impact of imputation, analyses were conducted which used only the observed data (**Table 15**).

	MDRI Score, n			t-tes	t	
Imputation	+2	+1	0	-1	Mean (SD)	P value
Imputed[a]	1	5	5	1	0,5 (0,80)	0,0527
Observed	1	5	6	0	0,6 (0,67)	0,0116

Table 15. Pre-specified MDRI Analyses in Study Study UX003-CL301

^a When any domains were missing for MDRI at vestronidase alfa Treatment Week 24, the domain at vestronidase alfa Treatment Week 32, if exists, was used for imputation. If the domain at vestronidase alfa Treatment Week 32 was missing, then the domain at vestronidase alfa Treatment Week 16, if available, was used.

Post-hoc Analyses of a Modified MDRI Including the Fatigue Score

The original proposal for the MDRI included fatigue as a key measure that could be assessed in a variety of MPS VII subjects, both severely and mildly affected. To evaluate the inclusion of fatigue in the MDRI as originally planned, a post-hoc analysis on a modified MDRI at vestronidase alfa Treatment Week 24 was performed **(Table 16)**.

 Table 16. Summary of Modified MDRI (Post-hoc Analysis Including Fatigue), in Study UX003

 CL301

	MDRI Score, n					t-test	
Imputation	2	1	0	-1	-2	Mean (SD)	P value
Imputed[a]	3	5	3	0	1	0,8 (1,14)	0,0433
Observed	3	5	3	1	0	0,8 (0,94)	0,0105

^a When any domains were missing for MDRI at vestronidase alfa Treatment Week 24, the domain at vestronidase alfa Treatment Week 32, if exists, was used for imputation. If the domain at vestronidase alfa Treatment Week 32 was missing, then the domain at vestronidase alfa Treatment Week 16, if available, was used.

Ancillary analyses

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17.	Summary o	f Efficacy	for trial	UX003-CL301
		· _ · · · · · · · · · · · · · · · · · ·		

Title: A Multicentre, (Pivotal Study UX003-	Randomized, Pla CL301)	cebo-controllec	I, Blind-Start, Single-crossover Phase 3 Study		
Study identifier	Pivotal Study UX003-CL301				
Design	multicentre, randomized, placebo-controlled, Blind Start, single-crossover Phase 3 study				
	Duration of main phase: 48 weeks				
	Duration of Run-in phase:		not applicable		
	Duration of Exte	ension phase:	study (UX003-CL202		
Hypothesis	Exploratory: descriptive comparison of the effect with the placebo phase of the study				
Treatments groups	Placebo group		Placebo. 0 to 24 weeks, 12 patients were randomized		
	Active treated g	group	4 mg/kg vestronidase alfa QOW 24 to 48 weeks, 12 patients were randomized>		
Endpoints and definitions	Primary endpoint	uGAG	reduction of uGAG excretion after 24 weeks compared to baseline		
	Secondary endpoint	MDRI	Multi-domain responder index the aggregate benefit or decline across multiple domains of clinical function. Six domains were planned: 6MWT, FVC, shoulder range of motion, visual acuity, and BOT-2 fine motor and gross motor function.		
	Secondary endpoint	6MWT	Change in meters in 6 minutes walking test compared to baseline		
	Secondary	FVC (%pred)	Change in percentage of the predicted FCV compared to baseline		

	Secondary endpoint Secondary endpoint Secondary endpoint Secondary endpoint Fine Motor Precision Manual Dexterity		degrees change of passive shoulder range of motion after 24 weeks treatment compared to baseline			
			Number of lines difference after 24 weeks treatment on the Snell chart			
			Change is scale after 24 weeks treatment compared to baseline Change is scale after 24 weeks treatment compared to baseline			
	Secondary endpoint	Balance	Change is scale compared to ba	after 24 weeks treatment aseline		
	Secondary endpoint	Running speed and agility	Change is scale compared to ba	after 24 weeks treatment aseline		
	Secondary endpoint	fatigue				
Database lock	04 May 2016					
Results and Analysis	-					
Analysis description	Primary Analysis					
Analysis population and time point description	other: all avail 24 weeks	other: all available results are included in the analysis 24 weeks				
Descriptive statistics and estimate	Treatment group		baseline	4 mg/kg vestronidase alfa QOW		
variability	Number of sub	ject	12**	12**		
	Change from Baseline in uGAG DS Excretion at Week 24 (mean)		N/A	-54.30%		
	SE		N/A	2.813%		
	Change from Baseline in 6MWT at Week 24 (mean)		N/A	20.8 m		
	SE		N/A	16.75		
	Change from Baseline in FVC(%pred) at Week 24		ND	ND		
	variability stat	variability statistic		N/A		
	Change from E Shoulder Flexio 24	Change from Baseline in Shoulder Flexion at Week		ND		
	variability stat	istic	N/A	N/A		
	Change from Baseline in visual acuity right eye at Week 24		N/A	0.9 lines		
	SE		N/A	0.51		
	Change from E visual acuity le Week 24	Baseline in eft eye at		1.0 lines		
	SE			0.63		

	Fine Motor Precision (scale score)	n	4.0	3.8
	SD		2.24	2.05
	Manual Dexterity score) (mean)	(scale	2.7	2.8
	SD		1.34	1.62
	Balance (scale scor (mean)	e)	2.6	3.4
	SD		2.61	3.36
	Running speed and (scale score) (mean)	agility	2.4	2.6
	SD		1.95	2.30
	Fatigue Total Score (PedsQL)		64.5	67.9
	SD		15.91	22.71
	Change from Baseline in MDRI at Week 24 (domains) (mean)		N/A	0.5
	SD		N/A	0.8
Effect estimate per	Primary endpoint	Compa	arison groups	Comparison to baseline
		Change in uGAG DS Excretion		-54.30%
		SE		2.813%
		P-value		p<0.0001
	Secondary	Comparison groups		Comparison to baseline
	enapoint	6MWT		20.8 m
		SE P-valu	A	16.75 n=0.2137
	Secondary	Comparison groups		Comparison to baseline
	endpoint	EVC		
		P-valu	le	NP
	Secondary	Comparison groups		Comparison to baseline
	endpoint	Shoulder Flexion		ND*
		P-value		ND*
	Secondary	Compa	arison groups	Comparison to baseline
	endpoint	Left Eye (uncorrected) LS		1.0 lines
		SE		0.63
		P-valu	le	p=0.1140
	Secondary	Comparison groups		Comparison to baseline
	endpoint	right Eye (uncorrected)		0.9 lines
		SE		0.51
		P-valu	le	p= 0.0906
	Secondary	Compa	arison groups	Comparison to baseline
	endpoint	Fine N	lotor Precision	-0.2
		SE		-0.23
		P-valu	e	0.3528
		1		

	Secondary	Comparison groups	Comparison to baseline		
	endpoint	Manual Dexterity	0.2		
		SE	0.21		
		P-value	0.4094		
	Secondary	Comparison groups	Comparison to baseline		
	enapoint	Balance	0.8		
		SE	0.46		
		P-value	0.0883		
	Secondary	Comparison groups	Comparison to baseline		
	endpoint	Running speed and agility	0.2		
		SE	0.12		
		P-value	0.1020		
	Secondary endpoint	Comparison groups	Comparison to baseline		
		Fatigue Total Score (PedsQL) (mean)	3.4		
		SE	2.64		
		P-value	0.1953		
	Secondary	Comparison groups	Comparison to baseline		
	enapoint	MDRI (domains)	0.5		
		SD	0.8		
		P-value	p=0.0527		
Notes	For the uGAG a comparison with the placebo phase was submitted further supporting the statistical significance of the difference.				
Analysis description	Other, analysis was performed compared to baseline.				

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Supportive studies

Study UX003-CL203

UX003-CL203 is an ongoing open-label, Multicentre, Phase 2 study to assess the safety and efficacy of vestronidase alfa in paediatric MPS VII subjects. The results from an interim analysis are presented (13 July 2017 data cut off).

The pre-specified primary endpoint was the mean percent change in uGAG excretion from baseline at Week 48. Available data for the primary efficacy variable are presented as the percent change in uGAG excretion from baseline by subject and time point.

Figure 18. Urinary GAG (Dermatan sulphate) Percent Change in Baseline by Subject (LC-MS/MS-DS) in Study UX003-CL203



2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Overall the population studied encompasses 23 patients with 12 included in the pivotal phase 3 study (UX003-CL301). All 12 patients enrolled in the pivotal study had comorbidities and complications in their medical history, as would be expected in this chronic multi-systemic progressive disease. Nearly all patients included in the various studies had cognitive disabilities manifesting as developmental delay, language delay and intellectual impairment.

Supportive data are provided by the dose finding study (UX003-CL201) and Study UX003-CL203, an ongoing open-label study of vestronidase alfa in paediatric MPSVII patients less than 5 years old. To date, 8 paediatric patients have been included.

Based on the medical history adult patients appeared to be mildly affected by the disease, in contrast to some of the paediatric patients enrolled. The age of diagnosis and the age at enrolment for these patients also suggest that the disease presentation and severity within the included patient population is heterogeneous.

Notably in study UX003-CL201, 2 of 3 patients had hydrops fetalis, in study UX003-CL203 2 of 8 patients had hydrops fetalis and in study UX003-CL301 two of 12 patients had hydrops fetalis. In study CL301 these two patients were diagnosed MSPVII around age 10 years, indicating that hydrops fetalis as such is not predictable for disease severity, in line with the conclusions drawn by Montaño *et al.*, 2016.

Given the rarity of the disease the number of patients included in the clinical development programme is considered acceptable.

The pivotal study, UX003-CL301 was a multicentre, randomized, placebo-controlled, blind start, single-crossover Phase 3 study to assess the efficacy and safety of vestronidase alfa in MPS VII subjects aged 5 to 25 years. All patients from study UX003-CL301 all have been transitioned to the open-label long-term follow-up study UX003-CL202.

Subjects were randomized to one of 4 groups, each representing a different treatment sequence, and crossed over to vestronidase alfa at different predefined time points in a blinded manner. The blind start, within patient design makes efficient use of the small number of patients. The placebo-control provides a valid comparator, even if treatment with placebo was only for a limited period.

The primary endpoint was the reduction of uGAG excretion after 24 weeks compared to baseline whilst the secondary endpoint was a multi-domain responder index which aggregated the benefit or decline across multiple domains of clinical function. Six domains were planned: 6MWT, FVC, shoulder range of motion, visual acuity, and BOT-2 fine motor and gross motor function. A minimally important clinical difference (MID) was determined for these endpoints, using available information from other diseases settings. An additional domain was used post-hoc to evaluate treatment-related changes in fatigue.

The 6MWT has been used as an efficacy endpoint in all MPS pivotal clinical trials and formed the basis of approval for 4 ERTs in the EU (Wraith *et al.*, 2004, Muenzer *et al.*, 2006, Harmatz *et al.*, 2006, Hendriksz *et al.*, 2015). Of note, the inclusion criteria in those studies ensured that enrolled patients could walk a minimum distance at baseline. The applicant selected the change from baseline in 6MWT for the most recently approved MPS ERT, elosulfase alfa, for MPS IVA as a basis for establishing the MID of 23 m in Study UX003-CL301. Due to rarity of the disease, enrolment was not restricted to patients who could walk a certain distance, and also included another MID criterion of a minimum 10% improvement in 6MWT for added rigor because 23 m would be a relatively small improvement in a patient who walks well, for example over 500 meters, at baseline.

For FVC, clinically relevant improvements in pulmonary function have been reported on the basis of changes in percentage predicted FVC (FVC% pred) across a wide range of diseases. Studies measuring bronchodilator response in asymptomatic adults with chronic obstructive pulmonary disease (COPD) report improvement in percentage predicted FVC% pred in the range of 4% to 9.6% (Toren *et al.*, 2017, Tan *et al.*, 2012). In a study of patients with Duchenne's Muscular Dystrophy (DMD), a 4.1% difference in FVC% pred with idebenone compared to placebo was significant (p = 0.004).

On the basis of the consistent range of 4% to 10% reported in the literature the applicant used a 5% absolute change in FVC% pred as the MID, along with a 10% relative change from baseline because of the anticipated broad range in baseline pulmonary function in this heterogeneous population.

The MID for shoulder flexion of 20 degree change of passive shoulder range of motion (ROM) was established on the basis of clinical results from other MPS ERT clinical studies (Wraith *et al.*, 2004, Harmatz *et al.*, 2006, Clarke *et al.*, 2009).

The MID for visual acuity of 3 lines, corrected, in both eyes is consistent with literature reports of clinically significant changes in visual acuity in studies of ophthalmological treatments (Reeves *et al.*, 1993, Arch-Ophthalmol 1999). If corrected visual acuity was not obtained at baseline, changes were assessed based on the uncorrected visual acuity.

Changes in fatigue were assessed by the Pediatric Quality of Life Inventory[™] (PedsQL)-Multidimensional Fatigue Scale, which has been widely used in various paediatric patient populations including chronic debilitating illnesses. An interventional study in paediatric cancer patients reported a significant change from baseline in fatigue total score of 9.2 after 1 year (Keats *et al.*, 2008). Due to the lack of available data in MPS VII, the applicant defined a change from baseline of 10 in fatigue total score as the MID in Study UX003-CL301.

Considering the rarity and heterogeneity of the disease the CHMP considered the selection of endpoints and the MIDs as determined by the applicant acceptable to evaluate the efficacy of vestronidase alfa as an enzyme replacement therapy in MPS VII. Moreover, the CHMP also considered that use of the MDRI was appropriate as it could have been expected that not all subjects would be able to perform all tests and thus using a responder analysis could potentially capture measurable meaningful responses to treatment within the short duration of a clinical trial.

However, the CHMP noted that evaluation of the effect of treatment on fatigue in this setting is very challenging and therefore the clinical relevance of the reported changes in fatigue is very difficult to interpret (see also Additional Expert Consultation).

Efficacy data and additional analyses

In the dose finding study (UX003-CL201) a total of three subjects were enrolled. For dermatan sulfate (DS), the mean reduction from baseline for the 3 subjects was 61.76% at the highest dose of 4 mg/kg QOW, compared with a 42.18% and 52.40% reduction at the 1 and 2 mg/kg QOW doses, respectively. These data support the results of the pre-clinical studies and the choice of the 4mg/kg QOW dosing regimen.

In the pivotal study, at baseline, the levels of uGAG DS were 27.5 (SD=7.74) fold above the upper limit of normal. At Week 24, the levels of uGAG DS were 9.95 (SD=1.69) fold above the upper limit of normal. This clear and consistent (over all patients) effect demonstrates the pharmacological action of vestronidase alfa. Additional analysis (uGAG Responder Analysis and Parallel Group Analysis of uGAG Reduction) support this conclusion.

The mean (\pm SE) improvement of the 6MWT was 20.8 \pm 16.75 m (p=0.2137). The patient population as a whole did not reach the MID of 23 meters. Further analysis showed that of the 6 patients with available 6MWT results, 4 showed an improvement over the defined MID with 2 patients reporting a stabilisation of the 6MWT after 72⁺ weeks of treatment in study UX003-CL202.

For FVC_{%pred} only information on 2 patients was available. No conclusions can be drawn for the respiratory endpoint.

Shoulder flexion showed little to no change (at 24 weeks mean reduction in flexibility was -6.5 (4.86) degrees) because most subjects had no appreciable joint restriction at baseline and all subjects had at least 110 degrees of mobility. This is in contrast to other MPS disorders in which limited range of motion is a frequent clinical problem. In the MPS I Phase 3 study without selection for joint disease, about half the subjects had < 90 degrees of shoulder flexion at baseline versus normal 160 degrees and only those with < 90 degrees contributed to the demonstration of efficacy in reducing joint stiffness/mobility (Wraith *et al.*, 2004).

Four subjects showed at least a 2 line improvement on the Snellen eye chart in one or both eyes. Only one patient reached the MID (applicant defined) of 3 lines. One patient reported a deterioration of 2 lines. No clear and consistent clinical relevant change can be observed.

For the BOT-2 related analysis each scale score showed a minimal mean change from baseline. No clear and consistent clinical relevant change can be observed.

A nominal increment of the Fatigue Total Score is seen for a number of patients. Given the difficulties in assessing fatigue especially in a condition like MPS VII, the clinical significance of these results remains unclear.

Based on the defined MID of the 12 subjects, six had a multi-domain responder index (MDRI) score of +1 or more. Five subjects had a score of zero (indicating no change). One subject had a score of -1 at the Week 24 visit. As about 32% of the results are missing any analysis is seriously hampered, described in more detail below. The results suggest that patients in general experience an increased stiffness of the shoulders. For the other endpoints no consisted beneficial or detrimental effect can be observed. Further no patient can be identified with beneficial effects on all evaluated domains.

The interpretation of the MDRI responder analysis is very complicated, due to the combination of the limited information on the natural course of the disease, the within patient variation during the

placebo period, the heterogeneity of effect between the patients, and the large number of missing values (23 out of 72 assessments could not be evaluated) and the imputation method used. If any domains were missing at treatment week 24 the value of week 32 – if existing – was used. If this measurement was also missing the value at week 16 was used. The fact that patients missed the moment of evaluation could lead to a selection of more positive measurements, due to the fact that the patient was unable to perform the measurement at the moment when the visit was missed.

In addition, the protocol describes that "If a subject is unable to reliably or safely perform a particular assessment, that domain will be scored as 0 for that subject", assuming no deterioration for this subject over time. This seems to be done for 3 patients (when the subject had a baseline measurement, but the 24 weeks post baseline value was not available and could not be imputed). Given the progressive nature of the disease it is unclear whether no change is the best assumption for patients that are unable to perform the measurement. However, with this small total number of patients, actual results are sensitive to this alternative (more conservative) imputation across 25% of the patients.

In addition, the 6 domains of the MDRI show considerable variation over time, also within the placebo period of one patient, so this variation cannot be attributable to any treatment effect. In contrast to a parallel clinical trial, the blind-start crossover design does not allow for a comparison with placebo over the full duration of the trial. The general pattern shows variability between and within patients, with the overall average pattern stable over time (fine motor skills (BOT-2 fine), visual acuity, and 6MWT). In most cases this average stability includes the placebo period; there are some patients that did show more clear improvement compared to their own placebo pattern (e.g., 2 patients in 6MWT, 1 (out of 5) in BOT-2 Gross motor). FVC and shoulder flexion data are considered not relevant; hence these are not discussed by here.

Overall, the data suggest that patients remained stable throughout 48 weeks treatment. Due to the open label setting and the limited number of patients no firm conclusions can be drawn.

The positive individualized clinical response (ICR) was defined as the single clinical measure with the highest impact on the individual subject as chosen by the subject. In this group of 12 patients 6MWT was chosen as ICR by 7 patients, 4 chose fatigue and 1 patient chose the BOT-2 fine score. Of the 7 patients choosing the 6MWT, 3 reported an improvement over the applicant's defined MID, none of the 7 patients reported deterioration. Of the patients with fatigue chosen as ICR, 1 deteriorated and the remaining 3 did not report any change. The patients with the BOT-2 fine score as ICR did not report a clinical relevant effect.

Based on the evaluated clinical endpoints in the clinical studies with vestronidase alfa, it can be concluded - that in most patients (11/12) in the pivotal study a positive trend towards improvement of part of the disease symptoms or at least stabilisation can be observed. Both stabilisation and improvement of disease symptoms are to be considered beneficial for the patient. The clinical relevance of these effects remains to be established.

In the adult patients the treatment effect may not be as obvious as observed in paediatric patients. Adult patients may have built up more irreversible damage (i.e. skeletal problems) which may hamper demonstrating a clear beneficial effect, on the other hand the adult patients may have milder disease problems, and thus less improvement is to be gained. Similar for paediatric patients for instance growth, and increased in lung capacity, may impact the observed results as well.

To make the physicians (and patient/caretaker) more aware, the applicant included an additional warning in SmPC section 4.4 to reflect that the administration of vestronidase alfa does not affect the irreversible complications (such as skeletal deformities).

Further due to the fact that not all patients respond with a clinical relevant improvement the applicant included a warning in SmPC section 4.4 stating that "the effects of treatment with

vestronidase alfa should be periodically evaluated and discontinuation of treatment should be considered in cases where clear benefits (including stabilisation of disease manifestations) are not observed."

The CHMP considering the totality of the data and the comments raised by the Ad-Hoc Expert Advisory Group concluded that the population that could be treated with vestronidase alfa should include patients of all ages. The CHMP noted that available data indicate that patients most likely to benefit the most are younger patients. Therefore, it is important that treatment is initiated as early as possible in patients in order to prevent damage from prolonged accumulation of polysaccharides in the various tissues.

Additional expert consultation

An Ad-Hoc Expert Advisory Group was asked to provide their view on the following issues:

Question 1

How do you judge the clinical relevance of the observed effects of vestronidase alfa on the pharmacodynamic and functional outcomes in patients with MPS VII?

The expert group highlighted the difficulties in ascertaining the clinical relevance of the observed effects with vestronidase alfa, given that the natural history of the diseases is not well characterised. In light of this as well as the slowly progressive course of the disease, the duration of the submitted trials limits the possibility to observe the effect of treatment on clinical outcomes.

The group however acknowledged the difficulties in investigating this condition given the rarity of the disease, the wide range of clinical symptoms and the variability in disease severity. In addition, the Group noted that a number of patients included in the trials were not able to perform some of the required tests to evaluate functional outcomes which further restricts the ability to evaluate clinical relevance of the treatment effect.

The group agreed that the submitted results demonstrate a clear pharmacodynamic effect (reduction in urinary accumulation of substrate (GAGs) in patients who had received vestronidase alfa. For an enzyme replacement therapy such an effect would be a prerequisite even though not sufficient on its own to confirm a clinical benefit. Given the difficulties in evaluating this condition, the group considered that it would be difficult to expect at this stage any additional data to provide further evidence of a positive treatment effect.

The group finally highlighted that even though fatigue is a very relevant variable for many patients including those with MPS VII, interpretation of results for this symptom is very difficult in this condition due to the lack of validated tools to objectively measure the pharmacodynamic effect on fatigue.

Question 2

Can the expected clinical benefits of vestronidase alfa be extrapolated to patients with MPS VII, not included in the clinical trial programme? For instance, can the experts give their views on the role of vestronidase alfa in the most severe manifestations i.e. patients with hydrops fetalis, hepatosplenomegaly and lung aplasia, asymptomatic patients or those with very mild symptoms or late onset of disease?

The group noted that in addition to the difficulties in demonstrating a clinical relevant treatment effect in MPS VII summarised in the response to Question 1, an additional limitation was the age of patients included in study UX003-CL301 (median age: 14 years). The group considered that it would be reasonable to expect that a more pronounced clinical effect could have been observed if patients had initiated treatment earlier in life. Therefore, the group advised that it would be

important not to place an age restriction to the patients that would be eligible for treatment as this could exclude patients with a high potential to benefit from vestronidase alfa.

The group also noted that despite the lack of data on patients with hydrops faetalis, there is no reason to expect that the benefits of vestronidase alfa could not be extrapolated to these patients. The group expressed some concerns over the need to treat patients with very mild symptoms or later onset of disease. These patients may have restricted disease, such as neurological or skeletal symptoms, which are not responsive to treatment. Initiation of treatment would thus have to be carefully considered by the treating physician on the basis of potentially reversible symptoms, with appropriate stopping criteria to be defined before treatment start. Treatment solely on the basis of the presence of fatigue should not be encouraged.

Question 3

Within the different phenotypes of Sly disease, are there any patients you would expect not to benefit from vestronidase alfa treatment? Are there any disease related or prognostic factors that can be helpful to decide which patients should be treated or not treated?

As mentioned above, available data on the natural history of the disease are limited and there are no prognostic factors which could help determine which patients should be treated or excluded from treatment.

The data available from the submitted trials also do not allow for identification of patients that would not benefit from treatment, again with the restriction that neurological or skeletal symptoms cannot be reversed by treatment.

Question 4

Given the rarity of the disease and the limited data available, further information in the post-marketing setting, most likely in the form of a registry, would be important. What would be the most relevant efficacy and safety outcome data for a disease registry to further evaluate the effects of vestronidase alfa?

The expert group emphasised the need for a disease registry, which could help to collect further information in this very rare condition. The experts considered that such a registry should ideally be under the governance of physicians with experience in treating patients with MPS. In addition the experts highlighted that given the lack of knowledge in this condition it would be of great importance if data collected in this registry could be available to clinicians or academics with a research interest in MPS to enhance the understanding of the disease.

In terms of data collection, the experts considered that it would be important to collect information on all proposed domains in the studies, including height, weight and growth in children as well as neutralising antibodies, GAGs and their potential impact on clinical efficacy and safety. For the purpose of biochemical markers and antibodies, an international biobank linked to the clinical data in the registry was suggested. It would also be important to measure respiratory function and that this should include outcomes for both restrictive and obstructive lung function. The experts also noted that given the wide spread of affected system organs it would be important to capture in the registry complications of the disease such as hospitalisations and surgical interventions.

Finally, the group advised that due to the limited number of available patients, data collection in this registry should be aligned worldwide as much as possible despite the possibly different regulatory requirements in different regions.

Additional efficacy data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical efficacy of Mepsevii under normal conditions of use could not be considered comprehensive as the clinical significance of the numerical improvements observed for a number of clinical endpoints following Mepsevii treatment cannot be established. Moreover, due to the heterogeneous nature of the disease, with various physical and cognitive limitations, not all clinical outcome tests could be performed by every subject which further hinders the evaluation of the reported effects of treatment.

The CHMP noted that it is not feasible to generate a comprehensive data set due to the rarity of the disease and the variability in clinical symptoms and severity of the condition which means that there is no disease specific validated clinically relevant endpoint. Moreover, due to the slowly progressing nature of the disease it is reasonable to expect that in order to demonstrate statistically compelling effects, clinical trials of longer duration would be required. Such placebo-controlled trials are not considered feasible due to ethical considerations.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to a specific obligation, the Mucopolysaccharidosis VII Disease Monitoring Program. This is a global, prospective, multi-centre, longitudinal study which will enable to further characterise MPS VII disease presentation and progression over time in patients and evaluate the long-term effectiveness and safety of treatment with Mepsevii. Data collection from this study will also enable further characterisation of longitudinal change in biomarkers, clinical assessments, and patient/caregiver reported outcome measures, and other possible predictors of MPS VII disease progression and mortality.

2.5.4. Conclusions on the clinical efficacy

A clear pharmacodynamic effect (in urinary accumulation of glycosaminoglycans) has been demonstrated for vestronidase alfa from the data submitted in patients with MPS VII. For the clinical endpoints available, a trend of numerical improvement was seen for some of the clinical endpoints evaluated which could suggest stabilisation of the condition of the patients included in the trials. Considering that disease progression is slow, the true magnitude of the treatment effect will probably require a treatment over longer periods of time than the conducted studies.

Therefore, it was concluded that vestronidase alfa is an effective treatment option for patients with MPS VII.

However, the CHMP considered that the available data set on the clinical efficacy was not comprehensive and that the specific obligation would be necessary to generate additional efficacy data in the context of a marketing authorisation under exceptional circumstances:

• The Mucopolysaccharidosis Type VII Disease Monitoring Program, to evaluate long term effectiveness of treatment and the long-term safety profile of Mepsevii

2.6. Clinical safety

Patient exposure

A total of 23 patients are included in the safety database from the for the UX003 clinical development program comprising of four clinical studies including: two completed clinical studies, UX003-CL301 (N=12) and UX003-CL201 (N=3), and two ongoing clinical studies, UX003-CL202 (data lock point (DLP: 12 June 2017, N=10) and UX003-CL203 (DLP: 23 May 2017, N=8). All

subjects from UX003-CL202 were rolled over from UX003-CL30I, however, subjects are counted only once in the cumulative analysis.

The cumulative analysis therefore includes 23 unique subjects treated with UX003 for a duration of up to 132 weeks as of the DLP.

Adverse events

95.7% of patients experienced a treatment-emergent adverse event (TEAE) during vestronidase alfa treatment. Most reported TEAE for the combined studies were: cough (47.8%), vomiting (47.8%), upper respiratory tract infection (43.5%), infusion site extravasation (34.8%), rash (30.4%), diarrhoea (30.4%) and pyrexia (30.4%).

The most common adverse reactions from 4 clinical trials in patients treated with Mepsevii were anaphylactoid reaction (13%), urticaria (13%), infusion site swelling (13%), infusion site extravasation (8.7%), pruritus (8.7%), diarrhoea (8.7%) and rash (8.7%).

Serious adverse event/deaths/other significant events

No deaths were reported in any of the vestronidase alfa clinical studies.

Serious Adverse Events

Eight patients experienced SAEs across all clinical trials (**Table 18**). No SAE term was reported by more than 1 subject across any clinical study and no subject discontinued treatment or withdrew from the study due to an SAE.

Table 18. Incidence of Serious TEAEs for Subjects Treated with vestronidase alfa across all Clinical

 Studies by Preferred Term

Preferred Term	UX003-CL301	UX003-CL202	UX003- CL201	UX003-CL203
	(N=12) n (%)	(N=10) ^a n (%)	(N=3) n (%)	(N=8) n (%)
Adenoidal Hypertrophy	0 (0.0%)	0 (0%)	0 (0.0%)	1 (12.5%)
Anaphylactoid Reaction	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asthmatic crisis	0 (0.0%)	1 (10%)	0 (0.0%)	0 (0.0%)
Bradycardia	0 (0.0%)	0 (0%)	0 (0.0%)	1 (12.5%)
Bronchospasm	0 (0.0%)	1 (10%)	0 (0.0%)	0 (0.0%)
Cervical cord compression	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Cerebral Ventricle Dilatation	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Cervical Spinal Stenosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Craniocerebral Injury	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Device Fastener Issue	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Febrile Convulsion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
Gastrorenteritis	0 (0.0%)	1(10%)	0 (0.0%)	0 (0.0%)
Headache	0 (0%)	1 (10%)	0 (0%)	0 (0.0%)
Head Injury	0 (0.0%)	1 (10%)	0 (0.0%)	0 (0.0%)
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Incarcerated Inguinal Hernia	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Inguinal Hernia Repair	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Oedema Peripheral	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Osteoarthritis	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)
Oxygen Saturation Decreased	0 (0.0%)	0 (0%)	0 (0.0%)	1 (12.5%)
Pneumonia	0 (0.0%)		0 (0.0%)	0 (0.0%)
Spinal Column Stenosis	pinal Column Stenosis 0 (0.0%)		0 (0.0%)	1 (12.5%)
Spinal Cord Compression 0 (0.0%)		0 (0.0%)	1 (33.3%)	1 (12.5%)
Spinal Instability	Spinal Instability 0 (0.0%)		0 (0.0%)	1 (12.5%)
Urticaria	0 (0.0%)	1 (10%)	0 (0.0%)	0 (0.0%)

^a All subjects in Study UX003-CL202 rolled over from Study UX003-CL301

Most of the reported SAEs were considered related to complications of MPS VII. Four SAEs were assessed as related to UX003 and are described below:

In Study UX003-CL301, there was one SAE of anaphylactoid reaction that occurred after inadvertent bolus infusion of the enzyme during the first hour of the infusion assessed as related to UX003 by the investigator and Applicant. The event resolved and the infusion was re-initiated that day without recurrence of symptoms; the infusion was completed.

In UX003-CL202, one subject experienced SAEs of bronchospasm and urticaria during UX003 administration assessed as related to UX003 by the investigator and Applicant. Infusion was interrupted and events resolved following treatment with antihistamine (clemastine) and salbutamol.

In the UX003-CL203 study, an SAE of febrile convulsion was assessed as related to UX003 by the investigator and Applicantthat occurred three days after diphtheria, tetanus, and pertussis (DTP) vaccination. The event resolved and subject continued on treatment

Adverse Events of Hypersensitivity

There have been two reports of hypersensitivity reactions in two different subjects, both in study UX003-CL301. One subject experienced a Grade 3 treatment-related anaphylactoid reaction following a too rapid (bolus) infusion during the first hour of vestronidase alfa treatment. The event resolved and the infusion was re-initiated that day without recurrence of symptoms; the infusion was completed. The subject received subsequent infusions without recurrent symptoms and completed the study.

The second subject experienced a Grade 1 treatment-related anaphylactoid reaction during the first dose of vestronidase alfa. The subject's symptoms included temperature 37.3 °C and diaphoresis. No treatment was given and the subject resumed vestronidase alfa treatment with no further complications. Hypersensitivity reactions did not recur with subsequent infusions and the subject completed the study.

Overall, across the clinical development program, there were only two reported events of hypersensitivity (anaphylactoid reaction) in 453 infusions (0.4%, including partial infusions).

Infusion-associated Reactions

Infusion-associated reactions (IARs) were defined as AEs occurring from the onset of the study treatment infusion up to four hours following the end of infusion, regardless of the Investigator's causality assessment.

In study UX003-CL301, two out of 9 (22.2%) subjects experienced two IARs (infusion site discomfort, body temperature increased) while on placebo treatment. Eight subjects experienced ten IARs during vestronidase alfa treatment, which mostly involved problems with the IV catheter (infusion site extravasation, infusion site swelling, and peripheral swelling). The majority of IARs reported were assessed as mild to moderate in severity with one Grade 3 treatment-related anaphylactoid reaction secondary to an infusion rate error. Observed IAR symptoms included respiratory distress, fever, diaphoresis, infusion site swelling and infiltration, pruritus, and ataxia.

All 12 reported IARs resolved with 9 resulting in drug treatment interruption and 3 requiring no treatment intervention. None of the subjects discontinued study treatment or discontinued from study participation as a result of an IAR.

In the Ongoing Open-label Under 5 Years of Age Phase 2 Study UX003-CL203, one subject experienced IARs of Grade 1 abdominal pain and diarrhoea on Study Day 281, which recovered/resolved without action.

Anti-drug antibodies

Sixteen out of 23 patients (70%) from 4 clinical trials developed anti-recombinant human betaglucuronidase (rhGUS) antibodies (ADA), nine of whom further developed neutralizing antibodies (NAb) on at least one occasion, but not consistently over time.

The median CL was slightly higher for patients who tested NAb positive at anytime during Study UX003-CL301 (0.0816 and 0.0603 l/hr/kg for NAb positive and negative, respectively). The median $t_{1/2}$ was 2.48 hr for the patients who tested NAb positive at anytime during the study compared to 2.94 hr for those patients who never tested NAb positive.

No general trend or relationship was observed between vestronidase alfa CL and total antibody titre. Similarly, no general association was observed between total antibody titre and vestronidase alfa $t_{1/2}$.

In Study UX003-CL201, only one patient tested positive for neutralizing anti-drug antibody (NAb) during the study. The positive NAb was reported at Week 72, 36 weeks after the last PK data were available for this patient.

No patient tested NAb positive at any time in Study UX003-203.

Spinal/Cervical Cord Compression

Three of 23 subjects experienced events of spinal/cervical column compression in the clinical development programme. One subject developed lower extremity paresis following inguinal hernia repair, and subsequently developed quadriplegia following spinal cord decompression surgery assessed as unrelated to treatment. Two other subjects developed spinal/cervical column stenosis without severe complications assessed as unrelated to treatment but rather a complication of MPS VII.

Febrile Convulsion

One patient experienced a febrile convulsion during treatment at the week 66, within 3 days of diphtheria, tetanus, pertussis vaccination. The infusion was stopped, the patient received anticonvulsants, antipyretics and antibiotics, and the febrile convulsion resolved. The patient

subsequently was re-challenged without recurrence and continued treatment. This event was assessed as possibly related to treatment due to the temporal association with the infusion.

Laboratory findings

Haematology

No clinically significant changes were observed in haematology laboratory values in any of the clinical studies.

Chemistry

The majority of chemistry laboratory values in the clinical studies with vestronidase alfa were not considered to be clinically significant; however, two subjects were found to have abnormal liver function tests (one case of elevations in serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and Gamma-Glutamyl Transferase (GGT), and one case of elevated ALT). In both subjects, no AEs were reported in association with the elevations in liver function tests and there was no treatment interruption or medical intervention required.

Four TEAEs were reported in association with observed abnormal chemistry laboratory values (increases in ALP, ALT and GGT) in study UX003-CL203. No treatment interruptions were required for these TEAEs.

Vital Signs

No clinically significant changes were observed in vital signs in any subject exposed to vestronidase alfa.

The subject who experienced an anaphylactoid reaction secondary to an accidentally high (bolus) infusion rate became diaphoretic with perioral cyanosis and oxygen saturation dropped to 82% during the event. The event resolved and the subject received subsequent treatment without further complications.

Safety related to drug-drug interactions and other interactions

The overall potential of drug interactions for vestronidase alfa is low, and therefore no specific *in vitro* drug interaction studies were submitted.

Discontinuation due to adverse events

No subjects discontinued from study drug or withdrew due to an AE.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety database is quite limited and includes data from 23 patients. Given the rarity of MPS VII this was considered acceptable, and additional information is expected to be collected from the MPS VII Disease Monitoring Program that the applicant will establish.

Most adverse event reported (≥20% reported) were respiratory infections, cough, vomiting, infusion site extravasation, diarrhoea, pain in extremity, rash and arthralgia. The observed

treatment adverse events were mostly mild to moderate in severity. There were no deaths during the studies.

In total, 12 infusion-associated reactions (IARs were reported in the clinical studies. Ten of those were reported in eight patients in study in study UX003-CL301. In the same study, 2 of the 9 patients in the placebo group also reported IARs. Nine of the IARs resolved with drug treatment disruption. No IARs were reported in UX003-CL201, and in study UX003 CL203 one patient reported an IAR.

Two patients experienced anaphylactoid reaction (one reported as grade 3). In the patient with grade 3 anaphylactoid reaction the adverse event was thought to be related to rapid infusion in the first hour, this reversed when the treatment was interrupted and emergency medication was provided. Other related adverse reactions were pruritus, local infusion site reactions such as infusion site extravasation and infusion site swelling, diarrhoea, rash, and rash popular. None of the patients discontinued study treatment or discontinued from study participation as a result of an IAR.

The product information includes a warning on hypersensitivity reactions including anaphylaxis and that appropriate medical support should be readily available when vestronidase alfa is administered. In addition, premedication with non-sedating antihistamines with or without antipyretics to be administered 30-60 minutes prior to the start of the infusion is recommended. Finally the importance of administration according to the recommended infusion rate schedule is highlighted, and that the infusion should be stopped immediately if severe hypersensitivity reactions occur, and appropriate treatment initiated.

In the pivotal study 6 patients were positive for NAbs. Only one of these patients had two consecutive positive outcomes for NAbs (at week 40 and week 46). Three patients from the other studies also developed NAbs. Based on the available pharmacokinetic data there seems to be a minor effect of NAbs on t1/2. The clinical relevance of this observation is unknown.

Overall, the analysis of the patients with NAbs did not indicate an apparent clinical impact in the measured outcomes, the applicant is expected to follow up and submit more data on the NAb status of the patients in the Disease Monitoring Program study. Immunogenicity is included in the RMP as an important potential risk, and further information will be collected through this Disease Monitoring Program that the applicant will perform.

Spinal /cervical cord compression is one of the expected complications of MPS VII that may be observed at clinical presentation and progression. During enzyme replacement therapy, spinal cord injury can occur due to improved neck and spine mobility. Therefore, spinal /cervical cord compression has been included in the RMP as a potential risk and patients with MPS VII receiving Mepsevii should be monitored for signs and symptoms of spinal cord compression or neck instability including neck or back pain, weakness of limbs, changes in reflexes or urinary and faecal incontinence. Appropriate clinical treatment should be immediately sought.

No clinically significant changes were observed in haematology and chemistry laboratory values in any of the clinical studies.

Safety in pregnancy and lactation as well as the safety of the product in patients with hepatic or renal impairment has not been characterised, as relevant patients were not included in the submitted studies. These issues have been included in the RMP as missing information, as well as long term use and will be addressed through the planned Disease Monitoring Program.

No drug-drug interaction studies were submitted. This was considered acceptable considering that vestronidase alfa is not a substrate of cytochrome P450 (CYP) enzymes and unlikely to be involved in drug-drug interactions (DDIs) due to CYP inhibition or induction. Furthermore, vestronidase alfa

is not a cytokine or cytokine modulator, and therefore has a low potential to act as a perpetrator in DDIs by altering the expression of CYPs and/or certain transporters.

Additional expert consultations

See discussion on clinical efficacy.

Additional safety data needed in the context of a MA under exceptional circumstances

Taking into account the totality of the available data, the CHMP was of the view that the data set on the clinical safety of Mepsevii under normal conditions of use could not be considered comprehensive due to the small size of the clinical trials and the limited duration of follow-up for a life-long condition with highly variable clinical manifestations and disease progression rates.

The CHMP acknowledged that the rarity of the disease and ethical considerations prevent the conduct of bigger and longer duration controlled trials.

The CHMP was therefore of the view that a marketing authorisation under exceptional circumstances should be granted subject to the specific obligation, of implementing the Mucopolysaccharidosis Type VII Disease Monitoring Program to evaluate the long term safety profile of Mepsevii and in particular with regards to the important identified an potential risks associated with vestronidase alfa use.

2.6.2. Conclusions on the clinical safety

Despite the limited size of the safety database, due to the rarity of MPS VII, the overall safety profile of vestronidase alfa is considered acceptable. The main safety concerns identified are of infusion associated reactions, immunogenicity and Spinal/Cervical Cord Compression which are addressed adequately through appropriate routine risk minimisation measures.

The CHMP considers the specific obligation is necessary to address the missing safety data in the context of a marketing authorisation under exceptional circumstances:

• The MPS VII disease monitoring program, to evaluate to evaluate long term effectiveness of treatment and the long-term safety profile of Mepsevii

2.7. Pharmacovigilance

Risk management plan

Safety concerns

Summary of safety concerns					
Important identified risks	 Infusion associated reactions – including severe hypersensitivity reactions 				
Important potential risks	Spinal/Cervical Cord CompressionImmunogenicity				
Missing information	 Use in pregnancy and lactation Use in patients with hepatic impairment and renal impairment Long term use 				

Pharmacovigilance plan

Study/Status	Summary of objectives	Safety concerns addressed	Milestone s	Due dates		
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation						
None	None	None	None	Non		
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances						

Study/Status	Summary of objectives	Safety concerns addressed	Milestone s	Due dates
UX003-CL401 Mucopolysaccharidosis Type VII Disease Monitoring Program (MPS VII DMP) Planned	 Characterise MPS VII disease presentation and progression over time in patients treated and not treated with Mepsevii. Evaluate Mepsevii long- term efficacy in patients with MPS VII Evaluate long- term safety including hypersensitivity and immunogenicity in patients with MPS VII Prospectively investigate the longitudinal change in biomarker(s), clinical assessments, and patient/caregiver -reported outcome measures, and other possible predictors of MPS VII disease progression and mortality 	 Infusion associated reactions including severe hypersensitivity reactions Spinal/Cervical Cord Compression Immunogenicity Use in pregnancy and lactation Use in patients with hepatic impairment and renal impairment Long term safety 	Annual progress reports	• To be submitted within annual re- assessments
Category 3 - Required	additional pharmacovig	gilance activities (by th	e competent . None	authority)
None			NOLE	NUTE

Risk minimisation measures

Safety concern	Risk minimisation measures
Safety concern 1 Infusion associated reactions – including severe hypersensitivity reactions	 The below listed sections in the SmPC ensures that patients and health care providers are adequately informed and provides detailed information on infusion associated reactions. Section 4.2 Posology and method of administration Section 4.4 Special warning and precautions for use Section 4.8 Undesirable effects
Safety concern 2 Spinal/ Cervical Cord Compression	Section 4.4 (Special warnings and precautions for use) of the SmPC contains precautionary text reflecting the current knowledge concerning spinal/cervical cord compression.
Safety concern 3 Immunogenicity	Section 4.8 (Undesirable effects) of the SmPC contains text reflecting the results of anti-drug antibody development and no definitive correlation between anti-drug antibodies and urinary glycoaminoglycans (uGAGs).
Safety concern 4 Use during pregnancy and lactation	Section 4.6 (Fertility, pregnancy and lactation) of the SmPC states that it is preferable to avoid the use of Mepsevii during pregnancy, unless clearly necessary. A decision on whether to continue/discontinue with Mepsevii should be made taking into account the potential benefit of Mepsevii to the mother and breast- feeding to the infant.
Safety concern 5 Use in patients with hepatic impairment	Mepsevii is identical to the naturally occurring enzyme and is not expected to be hepatotoxic in humans. There were no reported hepatic-related adverse clinical pathology or histopathology findings in repeat dose toxicology non-clinical studies.
Safety concern 6 Use in patients with renal impairment	There were no reported kidney-related adverse clinical pathology or histopathology findings in repeat dose toxicology non-clinical studies. SmPC Section 5.2 summarizes pharmacokinetics of Mepsevii:
Safety concern 7 Long term use	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 15.11.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. New Active Substance

The applicant declared that vestronidase alfa has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers vestronidase alfa to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemption

A request of translation exemption of the vial label in accordance with the third subparagraph of Article 63(1) of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed to this request (vial label in English only) on the basis of the prevalence of the disease (i.e. less than 25 living patients have been identified in the EU to date), thus qualifying this disease as ultra-rare.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Mepsevii (vestronidase alfa) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

MPS VII, also known as Sly Syndrome, is an inherited metabolic disorder, caused by an enzyme deficiency in the processing of the GAGs dermatan sulfate (DS), heparan sulfate (HS), and chondroitin 6 sulfate (CS).

Patients with MPS VII may experience joint stiffness, short stature, an enlarged spleen and liver and heart / lung complications. MPS VII also causes a characteristic facial appearance and can lead to a progressive skeletal dysplasia. Hearing loss, cataracts and clouding of the corneas are also symptoms of patients with MPS VII. In more severe cases, there may be developmental delay. MPS VII has a high rate of neonatal non-immune hydrops fetalis, which is associated with high perinatal mortality rates.

The disease is considered progressive with most of the disease manifestations occurring as a result of accumulation of GAGs.

3.1.2. Available therapies and unmet medical need

The current treatment of MPS VII is symptomatic and supportive. Bone deformities and hernias may require orthopaedic correction. Ocular and cardiovascular abnormalities may also be treated surgically. Limited data on patients treated with hematopoietic stem cell therapy (HSCT) are reported in literature, which have suggested that HSCT can slow down or even prevent further neurological complications, but has little to no effect on the skeletal deformities unless it is performed in an early stage.

Therefore, there is a clear unmet medical need in this condition for which there is currently no authorised medicinal product.

3.1.3. Main clinical studies

UX003-CL301 was a multicentre, randomized, placebo-controlled, blinded start, single-crossover phase 3 study to assess the efficacy and safety of vestronidase alfa in MPS VII patients (diagnosed based on enzyme assay or genetic evaluation) aged 5 to 25 years. Patients whom had undergone a successful bone marrow or stem cell transplant or had any degree of detectable chimaerism with donor cells were excluded. Twelve (12) patients were included in the study. During the blinded period of the study, 12 subjects were randomized 1:1:1:1 to one of four treatment sequence groups (Group A, B, C or D; 3 subjects per group) to either start treatment with 4 mg/kg vestronidase alfa (Group A), or placebo and cross over to 4 mg/kg vestronidase alfa at different pre-defined time points (Group B after 8 weeks, Group C after 16 weeks and Group D after 24 weeks). Subjects were dosed every other week (QOW) through Week 46. All groups received a minimum of 24 weeks of treatment with 4 mg/kg vestronidase alfa QOW.

3.2. Favourable effects

The percent reduction of uGAG excretion after 24 weeks compared to baseline was the primary endpoint with various secondary, clinical endpoints (6MWT, FVC (%pred), visual acuity, BOT-2 and fatigue) and their combined analysis.

After 24 weeks of treatment with vestronidase alfa, a significant reduction in uGAG (DS) excretion was achieved with a LS mean (\pm SE) percentage change of -64.82% (\pm 2.468%) (p<0.0001).

Treatment response as assessed by multi-domain responder index (MDRI) at Week 24 showed a mean score (\pm SD) improvement of +0.5 domains (\pm 0.8) (compared to placebo p=0.0016). Of the 12 patients, six had a MDRI score of +1 or more. Five patients had a score of 0 (indicating no change), indicative of no worsening of this progressive disease. One patient reported with -1 MDRI score.

Seven patients had at least two post-baseline 6MWT results, six of whom had 6MWT results at Treatment Week 24. Three of these six (50%) met the pre-defined MID (\geq 23 m and \geq 10% change from baseline) at Treatment Week 24 and had significant and sustained walking improvements of 65 meters, 80 meters and 83 meters.

3.3. Uncertainties and limitations about favourable effects

Evaluation of the clinical relevance of the observed effects is difficult, as the data on natural history are very scarce and the evolution of the pathology is not well understood. However, it is generally accepted that this is a slowly progressive disease and therefore the duration of the study might not be long enough to allow full evaluation of the treatment effect.

In the studies submitted by the Applicant no patient with neonatal non-immunologic hydrops fetalis is included.

In order to make a responder analysis possible the Applicant defined a MID for each secondary endpoint. When possible the MID is based on literature including other MPS diseases otherwise results from non-MPS diseases are used. This approach results in a broad range of possible values for the various MICD. The chosen MICD all fall within the found range.

The individualized clinical response (ICR) is chosen by the patient as the clinical endpoint with the highest impact on the QoL for this patient. As the choice might be unrealistic the use of the ICR is limited.

The mean results observed for the various clinical endpoints do not reach clinical relevance as they do not reach the pre-defined MID or were practical not available ($FVC_{\%pred}$). On an individual basis no consistent improvement could be observed during the treatment period for either endpoint.

The results are also difficult to interpret, as the numbers of patients analysed are limited, and most patients were not able to perform all the required tests

3.4. Unfavourable effects

Most adverse event reported ($\geq 20\%$ reported) were respiratory infections, cough, vomiting, infusion site extravasation, diarrhoea, pain in extremity, rash and arthralgia.

In study UX003-CL301 eight of 12 patients reported infusion-associated reactions (IARs) (66.7%), 2 of 9 patients in the placebo groups also reported IARs. Nine of the IARs resolved with drug treatment disruption. Two patients experienced anaphylactoid reaction (one reported as grade 3). In the patient with grade 3 anaphylactoid reaction due to rapid infusion in the first hour, this reversed when the treatment was interrupted and emergency medication was provided.

In the pivotal study 6 of 12 patients were positive for NAbs.

3.5. Uncertainties and limitations about unfavourable effects

The overall size of the database is limited due to the rarity of the condition. The lack of a comparative historical data precludes an evaluation comparing the natural time course of the disease using SOC.

The analysis of the patients with NAbs did not indicate an apparent clinical impact in the measured outcomes, however the potential effect of Nabs cannot be determined at this stage and will require further characterisation.

3.6. Effects Table

Table 19. Effects Table for Mepsevii for the treatment of non-neurological manifestations of MPSVII (data cut-off: 28 Feb 2017)

Effect Sh	nort description	Unit T	reatment	Contr	rol	Uncertainties / Strength of evidence	References
Favourabl	Favourable Effects						
Change in urinary GAG excretion	Percent decrease from baseline	% LS Mean (SE)	-64.82 (2.468) 95% CI - 69.66, -59 p-value <0.0001	.98	-		UX 003-301
Modified MDRI	6 pre- specified domains plus fatigue domain	N/A	+ 0.8 (1.1	14)		For some domains, data were imputed	
Unfavourable Effects							
Anaphylacto Reaction	bid	Ν	2			1 SAE	Cofoty /
IAR		Ν	12				Salety
ADA		Ν	10		1	6 patients tested positive for Nab	uatabase

Abbreviations: GAG: glycosaminoglycan, LS Mean: Least Squares Mean, MDRI: Multi-Domain Responder Index, IAR: Infusion associated reaction, ADA: Anti-Drug Antibodies, NAb: Neutralising Antibody

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clear and consistent pharmacodynamic effect is demonstrated by the decrease in uGAG. This strongly suggests a decrease in accumulated substance which may lead to a deceleration of the organ damage. These results are consistent with what has been observed with other ERTs.

After 24 weeks of vestronidase alfa treatment some small improvement was observed for the secondary functional and clinical endpoints (MDRI) in some patients. Overall, in most of the patients at an individual level a small numerical improvement or stabilisation was observed in one or more of the secondary functional and clinical endpoints. The experts from the AHEG agreed that the limited duration of the trial limits the possibility of observing the true magnitude of the treatment effect but acknowledged the importance of demonstrating a pharmacodynamic effect in the context of an enzyme replacement therapy.

Limited safety data only 23 patients are available. The observed treatment adverse events were mild, and in line with the experience from other ERT.

3.7.2. Balance of benefits and risks

The pharmacodynamic effect of vestronidase alfa in MPS VII patients has been clearly demonstrated. The exact clinical relevance of this pharmacodynamic action remains to be

established. Some beneficial findings (as compared to placebo were observed in the secondary, clinical endpoints were observed. Long-term (72^+ weeks) comparison with baseline showed stabilisation/improvement for a portion of the endpoints and patients. Given the progressive character of the disease a stabilisation of the disease burden can be considered a beneficial clinical effect.

Neonates with hydrops fetalis (considered to represent the most severe form of the condition), or patients with milder forms of MPS VII with diagnosis established in early adulthood were not included in the study. However, the treatment effect in these groups of patients can be expected to be comparable with that of the overall population included in the studies. This assumption was endorsed by the AHEG (see Additional expert consultation).

As expected and in line with other ERTs, vestronidase alfa does not cross the blood-brain-barrier therefore no direct effect on neurological manifestations can be expected. Hence, the CHMP considered that the indication should be restricted to the treatment of non-neurological manifestations of MPS VII.

Limited safety data is available. The main safety concern pertains to anaphylactoid and infusion associated reactions with clear recommendations for managing such adverse effects in the product information. Although the overall safety profile of vestronidase alfa does not raise any particular concerns, the long-term effect of treatment on safety in MPS VII patients will be further evaluated in the MPS VII Disease Monitoring Program.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, but also that in the present state of scientific knowledge, comprehensive information cannot be provided. Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall B/R of Mepsevii is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Mepsevii is favourable in the following indication:

treatment of non-neurological manifestations of Mucopolysaccharidosis VII (MPS VII; Sly syndrome).

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being a marketing authorisation under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to obtain long-term data on effectiveness and safety of treatment with	Reports to be
Mepsevii and to characterize the entire mucopolysaccharidosis VII, including variability	submitted as part of
of clinical manifestation, progression and natural history, the MAH is requested to	the annual re-
submit the results of a study based on adequate source of data deriving from a	assessment
Disease Monitoring Program of patients with mucopolysaccharidosis VII.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that vestronidase alfa is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.